"The Feasibility of a Cochlear Nucleus Auditory prosthesis based on microstimulation"

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INTRODUCTION

The overall goal of this contract was to develop an auditory prosthesis based on multisite microstimulation within the cochlear nucleus, and to determine if microelectrodes implanted within the human cochlear nuclei will provide the patient with better auditory performance than is possible with the preset version of the auditory brainstem implant (ABI) , which uses electrodes on the surface of the cochlear nucleus. The primary contract is held by HMRI, which has the responsibility for animal studies dealing with safe stimulation, including the relationship between electrode design and tissue damage and the relationship between stimulation levels and neural injury and excitability. The subcontract to HEI deals with aspects of the work that relate specifically to use of the device in humans. This includes design of the electrode array to fit the human cochlear nuclei, electrode testing in unfixed human brainstem tissue, adaptation of the insertion tool to fit the surgical approach, and development of psychophysical tests that can be used in patients to monitor device function.

I: ANIMAL STUDIES

(These studies were conducted at HMRI. Personnel from both HMRI and HEI participated in some phases of the work).

I-1 Methods

The animal studies used adult, non-deafened cats. During the past three years, the animal studies aimed at determining protocols for safe stimulation in the cochlear nucleus have progressed to the point where safe and effective stimulation protocols for the first human trials can be specified.

Activated iridium stimulating microelectrodes were fabricated from lengths of pure iridium wire, 50 μm in diameter. A Teflon-insulated lead wire was welded to one end of the wire, and the other end was shaped to a conical taper, by electrolytic etching. The entire shaft and wire junction was then coated with 3 thin layers of Epoxylite 6001-50 electrode varnish. The insulation was removed from the tip by electrolytic destruction of the insulation, leaving an exposed surface area of approximately 500 μm^2 +/- 5%, as

determined from the electrode's double layer capacitance. The individual electrodes were then assembled into an integrated array of 3 or 4 microelectrodes spaced 400 to 500 μm apart. The integrated array, with its closely-spaced microelectrode shafts, was designed to approximate the dimensions of an array that can be implanted into the human posteroventral cochlear nucleus using a tool inserted through the translabyrinthine surgical approach.

The arrays of microelectrodes are implanted chronically into the posteroventral cochlear nucleus of young adult cats, using aseptic surgical technique and general anesthesia. A pair of stainless steel recording electrodes is inserted by stereotaxis into the right inferior colliculus through a small craniectomy. The array of iridium stimulating microelectrodes is inserted into the left posteroventral cochlear nucleus (PVCN), using an axial introducer to minimize tissue injury.

Throughout the stimulation protocols, the cats were able to move about freely and the stimulation was conducted using a two-way radiotelemetry stimulation and data acquisition system. This telemetry system and its companion software allows continuous monitoring of the access resistance of the stimulating microelectrodes, and of the compound action potential induced in the inferior colliculus by the stimulating microelectrodes.

I-2: Minimizing tissue injury during electrode insertion

We first evaluated, in the cat model, the implantation of an array of 4 long (4 mm) closely-spaced (400 μm) microelectrodes, whose length and spacing are comparable to those that can be implanted into the human cochlea nucleus, near the auditory nerve root.

The results from these experiments were somewhat disappointing, in that an unacceptable high percentage (3 of 6) of the implants failed, and the cochlear nuclei were infarcted by the 4-element arrays. There was evidence from the histologic evaluations that the injury was due to mechanical distortion and shearing of tissue and blood vessels that occurs when closely-spaced electrodes are inserted. The problem may be exacerbated when the electrode shafts are slightly misaligned from the axis of

insertion.

We then modified our procedure for aligning the microelectrode shafts and we also modified the electrode tip configuration. The electrodes were fabricated with very blunt tip (approximately 12 μm in diameter) and this modification has yielded encouraging results. Based on physiologic measurements and histologic analysis, only 2 or 3 of the approximately 56 blunt electrodes implanted into the posteroventral cochlear nucleus of the most recent 15 cats (for which histology is available) induced small microhematomas during or subsequent to implantation. (QPR #1,3,5)

I-3: A characterization of stimulation-induced depression of neuronal excitability during prolonged pulsing in the PVCN

Highly localized, long-lasting stimulation-induced depression of neuronal excitability (SIDNE) is a consequence of prolonged, high-frequency microstimulation in the CNS. It represents a persisting refractory state in the neurons and axons near the stimulating microelectrode, that occurs in the absence of histologically-detectable tissue injury. It does not involve a change in synaptic efficacy, and in this respect, it differs from the more familiar phenomenon of Long-Term Depression (LTD).

