"A Cochlear Nucleus Auditory prosthesis based on microstimulation"

Contract No. **No. NO1-DC-1-2105**
Progress Report #4

HUNTINGTON MEDICAL RESEARCH INSTITUTES
NEURAL ENGINEERING LABORATORY
734 Fairmount Avenue
Pasadena, California 91105

D.B. McCreery, Ph.D.
W.F. Agnew, Ph.D.
L.A. Bullara, B.S.
A.S. Lossinsky

HOUSE EAR INSTITUTE
2100 WEST THIRD STREET
Los Angeles, California 90057
R.V. Shannon Ph.D
S. Otto M.S.
M. Waring, Ph.D

ABSTRACT

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.

Our contract's work scope includes the development of a 16-site microstimulation array based on silicon substrate probes. In collaboration with Jamile Hetke of the Center for Neural Communication at the University of Michigan, We have finalized the design of two multisite-probes that will be fabricated using their conventional thin-film process. In the interim, we have been developing a procedure for incorporating these probes into 3-dimensional array, using probes designed for the feline sacral spinal cord. One probe was implanted into a cat's spinal cord for 73 days.. Histologic evaluation of the tissue revealed no evidence of hemorrhages or inflammatory response near any of the 6 shanks, and the gliotic scarring around and ventral to the tip of the track was remarkably minimal. These results indicates that these silicon electrodes can be implanted at high velocity with an acceptably amount of tissue injury.

We have been investigating procedures for tethering the shanks of the silicon substrate probes so that if they do fracture from the superstructure, the detached shanks or fragment does not migrate down into the brain. We have found previously that an epoxy backing will delaminate from the shanks after 30 days *in vivo*, so this type of backing is not a reliable method of restraint. We encapsulated probes within 3-4 ：m of Parylene-C, and then ablated the Parylene from the electrode sites with an excimer laser. This worked well, without damaging the probe or the photolithographic features. The probes were then intentionally fractured. When the probes were stressed at a right angle to the plane of the probe, the Parylene remained as an intact hinge which tethered the probe. However, when the probe was deflected to either side, the hinge of Parylene was torn. This demonstrated that 4 ：m of Parylene-C will not yield a reliable tether. During the next, quarter, we will investigate a modification of this procedure.

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.

As a test of the biocompatibility of the arrays fabricated in Sydney, one of the prototype arrays was implanted into the lumbar spinal cord of a cat, for 29 days, using the hand-held inserted tool. After 29 days, the epoxy array superstructure was surrounded by a capsule of connective tissue approximately 200 ：m in thickness. The neural tissue (dorsal column of the spinal cord) immediately beneath the capsule appeared healthy. Neurons and neuropil surrounding the sites of the electrode tips appeared healthy. Some spongy changes were noted around the some of the electrode shafts, where they penetrated through fiber tracks. Overall, the histologic features of the implant site of the prototype human array were typical of those seen in the feline cochlear nucleus and spinal cord after implantation of microstimulating arrays fabricated entirely at HMRI, and inserted either by stereotaxis or with the hand-held high-speed inserter tool.

I: Development of silicon-substrate microstimulating array

Our contract's work scope includes the development of a 16-site microstimulation array based on multisite silicon substrate probes. Figure 1A and 1B show two electrodes arrays that we have been developing in collaboration with Jamile Hetke of the Center for Neural Communications at the University of Michigan. The short (2mm) array is sized for the feline cochlear nucleus. The longer array is sized for the human cochlear nucleus, and will be evaluated in the feline lumbar spinal cord.

