"A Cochlear Nucleus Auditory prosthesis based on microstimulation"

Contract No. **No. NO1-DC-1-2105**

Progress Report # 3

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SUMMARY

The overall goal of this project is to develop a central auditory prosthesis based on an array of microelectrodes implanted into the ventral cochlear nucleus, in order to restore hearing to patients in whom the auditory nerve has been destroyed bilaterally.

As part of our evaluation of the safety of prolonged implantation and stimulation of intranuclear microelectrodes, we sacrificed cat cn139 at 53 months after implanting 3 iridium stimulating microelectrodes into its posteroventral cochlear nucleus. The electrodes were insulated with Epoxylite 6001 electrode varnish. The threshold of the electrical response evoked from the microelectrodes had remained quite stable throughout the period of implantation, but over the course of the 53 months, the connections to two of the 3 electrodes failed at the junction with the percutaneous tower, and this was the basis of the decision to sacrifice the cat (while the connection to at least one electrode remained intact). During the 2.5 years *in vivo*, the threshold of the evoked response increased slightly, from about 6 ：A to approximately 8 ：A. This longevity of the intranuclear electrodes is similar to that seen in previous long-term implants. Histologic evaluation of the electrode sites revealed that the upper parts of the Epoxylite-insulated electrode shafts were surrounded by a chronic inflammatory process, similar to what we have observed previously. Its frequent occurrence appears to justify our decision to insulate our electrode shafts with Parylene-C rather than with Epoxylite. Deeper in the nucleus, the sheath around the electrodes was thinner and there was less evidence of the chronic inflammation. The tip sites of all of the microelectrodes were surrounded by a very thin gliotic sheath . Outside of this capsule, the neuropil and neurons ventral to the tip site was somewhat compressed and distorted ventrally but otherwise appears to be normal and healthy. These findings are consistent with the good stability of the evoked responses over the period of implantation.

I: Long-term implantation of stimulating microelectrodes into the ventral cochlear nucleus of cat cn139.

METHODS

On Nov 1, 1999, three iridium microelectrodes insulated with Epoxylite varnish were implanted by stereotaxis into the left posteroventral cochlear nucleus of cat cn139. These microelectrodes were insulated with Epoxylite 6001 electrode varnish but their geometry and dimensions were identical to those that will be used in the human trials of the penetrating auditory brainstem implant. A scanning electron micrograph of such a microelectrode is shown in Figure 1. A pair of recording electrodes was also implanted into the right inferior colliculus.

During the next 2.5 years, the connections between two of the intranuclear microelectrodes and the percutaneous tower were damaged. The third electrode continued to function until the cat was sacrificed on March 29, 2002, 53 months after implantation of the electrodes.

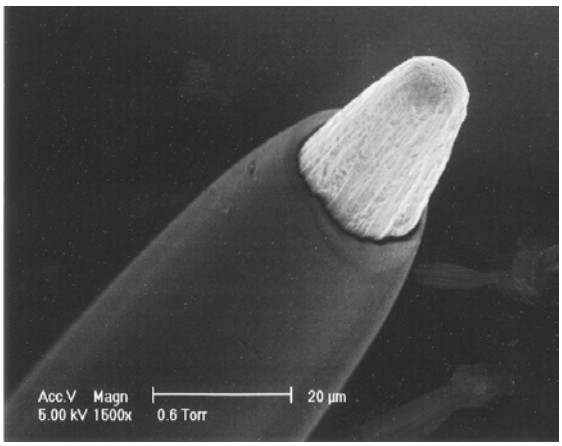
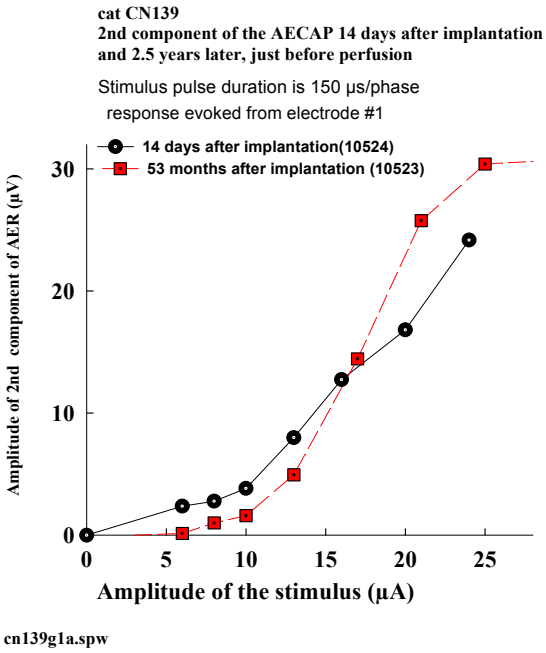