SIDNE in the feline ventral cochlear nucleus was quantified according to the changes in the response growth functions (recruitment curves) of the averaged responses evoked by the stimulating microelectrodes and recorded via the electrodes implanted chronically in the inferior colliculus. Prior to the start of each daily session of stimulation and immediately after the end of each session, the compound action potentials evoked by the microstimulation were recorded in the contralateral inferior colliculus. Due to the low amplitude of the response evoked by the microstimulation, the responses evoked by 1024 to 4096 consecutive stimulus pulses were averaged to obtain an averaged evoked compound action potential (AECAP). The AECAP's were generated by stimulating at the same site in the cochlear nucleus that received the continuous test stimulus, but the pulse repetition rate was only 50 Hz, rather than at 100 to 500 Hz, as used during the test stimulus.

The severity of the SIDNE is strongly dependent upon both the instantaneous

frequency and the duty cycle of the electrical stimulation. The character of the SIDNE, including its localization to the immediate vicinity of the stimulating microelectrodes, suggests that the phenomenon is a direct consequence of the prolonged electrical excitation of the neurons close to the microelectrode. Although the SIDNE may persist for several days after the end of the stimulation protocol, it does not become more severe from day to day when the stimulation protocol is repeated on successive days.

The problem of designing microstimulation systems that allow high-frequency stimulation of a neural substrate, while minimizing SIDNE, should be considered in the context of its salient characteristics. We have found that the obvious approach to compensating for the SIDNE; namely, increasing the baseline stimulus amplitude to compensate for the increase in the response threshold, is not effective since this only worsens the SIDNE and causes the response threshold to increase further. SIDNE develops over an interval of several hours of high-rate stimulation and the short-term structure of the stimulation appears to be relatively unimportant in determining its severity. Thus 7 hours of continuous stimulation at 500 Hz, with a 25 % duty cycle (the artificial voice-modulated stimulus is present for 15 out of every 60 seconds) induces much less SIDNE than when the duty cycle is 100% , in the same way that the depression of neuronal excitability is ameliorated by reducing the stimulus frequency . Thus, one approach to ameliorating the SIDNE is to rotate the stimulus across several microelectrodes, thereby reducing the duty cycle at each microelectrode. At the shortest time frame, the stimulation can be interleaved from one pulse to the next across several closely-spaced microelectrodes (thereby reducing the stimulus frequency at each microelectrode). The frequency of prolonged pulsatile microstimulation should not exceed what is absolutely necessary in order to achieve the required experimental objectives or to maximize the clinical benefit, for the individual animal subject or patient. In general, this problem can be envisioned as a 3-way optimization between temporal resolution (determined by stimulus frequency), spatial resolution of the stimulation in the neural space (determined by the number of closely-spaced microelectrodes in the interleaved pulsing sequence), and the stability of the neural response over time (severity of the SIDNE).

The findings from this study were published in the IEEE Transactions on Biomedical Engineering , in September of 1997. (Also, QPR # 1,3,5,7,9,10)

I-4: Reducing the severity of SIDNE by interleaved pulsing

We examined, in our cat model, whether interleaved pulsing of closely-spaced microelectrodes in the posteroventral cochlear can moderate the stimulation-induced depression of neuronal excitability (SIDNE) that develops during prolonged, high-rate pulsing. In three cats, We pulsed the electrodes for 7 hours per day on each of three successive days. In the first cat (cn102) the three microelectrodes were pulsed simultaneously, and in the second session, conducted 20 days later, the stimulation was interleaved. The order (simultaneous/interleaved) was reversed in the second and third cats. The SIDNE was significantly less when the microelectrodes were pulsed in the interleaved mode. The results are consistent with our hypothesis that the SIDNE reflects depression of the electrical excitability of neurons, rather than depression in the efficacy of synapses. Thus, interleaved pulsing would be expected to reduce SIDNE only when the electrodes are close enough together so that the current fields overlap significantly. The SIDNE that results from excitation of neurons only by the individual microelectrodes must be managed by other means (QPR #3).