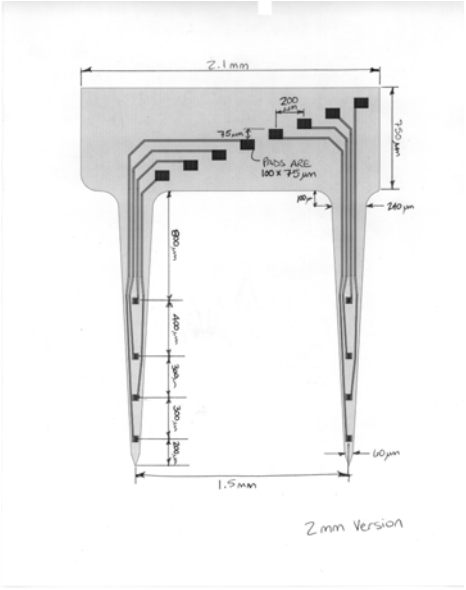

Figure 1A

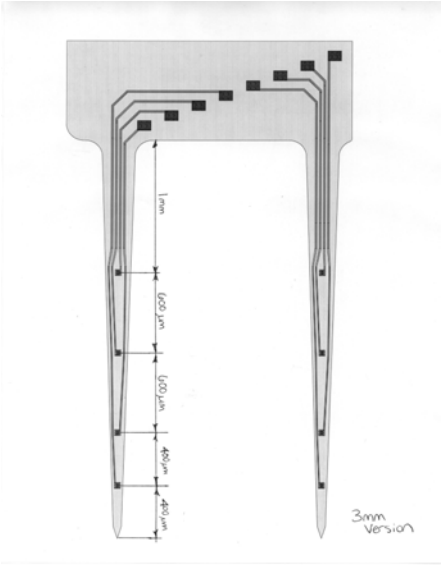

Figure 1B

At the University of Michigan, the multisite probes are fabricated using the thin-film process which limits their thickness to 15 ：m. The relative fragility of these probes is a concern, particularly when future implantation into human patients is considered. We had planned to have the probes fabricated via a novel process developed at the U of M; the "box-beam" configuration, in which the probe shank is strengthened by a reinforming beam that is molded onto its rear surface. However, the U of M Microdevices laboratory has discontinued this process. We therefore decided that the probes should be fabricated using the conventional thin-film process, and both probe types have been incorporated into the current mask set. In the meantime, we have been developing the procedure for incorporating the probes into three-dimensional arrays and evaluating the tissue reaction to their implantation using probes that Ms Hetke has designed for implantation into the sacral spinal cord. Development of a silicon microstimulation array also is included in the workscope of our contract to develop techniques for functional microstimulation of the sacral spinal cord (contract N01-NS-1-2340), so the work described in this report was supported by both projects. In particular, the cost of developing and fabricating the arrays (Figure 2) and

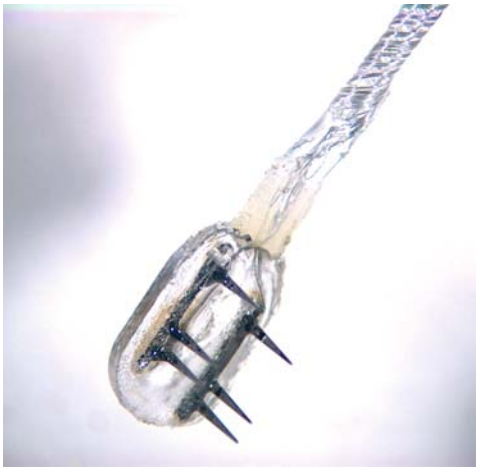

Figure 2

histologic analysis of the tissue are shared between the projects, and the cost of the surgical procedure, animal maintenance and physiologic evaluations are supported entirely by contract N01-NS-1-2340.

Implantation of any microstimulating array into the human cochlear nucleus can be accomplished only with a hand-held inserter tool, and the requirement that the tool must be supported in the surgeon's hand dictates that the electrode insertion occur at high speed. We have developed a new procedure for fabricating 3-dimensional microstimulating arrays from 2-dimensional planar silicon substrate probes (QPR #2). The process includes a provision to reinforce the critical junction between the probe shanks and the supporting spine (the location at which these probes tend to fracture during high-speed insertion into the spinal cord). A complete array with a helical cable is shown in Figure 2. The silicone shanks extend from a superstructure of EpoTek 301, a casting epoxy which carries a USP category VI certification.

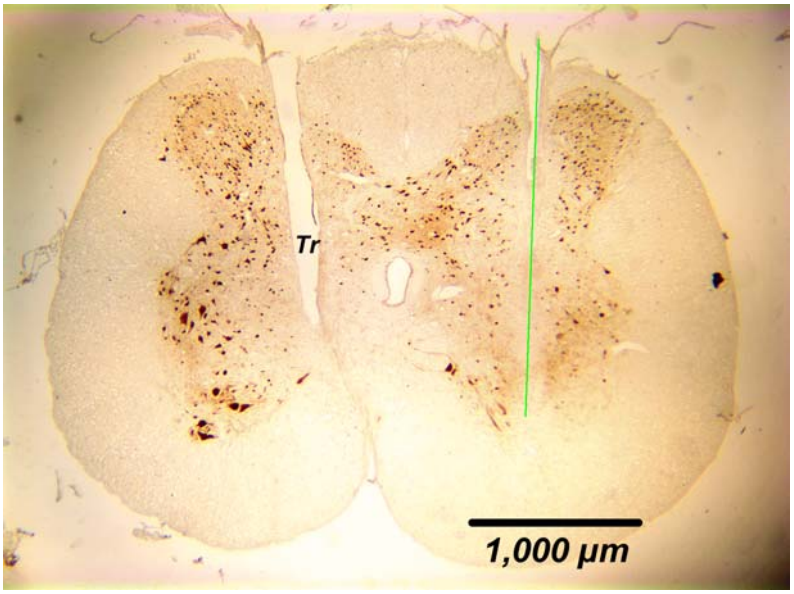

Figure 3

One array was implanted into the sacral cord of a cat for 72 days. Throughout this interval, we were able to record the action potentials from single spinal neurons, indicating that the neurons close to the electrode sites remained viable.