Figure 1

At intervals throughout the period of implantation, the responses evoked from the stimulating microelectrodes in the ventral cochlear nucleus were recorded in the inferior colliculus, and these responses were summated (averaged) to obtain averaged evoked responses (AERs). Response growth functions (RGFs), which represent the recruitment of neural elements surrounding the microelectrodes, were generated by plotting the amplitude of the AER against the amplitude of the stimulus current that evoked the AER. The “probe” stimulus applied to the intranuclear microelectrodes was a train of cathodic-first, biphasic current pulses, 150 ：s/ph in duration and at a rate of 50 Hz.

In preparation for histologic evaluation of the implant sites, the animal was deeply anesthetized and perfused through the aorta with a fixative containing 4% formalin and 0.25% glutaraldehyde. The electrodes were removed from the cochlear nucleus, the nucleus was embedded into paraffin, sectioned at 8 ：m and stained with Toluidine blue.



RESULTS

Figure 2 shows RGFs generated from AERs recorded in the IC from electrode #1 of cat cn139. Initially the threshold of the evoked response was below 6 ：A, for biphasic cathodic-first pulse pairs, 150 ：s/phase in duration. When the animal was sacrificed 53 months later, the threshold of the evoked response had increased to about 8 ：A. During the 53 months *in vivo*, the slope of the RGF did not decrease, and this indicates that the excitation threshold increased only for those neurons that were very close to the tip of the stimulating electrode. It is notable that during the 53 months in vivo, this animal had undergone several regimens of prolonged stimulation, including one 21-day regimen (McCreery et al 2000), which was conducted about 9 months after implanting the electrodes. Although these stimulations produced marked reversible depression of neuronal excitability, the long term effect on neuronal excitability was not remarkable, as shown in Figure 2.

The histologic evaluation showed that the microelectrodes entered the ventral cochlear nucleus near the junction between the posteroventral and anteroventral CN. Near the point of entry (Figure 3A) , there is evidence of an ongoing (chronic) inflammatory response, probably a response to the Epoxylite electrode vanish or to a contaminant on the surface of the electrode shaft. The rather frequent occurrence of this type of chronic response appears to justify our decision to insulate all of our electrode shafts with Parylene-C rather than with Epoxylite.

Deeper in the nucleus, the sheath around the electrodes was thinner and there

was less evidence of the chronic inflammation (Figure 3B). The tip sites of all of the microelectrodes were surrounded by a very thin gliotic sheath (Figure 3C,4,5A,5B). Outside of this capsule, the neurons and neuropil ventral to the tip site was somewhat compressed and distorted ventrally but otherwise appears to be normal and healthy. These findings are consistent with the good stability of the evoked responses over the period of implantation (Figure 2) and demonstrates that the sheath around the tip sites does not continue to thicken throughout the life of the implant.