I-5: The physiologic & histologic responses to prolonged high-rate stimulation

In our prolonged stimulation regimens, we have simulated an acoustic environment by using a computer-generated artificial voice which reproduces many of the characteristics of real speech, including the long-term average spectrum, the short-term spectrum, the instantaneous amplitude distribution, the voiced and unvoiced structure of speech, and the syllabic envelope. The artificial voice signal is then passed through a full wave rectifier and then undergoes logarithmic amplitude compression, before being sent through an appropriate anti-aliasing filter. The amplitude of the signal from the filter then sets the amplitude of the charge-balanced stimulus pulses which are delivered to each electrode at 250 or 500 Hz, in an interleaved manner. The range of spike amplitudes is shifted, and acoustic silence (artificial voice amplitude of 0) is

represented by a stimulus amplitude of 6 μA, which is close to the response threshold of the neurons near the tip of the properly functioning microelectrodes.

We have made extensive use of the response growth function (recruitment curve) of the compound response that is evoked by the microelectrodes in the ventral cochlear nucleus and recorded in the central nucleus of the inferior colliculus. The "non-embedded" recruitment curves are acquired at a stimulus pulse rate of 50 Hz, to allow sufficient time between pulses (20 msec) to capture the entire evoked response. When measured before and at various times after several hours of high-rate stimulation the "non-embedded" recruitment curves reveal any persisting stimulation-induced depression of neuronal excitability (SIDNE). While such persisting effects are relevant to the question of the safety of the stimulation regimen, the curves so acquired do not reveal short-acting refractory or inhibitory effects that may be relevant to the performance of an implant based on intranuclear microstimulation. To address the latter, we developed a computerized data acquisition scheme in which the acquisition of the recruitment curves is embedded in the high-rate artificial voice signal.

We have used these "embedded" recruitment characteristics, as well as our "non-embedded" recruitment characteristics, as part of the long-term stimulation protocols in cat cn108 and all later animals (the most recent 18 cats, as of this writing). The embedded responses have revealed some short-term depression of synaptic transmission in the lower auditory pathway that is not apparent in the non-embedded recruitment curves that are generated shortly after the end of the prolonged, high-rate stimulation. Although the short-term effects are not really a safety issue, they are relevant to the performance of an auditory prosthesis based on intranuclear microstimulation, and in this context, they suggest that the stimulus pulse rate during prolonged stimulation regimens should not exceed 250 Hz per microelectrode (QPR #5,7,9,10).

I-6: Extending the duration of stimulation regimen

For cats cn108 through cn126, the stimulation regimens were extended, so that the animals received 7 hours of stimulation per day on each of 10 to 15 successive

days (weekends included). In one case, the regimen was 26 days in duration. The regimen was conducted 2 to 5 months after implantation of the arrays of microelectrodes. The stimulus was a 250 Hz pulse train, modulated over the range of 6 to 20 μA, according to the logarithmically-compressed artificial voice signal . The duty cycle of the artificial voice was 50% (15 sec on, 15 sec off, at 6 μA). In most cases, there was little or no cumulative effect on neuronal excitability beyond the second day of stimulation, and in most cases, the SIDNE actually decreased slightly by the third day of stimulation. Histologically, the neural tissue and neurons surrounding the electrodes sites was indistinguishable from the tissue surrounding the unpulsed site.(QPR #5,7,9,10)

I-7: The effect of increasing the stimulus amplitude

Prior to cat cn111, we had limited the stimulus pulse amplitude to 3 nC/phase (20 μA, with a pulse duration of 150 μs/phase). In two cats, three microelectrodes were pulsed in the interleaved mode, at 250 Hz per electrode, and the maximum amplitude of the stimulus pulses, as modulated by the artificial voice signal, was increased to 32 μA (4.8 nC/phase).The electrical excitability of the neurons near the stimulating microelectrodes was assessed on the basis of the changes in the "non-embedded" and "embedded" recruitment characteristics of the compound evoked response recorded in the contralateral inferior colliculus. Marked depression of neuronal excitability developed during the prolonged stimulation, and most of the depression developed during the first 7-hour session of stimulation. These findings imply that the pulse amplitude should not exceed 3 nC/phase.