The cat was sacrificed 72 days after implanting the array. The tissue was processed for immunohistochemical visualization of the NeuN protein, which is specific to neurons.

Figure 3 shows an 8 ：m tissue section through the cat's sacral spinal cord. The section is through the tract (Tr) of one of the silicon shanks and also through the tissue immediately adjacent to another shank in the opposite side of the cord. Neurons are stained brown by the NeuN- DAB peroxidase reaction. The tissue section is perpendicular to the plane of the shank (parallel to their long axis), and the shank's wide track on the left side of the cord is partly artifactual whereby the section hinged open during processing. However, it is clear that the

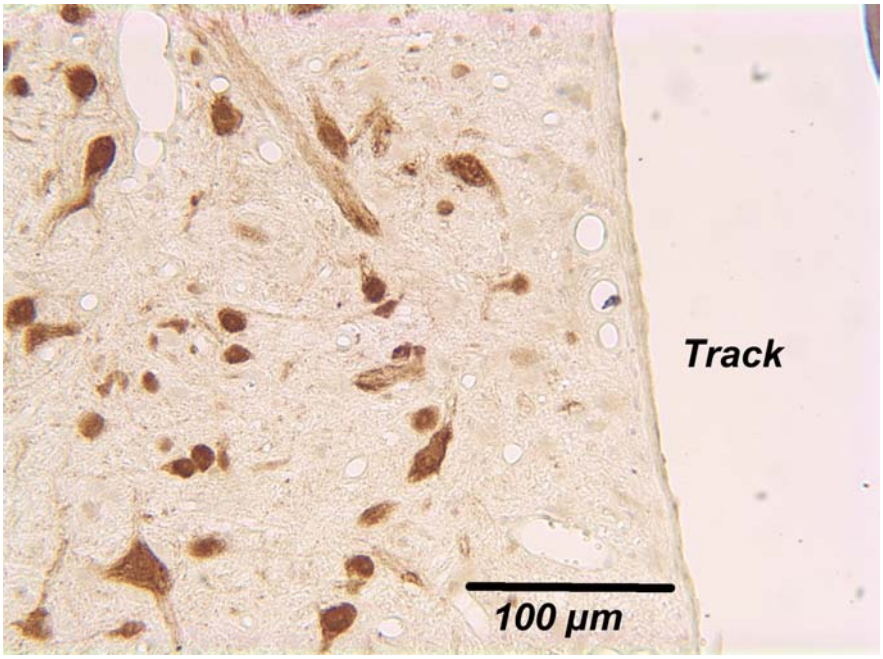

Figure 4

shank is surrounded by a region in which there is a reduction in the density of the NeuN staining. The extent of this zone (approximately 200 ：m in total width) of reduced staining is seen most clearly in the tissue in the right side of the cord.

Figure 4 shows the tissue adjacent to the shank track, at high magnification. Normal-appearing neurons are located 100 ：m from the track. The reduction in the density of NeuN staining close to the track may reflect a residual stressor for the implant procedure or a stressor associated with the ongoing motion of the rigid probe embedded in the soft tissue. However, there was no evidence of hemorrhages or inflammatory response near any of the 6 shanks and the gliotic scarring around and ventral to the tip of the track was remarkably minimal. As noted above, we were able to record the action potential from single neurons throughout the 72 days

in which the array was in situ. These results indicate that these electrodes can be implanted at high velocity with an acceptable amount of tissue injury.

Restraining fractured probe shanks.

When considering the use of silicon-substrate probes in human patients, we must develop a procedure for tethering the shanks so that if they do fracture from the superstructure, the detached shanks or fragment does not migrate down into the brain. We have found that an epoxy backing will delaminate from the shanks after 30 days *in vivo*, so this type of backing is not a reliable method of restraint. Another approach is to encapsulate the completed probes with 3-4 ：m of Parylene-C. The Parylene can then be photo-ablated from the electrode sites using our excimer laser.