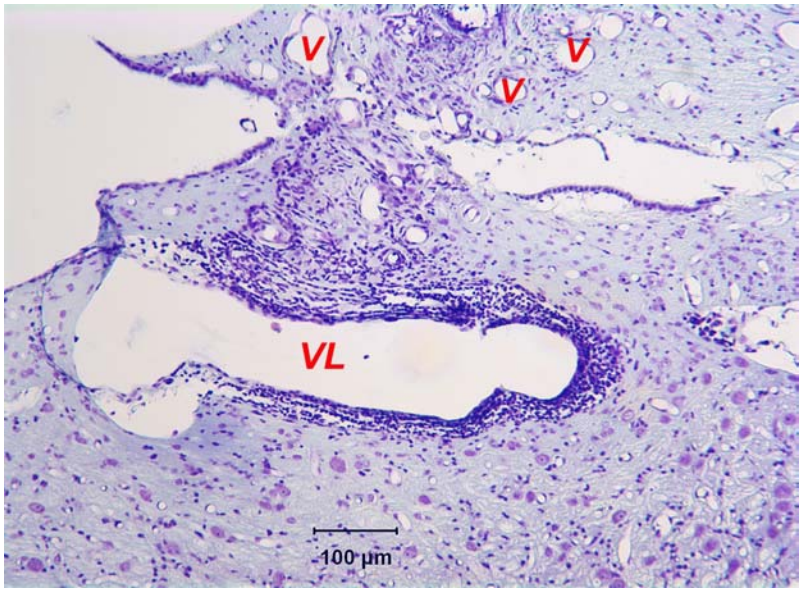


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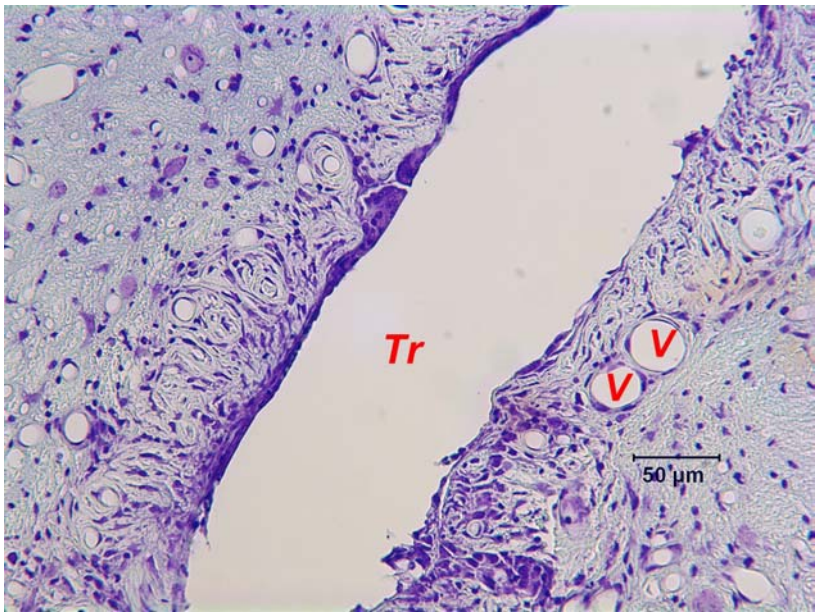
Figure 3A. A section through the dorsal aspect of the ventral cochlear nucleus of cat CN139. The section is near the point of entry of electrode #1, and about 50 ：m caudal of the electrode track itself. This part of the electrode track is accompanied by vascular hypertrophy (V) and by manifestations of a chronic inflammatory response, including perivascular cuffing (notably around the very large vessel, VL), vasculitis and infiltration of inflammatory cells into the



sheath surrounding the track

Figure 3B. A section through electrode track 1, about 0.5 mm below the surface of the cochlear nucleus. At this depth, the inflammatory response less evident, but there is still vascular hypertrophy (V) within the thickened sheath around the shaft. Neurons and neuropil 75 ：m from the lumen of the track appear normal.

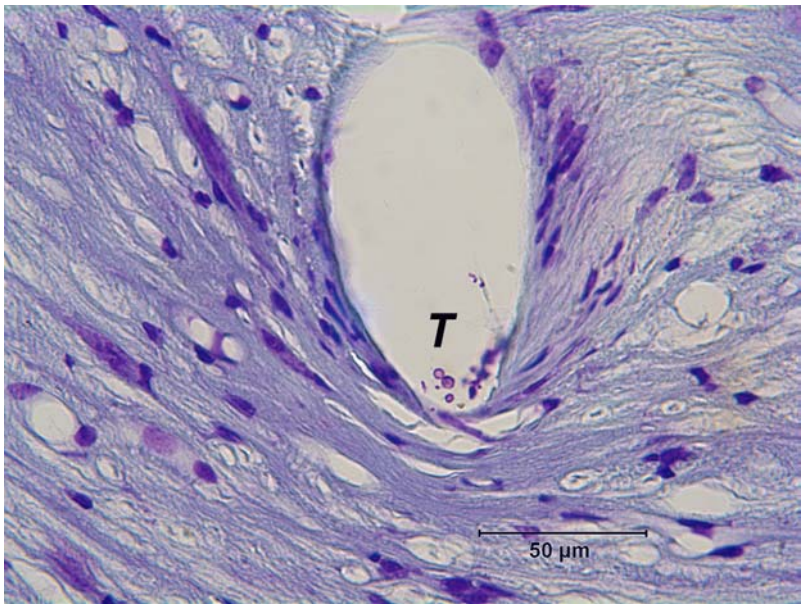


Figure 3C. The tip site (T) of microelectrode 1, near the junction of the posteroventral and anteroventral cochlear nucleus. The immediate tip is surrounded by a very thin capsule of connective tissue, and the surrounding neuropil appears quite normal