Although there was marked depression of neuronal excitability, histological evaluations of the electrodes sites did not reveal any tissue injury attributable to the prolonged electrical stimulation. This implies that the depression of neuronal excitability would eventually disappear (QPR #5,7).

I-8: Effect of the number of microelectrodes, the duration of the daily stimulation

session, and the total duration of the stimulation.

One cat (cn122) was stimulated on 26 consecutive days, beginning 86 days after implantation of the microelectrode array into the PVCN. The stimulus was biphasic current pulses whose amplitude was modulated according to the logarithmically-compressed artificial voice signal. Each microelectrode was pulsed at 250 Hz, and the stimulus was interleaved across the ensemble of microelectrodes. The protocol in this animal differed from that used in all previous cats, in that all 4 microelectrodes eventually were pulsed. During the first three days of the regimen, only two of the microelectrodes were pulsed for 7 hours per day. On day 4, the remaining two microelectrodes were added, and henceforth all 4 were pulsed for 7 hours per day at 250 Hz , in the interleaved mode. On the day 23-26, the stimulation regimen was increased to 12 hours per day. The cat was sacrificed for histologic evaluation after the 26th session.

The electrical excitability of the neurons near the stimulating microelectrodes was assessed according to the changes in the recruitment characteristics of the compound evoked response recorded in the contralateral inferior colliculus. We generated the non-embedded recruitment characteristics from data acquired during low-frequency pulsing after each of the 7- or 12 hour sessions. The embedded curves were generated during (near the end of) the 7- or 12 hour sessions of stimulation from the pulses embedded in the artificial voice signal.

Thus, in cat 122, we were able to examine three phenomena: (1) The histologic effects, and the effects on neuronal excitability (both direct and transsynaptic) during 26 days of stimulation (2), the effects on neuronal excitability resulting from increasing the number of pulsed microelectrodes in an ensemble of closely -spaced microelectrodes , and (3), the effects on neuronal excitability resulting from increasing the number of hours per day that the electrodes are pulsed.

Most of the physiologic effects of prolonged interleaved pulsing of closely-spaced microelectrodes were apparent by the end of the first day of the regimen . For the stimulus parameters used in this animal, there was mild depression of the electrical

excitability of the neurons close to the microelectrodes, and the amount of depression varied slightly between microelectrodes. Overall, the effects were comparable to what we have seen in other animals stimulated for up to 15 days with these same parameters. There was a transient additional decrease of the excitability of neurons near the microelectrodes that had been pulsed since the first day, where the two remaining microelectrodes were added to the ensemble, but the neuronal excitability recovered after a few days. Lengthening the daily stimulation sessions (from 7 hours per day to 12 hours per day) had virtually no effect on neuronal excitability, and the directly- evoked, and transynaptically evoked components of the non-embedded or the embedded recruitment curves remained essentially unchanged. Over the 26 days of the stimulation regimen, the microelectrodes' access resistances, and their cathodic voltage transient (an index of their charge capacity) remained quite constant, and showed no clear trends.

The histological evaluations of the electrodes sites did not reveal any tissue injury that could be attributed to the prolonged electrical stimulation. There were no unpulsed (control) electrodes, but the neurons and neuropil near each of the 4 microelectrode tips appeared to be quite normal. The surrounding neuropil did not contain edematous axon segments, which is the cardinal feature of stimulation-induced tissue injury in the cochlear nucleus . There was no evidence of healed micro-hemorrhages anywhere in the cochlear nucleus, a finding that attests to the merits of blunt-tipped microelectrodes for chronic implantation and microstimulation. The only problem noted in the histologic evaluation was a localized inflammatory response near a segment of the upper shaft (but not at the tip) of microelectrode #3. This was probably due to a localized contaminant on the electrode shaft. We are preparing to transfer part of our microelectrode fabrication to a clean-room, to reduce the chance of contamination of the uncured Epoxylite varnish by airborne particles. (QPR # 10).

I-9: Long-term stability of chronically implanted microelectrodes arrays in the PVCN

Normally, we allow at least 60 days (typically 90 to 120 days) to elapse after implantation of the stimulating electrodes, before initiating the stimulation protocols.

However, four animals (CN41, CN42, CN74 and CN107) were reserved as long-term subjects in order to monitor the long-term stability of the chronically-implanted microelectrodes.

We have been following the performance of stimulating microelectrodes that have been implanted in cat cn74 for more than 1800 days, and in cat cn107, for more than 900 days. Three of the 4 microelectrodes in the two cats are still functioning well One microelectrode in cat cn108, has failed, probably as a result of the failure of the weld junction between the microelectrode shafts and the platinum cable. The threshold and the slope of the recruitment curves of the evoked response have remained quite stable. This confirms our earlier findings that the connective tissue capsule around the tips of these microelectrodes does not continue to thicken over time, and also demonstrates that there are no large changes in the number or in the excitability of neurons and axons in the tissue surrounding the site of the electrode tip. For microelectrode #1, the threshold of the evoked response actually decreased over time, and there was little change in the slope of the recruitment curve (a function of the number of neurons excited) . The low threshold of the electrically- evoked response also confirms that the tip of the stimulating microelectrode has remained within the PVCN through the long period in situ

I-10: Accessing the tonotopic axis of the ventral cochlear nucleus by intranuclear microstimulation

(This study was conducted jointly by personnel from HMRI and HEI)

The functionality of an auditory prosthesis based on microstimulation in the cochlear nucleus is dependent on its ability to access the tonotopic organization of the human ventral cochlear nucleus in an orderly fashion. In these studies we utilized the homologies between the human and feline ventral cochlear nuclei and the known tonotopic organization of the central nucleus of the inferior colliculus (IC). In anesthetized cats, stimuli were delivered to 3 or 4 locations along the dorsal-to-ventral axis of the posteroventral cochlear nucleus (PVCN) , and for each stimulus location, we recorded the multiunit neuronal activity and the field potentials at 20 or more locations along the dorsolateral-ventromedial (tonotopic) axis of the IC. The current source-sink

density (CSD), which localizes regions of neuronal activity, was computed from the sequence of field potentials recorded along this axis. The multiunit activity and the CSD analysis both showed that the tonotopic organization of the PVCN can be accessed in an orderly manner by intranuclear microstimulation in several regions of the PVCN, using the range of stimulus pulse amplitudes that have been shown in previous studies to be non-injurious during prolonged intranuclear microstimulation via chronically implanted microelectrodes.

Our data indicate that over the range of 8-24 μA, it should be possible to convey at least 4 separate channels of acoustic information into the cochlear nucleus using microelectrodes spaced 300-500 μm apart along the dorsoventral axis. In human subjects, 4 channels appears to be sufficient for good intelligibility of speech.

A manuscript describing these results has been accepted by the IEEE Transactions on Rehabilitation Engineering, and will be published in December of 1998

II: THE DEVELOPMENT OF MICROELECTRODE ARRAYS AND A MICROELECTRODE INSERTION TOOL FOR CLINICAL USE.

(This work was conducted jointly by personnel from HMRI and HEI)

II-1: Mechanical design of the insertion tool (HMRI and Altair Instruments, Inc).

An instrument that is to be used to insert an array of discrete iridium microelectrodes or an array of silicon microprobes into the cochlear nucleus must completely enclose and protect the array until the instrument has been maneuvered into its final position and the array is ready to be injected into the brainstem. Another reason for enclosing the array is to allow the instrument's barrel to push aside the cable from the surface array that will be implanted within the lateral recess. The instruments must insert the electrodes precisely along their axis, in order to avoid damage to the electrodes and to avoid slashing the brainstem. It must insert the array at a specified velocity. It must hold the array securely during the entire insertion process (so that the cable trailing from the array does not disturb the axial alignment of the electrodes), then release the array cleanly at the end of the insertion. The array itself must have a very low profile above the pia, so that it is not displaced when the surgeon packs the lateral

recess with Teflon felt, in order to stabilize the surface array. The insertion instrument must allow the array of electrodes to be injected at an angle approximately 55° relative to the long axis of the instrument (Section II-2). Furthermore, the maximum diameter of the surgical aperture is approximately 2 cm, and the axis of the surgical opening is not aligned with the tonotopic axis of the ventral cochlear nucleus. This means that the force required to inject the electrodes into the brainstem must be transferred around a bend with a relatively small radius of curvature.