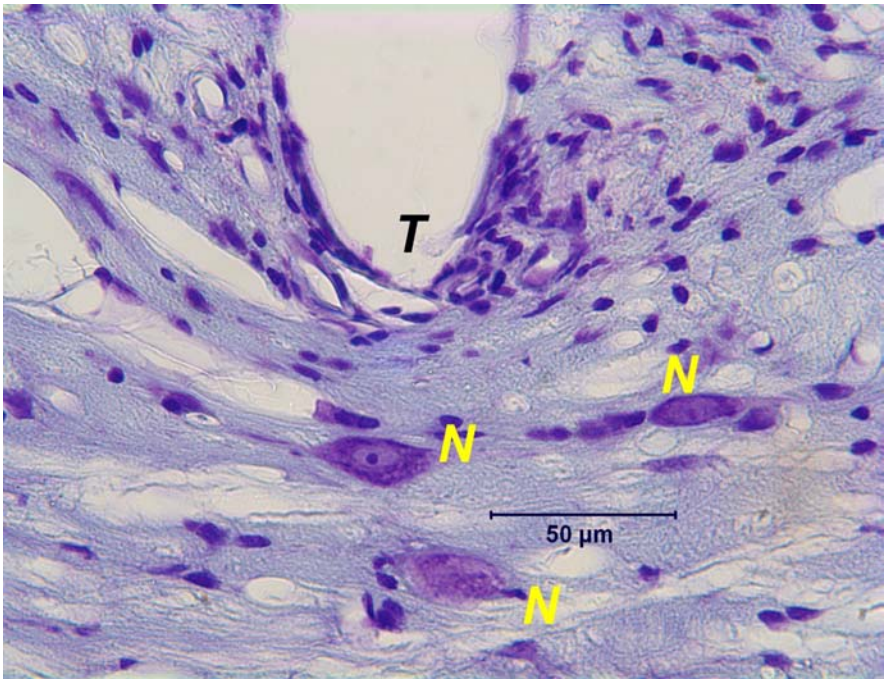


Figure 4. The tip site of microelectrode #2., in the VCN. The tip site is surrounded by a very thin sheath, and a few glial cells or microglia. The surrounding neuropil and neurons (N) within 50 ：m of the tips site appear quite normal.

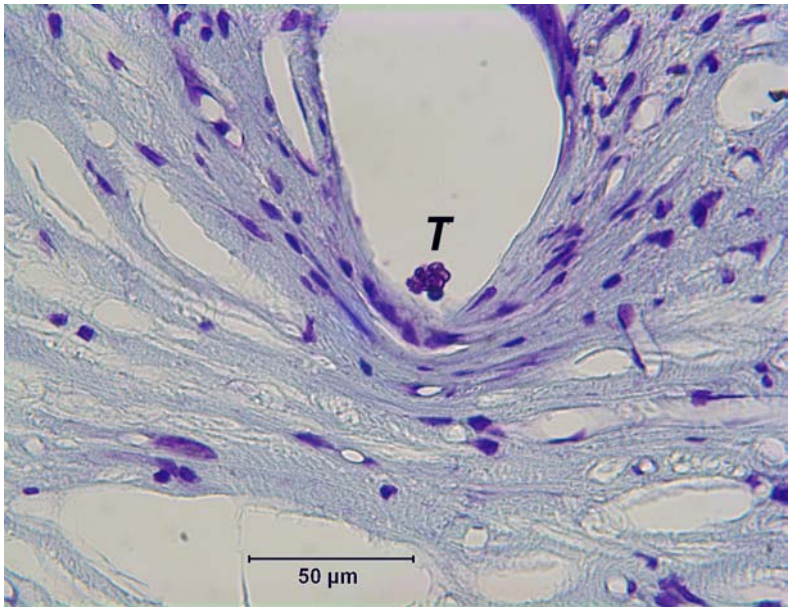


Figure 5A. A section through the tip site of microelectrode 3, in the VCN. The tip site is surrounded by a thin sheath, surrounded in turn by normal-appearing neuropil.