Prior to its deployment, the microelectrode array is enclosed and protected within the end of the curved barrel, and a vacuum holds the array against the end of a hollow slide piece within the barrel. The distal end of the barrel is slotted to accommodate the cable. The barrel is only 3 mm in diameter to minimize obstruction of the surgeon's view of the brainstem and landmarks. The orifice of the barrel is placed against the landmark, and when the spring is released, the slide within the barrel is pushed forward by a flexible wire which carries the force around the bend in the barrel. The array, still held by the vacuum against the end of the slide, is pushed into the tissue at a moderate velocity (50 - 150 mm/sec). The speed of insertion is controlled by the spring tensioning adjustment screw, by the amount of vacuum within the chamber, and by a magnetic brake enclosed within the instrument's body. When the slide reaches the end of its travel, the shuttle valve interrupts the vacuum line and opens a vent to a source of (positive) air pressure. The puff of air collapses the vacuum so that the array is released quickly from the end of the slide.

A prototype of the insertion instrument has been designed and constructed. The tool was constructed by Altair Instruments, Inc, using mechanical specifications provide by the Principle investigator at HMRI, and anatomical data provided by the personnel at the House Ear Institute (Section II-2). The velocity at which the array is inserted can be adjusted according to the outcome of studies of the insertion of arrays into unfixed human brainstems (Section II-4).

II-2: Anatomical studies of the human auditory brainstem

(This work was conducted by personnel at the HEI):

The HEI Temporal Bone and Brain Bank has assembled the brainstems of over 40 human subjects with normal hearing, and from those with mild-to-severe hearing loss, and acoustic neuromas. All patients with Neurofibromatosis II (NF2) who receive an ABI sign pledges to donate their brainstems to HEI in the event of their death. This collection of histologically processed brainstems is the basis for our work in adapting design of the microelectrode arrays and insertion tool to the actual dimensions of the human brainstem and cochlear nuclei.

Because the electrode array must "fit" the human cochlear nuclei, our approach to electrode design has been a computerized, three-dimensional reconstruction of cochlear nuclei and surrounding structures, carried out in PC3D and AutoCAD programs. The background for these studies is earlier work on cytoarchitecture and axonal organization of the human CN . Morphometric studies carried out in brainstems of subjects with profound bilateral deafness have demonstrated that neurofibromatosis 2 (NF2), coupled with acoustic neuroma surgery, results in extreme shrinkage of the CN, down to 1/2-2/3 normal volume, but causes much less neuronal degenerative change than etiologies such as meningitis and genetically-induced deafness.

During the past three years, we have developed hardware and software for three-dimensional reconstruction and manipulation of images of the entire head. After histological processing of the brainstem of a deceased NF2 patient, we digitized sections through the pontomedullary region into the PC3D program (Jandel) and created 3D wireframe images of the brainstem segment. PC3D did not, however, have the capacity to generate fully shaded displays. In order to utilize the human cochlear nucleus data bank in an AutoCAD format, we developed a program (3D2CAD.EXE) to convert PC3D ASCII files into a DXE file which could then be loaded into AutoCAD. The addition of the graphics engine (MG-3D, Matrox Systems) enhanced the display resolution and provided fully shaded 3D views of rendered objects. This system allowed us to dynamically "walk through" the implant site and identify the surgeon's angle of view. The AutoCAD versions of the brainstem reconstruction were then fitted into a generic head/skull/brain model (Viewpoint Datalab). By deleting meshes of the head surface and skull, we were able to create a translabyrinthine "surgical opening"

and visualize this opening in all planes of section in wire frame and solid images. At this time, we made the first computerized model of an electrode insertion tool, indicating the length and tip bend which would be necessary to reach the ventral cochlear nucleus (VCN). Because our brainstem model included the orientation of isofrequency planes in the VCN, we could determine if the electrode would cross the tonotopic gradient of the nucleus.

In the generic head model, the skull module is highly accurate in its depiction of the external skull surface, but it did not include the internal bony surface or dural/vascular structures such as the tentorium, sigmoid sinus, and jugular vein. Thus the translabyrinthine approach was only approximated by a cone narrowing towards the surface of the brainstem. In an actual patient, the operative field is constrained by anatomical features such as the sigmoid sinus and facial nerve, which restrict the length and width of the surgical opening. In order to create a more realistic representation of the surgical opening, we decided to return to radiologic images and utilize CAT scan data of a cadaver head with bilateral translabyrinthine surgical openings. In this process, 24 CT scans through the mid brainstem region were imported into AutoCAD. The original 9 track magnetic tape from the CT scan was brought into a Unix SPARC station equipped with a tape drive. A custom "C"-computer language program was used to reformat the files and extract the images, which were than transferred into the NIH Image program. Another useful capability of the program is to trace the edges of the structures and save them in D.F. format. The edge files were reconstructed into a 3D image in AutoCAD, and the reconstruction of the CT data was fitted into the generic head model. Using this process, we were able to portray all of the anatomical features likely to limit maneuverability of the tool during surgery, such as the petrous wing of the temporal bone, the dural tentorium, and the sigmoid sinus-jugular bulb complex. Working in AutoCAD, we experimented with insertion tools of various sizes and angles. Based on the modeling, Altair Instruments constructed two prototype tools of titanium. The tools were similar in length, but differed in the angle between the shaft and the terminal segment which would house the electrode array. Both prototypes were sterilized and manipulated by the neurosurgeon during tumor removal surgery. This

trial demonstrated no problem with the petrous wing or the sigmoid sinus limiting the maneuvering of the tool. Because the computer reconstructions indicate that the tool with an acute angle of 55° is more likely to place an electrode array within the ventral cochlear nucleus (VCN), Altair Instruments has fabricated a fully operational tool with a length of 16 cm and a tip bend of 55°-60° which will traverse the translabyrinthine surgical opening and contact the cochlear nuclei.

II-3: Surgical landmarks for implanting the array into the human cochlear nucleus

(This work was conducted by personnel at HEI)

Because the human cochlear nuclei are not visible on the brain surface, a visible surface landmark is required to locate the point of entry of the electrode into the CN. In our first studies, we modeled electrode insertion though the most obvious surface feature, the eighth nerve stump. These studies demonstrated that the vestibular nerve root often does not overly the VCN, and that a cochlear nerve stump in not present in 50% of the neuronectomy cases. Furthermore, electrode insertion through the cochlear nerve root places the stimulation sites outside the VCN or in the spherical cell area at its rostral most tip. Stimulation experiments in cats at HMRI showed that electrical stimulation of the posterior and central VCN induced neuronal activity in the Inferior colliculus, but stimulation in the rostral tip of the VCN did not. These factors have led us to reject the eighth nerve as a usable landmark for surgical placements and to consider use of the taenia choroidea to guide implantation. The taenia choroidea is visible to the surgeon and is routinely used to locate the mouth of the lateral recess in order to place the surface ABI array. Because the taenia crosses the posteroventral cochlear nucleus, insertion here should place the electrode array in relation to populations of neurons which carry monaural information to the inferior colliculus. With this approach, the electrode shafts will cross the tonotopic gradient obliquely, rather than orthogonally. Within the coming months, we will carry out computer simulations of electrode insertions through the taenia into the posteroventral cochlear nucleus, in order to specify the optimal geometry of both iridium wire and silicon substrate arrays. Using the same techniques as previously used (scanning or digitization of drawings of

stained sections, creation of three-dimensional reconstructions in PC3D and AutoCAD), we will model insertion of both discrete iridium microelectrodes and silicon substrate electrodes.

II-4: Electrode insertion studies

(This work was carried out by personnel from HEI and HMRI)

From its inception, one of the goals of these contracts has been to adapt the University of Michigan (UM) silicon-substrate microstimulation arrays for use as an auditory implant. The UM probes packs stimulation sites more density, but they have fractured when we attempted to insert them into unfixed human brainstems These tests are carried out with an insertion force apparatus develop at HEI, in which a precision stepper motor controls the position and velocity of an electrode carrier. The tests demonstrated that UM electrodes fracture before they penetrate through the glia limitans on the surface of the human brainstem. As a result, two type of microelectrode arrays are being developed. Changes are being made in the UM silicon-substrate device, and HMRI iridium wire stimulating microelectrodes are being fabricated into a device for human use, with 5 discrete iridium probes embedded in an epoxy disk. Insertion studies have demonstrated that HMRI electrode arrays of this type reliably penetrate into the cochlear nuclei at moderately high velocity (app. 75 mm/sec), but not at low velocity (app. 12 mm/sec).