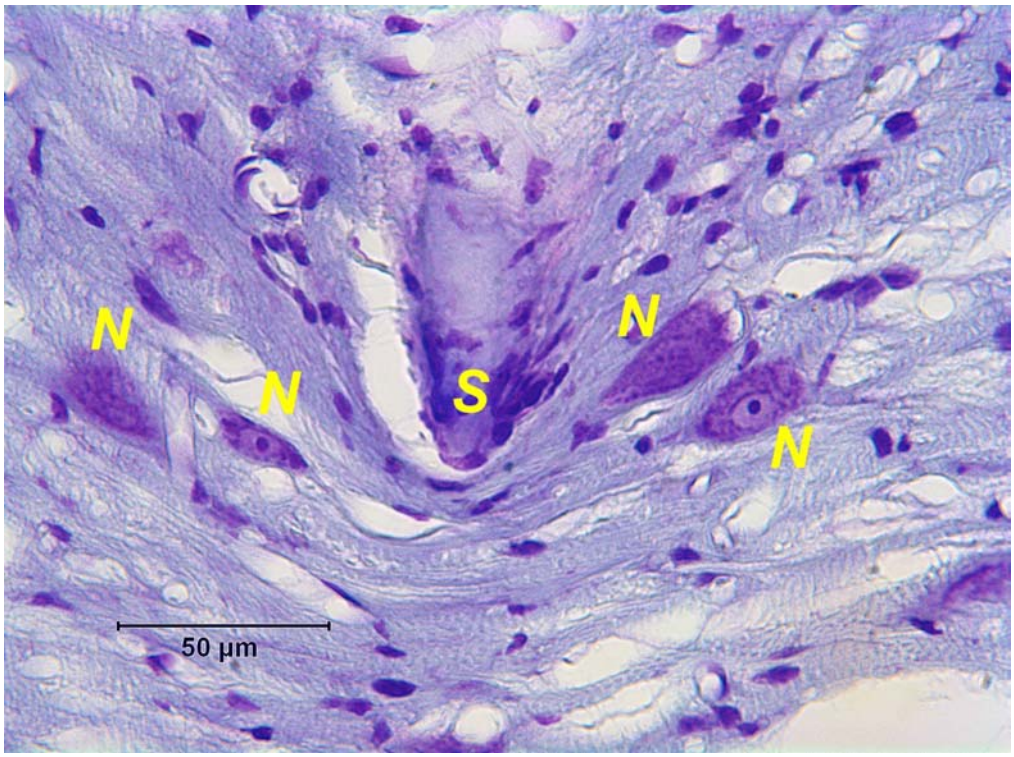


Figure 5B. A section about 20 ：m anterior to the one shown in figure 5A. This is a grazing cut through the thin sheath (S) surrounding the tips site . Nearby neurons (N), some within 25 ：m of the tips site, appear normal.

Validation of sterilization protocol for the array inserter tool.

We have developed an instrument for inserting the electrode array into the human cochlear nucleus. As a condition for granting an Investigational Device Exception to proceed with human trails, the U.S. FDA has required that we demonstrate that the tool can be sterilized to the standard for surgical instruments (SAL 10^{-6}). The extant version of the tool contains a velocity dampening mechanism which will not withstand the autoclaving cycle that is necessary to guarantee SAL 10^{-6}. We have therefore contracted with IBA Analytical Laboratories, and have been working with them to validate sterilization of the tool by Ethylene oxide gas. We have constructed 5 mockups of the portion of the tool for which sterilization will be most problematic. IBA completed the protocol on April 24, 2002, and has validated that the tool can be sterilized by ethylene oxide to the SAL 10^{-6} standard.

We also have been working with the tool's manufacturer, Altair instruments, to modify the velocity dampening mechanism so that the tool can be sterilized by autoclaving. Two of the modified tools are scheduled to be delivered to HMRI in late April, for final fitting and tuning.

Progress on the construction of the human array by Cochlear Ltd.

The microelectrode arrays for the first human implantations are being assembled in Sydney, Australia by Cochlear Ltd using discrete iridium microelectrodes fabricated at HMRI. At HMRI, we fabricate the electrodes, insulate the shafts, and expose and activate the electrode tips. In Sydney, they are incorporating these into arrays, using the specifications developed at HMRI and HEI.

Cochlear now is completing the electrical leakage tests and the sterility validations. They project that implants will be available by September. They propose to construct 10 implants and HMRI will supply an additional 50 electrodes in order to met this schedule. After that shipment, HMRI will devote its electrode fabrication capacity to the development of the two versions of the 16-site microelectrode array described in our response to the contract's RFP.

REFERENCE CITED

McCreery, D. B., T. G. Yuen, and L. A. Bullara.. Chronic microstimulation in the feline ventral cochlear nucleus: physiologic and histologic effects. Hear Res 149: 223-38, 2000.