III: DEVELOPMENT OF HUMAN PSYCHOPHYSICAL TESTS

The main objective of a Penetrating-electrode Auditory Brainstem Implant (PABI) is to achieve better speech recognition performance than is possible with the surface electrode ABIs, by localized stimulation of multiple sites along the tonotopic axis of the ventral cochlear nucleus. For this goal to be achieved we must quantify perceptual similarities and differences between stimulation with surface electrodes and penetrating electrodes. Speech processing strategies must be designed and optimized for individual patients based on their pitch range, number of electrodes, and electrode interaction. Over the past three years we have defined methodologies for measuring

electrode interactions and have demonstrated that spectral-tonotopic alignment is critical for good speech recognition.

Unfortunately, in a PABI device we have little control over the absolute tonotopic location, and incomplete control of the amount of interaction between the microelectrodes. Thus, methods must be developed to assess the absolute tonotopic location of the electrodes and to design a speech processor for that patient that matches the appropriate frequency information in speech to the location of their electrodes.

To optimize the effectiveness of penetrating electrode ABIs, we must:

1. Establish a baseline of psychophysical and speech recognition performance in patients with the existing surface-electrode ABI against which to compare performance with penetrating electrodes.
2. Quantify similarities and differences in basic perceptual capabilities with surface and penetrating electrodes.
3. Quantify the tonotopic locations of the penetrating electrodes.
4. Develop fitting procedures to customize the speech processor to the penetrating electrode locations and to the capabilities of the individual patient.

We anticipate that the primary difficulty in implementing point #4 is in matching the spectral information in speech to the location and extent of the neurons stimulated by each electrode. Studies in cochlear implant patients have shown that speech recognition is highly sensitive to warping and/or misalignment of the speech spectral information and the tonotopic location and spacing of the electrodes. Identifying the tonotopic location of the penetrating electrodes in the PABI is more difficult. The location of the tonotopic axis of the PVCN relative to the axis of insertion of the penetrating electrodes cannot be determined with certainty. We propose to measure electrode interactions to assess potential overlap of percepts elicited by the penetrating electrodes. Absolute pitch estimates will also be elicited. The spectral center-frequency and width of the speech analysis filters will be adjusted to match the pitch of

Combinations of four noise bands will be selected as carrier bands simulating four electrode locations. The center frequency and bandwidth of each band will be varied. A second experimenter who is blind to the actual noise band conditions will then adjust the processing parameters to "fit" the selected noise bands. Different methods for quantifying the relative and absolute pitch locations of the electrodes will be assessed. One aspect of intranuclear microstimulation that will require special care in the design of a speech processor, is stimulus-induced depression of neural excitability (SIDNE), which may persist for several days after termination of the stimulation. Animal studies conducted under this contract have demonstrated long-term depression in neural excitability following exposure to high rates of electrical stimulation. This depression of excitability is more severe when each microelectrode is pulsed at 500 pps or greater. To avoid SIDNE, speech processors for the PABI may require relatively low rates of stimulation (e.g, 250 pps. per microelectrode). We will measure speech recognition with low-rate speech processors on patients with surface electrode ABIs.

IV: CURRENT SPREAD FROM SURFACE ELECTRODES IN A PATIENT

(This study was conducted by personnel at HEI)

The death of an a patient with an ABI gave us the opportunity to examine the relationship between electrically-induced auditory perceptual thresholds and current spread through the brainstem, for electrodes implanted on the surface of the brainstem, over the cochlea nucleus. We were able to obtain the intact brainstem of this subject, with the ABI device *in situ*, from the office of the Los Angeles County Coroner. The brainstem, including the electrodes and lead wires, was embedded in celloidin and sectioned according to our standard protocol. Reconstruction of the brainstem segment through the pontomedullary junction allowed us to determine the distances from the two electrode plates to the nearest boundary of the cochlear nuclei. When these distances were compared with premortem perceptual thresholds, the threshold-distance data were found to fall within the range determined from previously published animal studies (Shannon, et al., 1997). These findings give us a greater degree of confidence that standards for safe stimulation levels now being developed by HMRI can be generalized

to a human prosthetic device.

IV: PUBLICATIONS of work funded all or in part by contract NO1-DC-5-2105

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