Figure 5A and 5B show two electrodes sites that have been exposed by photoablation of the overlying Parylene. This was easily accomplished without damaging the probe or the photolithographic features. The probes were then intentionally fractured. When the probes were stressed at a right angle to the plane of the probe, the Parylene remained as an intact hinge which tethered the probe (Figure 6A). However, when the probe was deflected to either side,

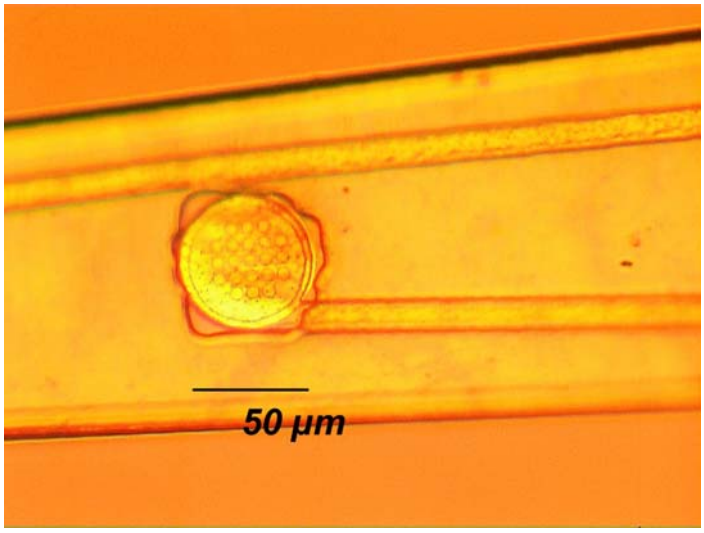

Figure 5A

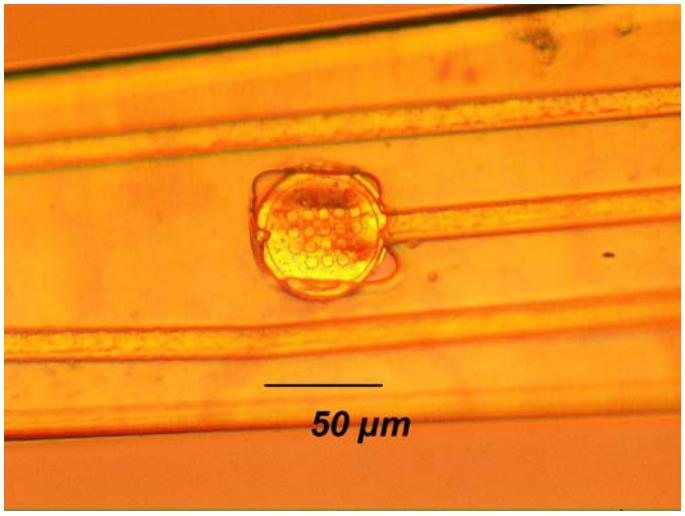

Figure 5B

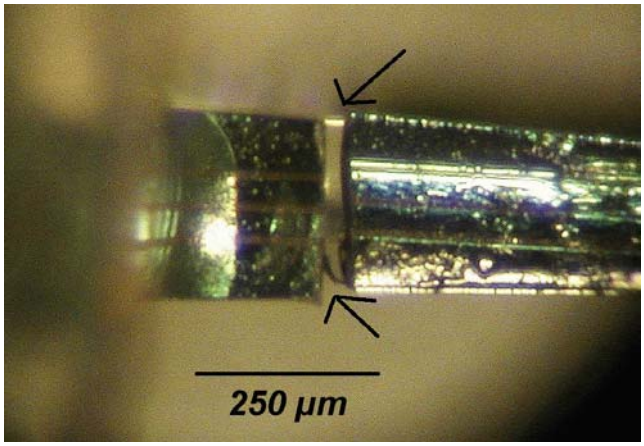

Figure 6A

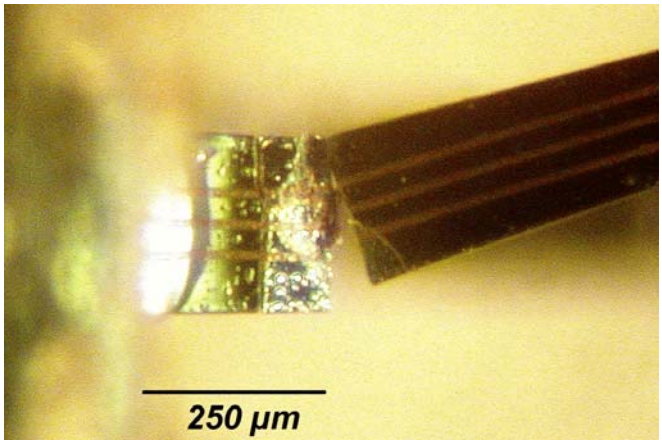

Figure 6B

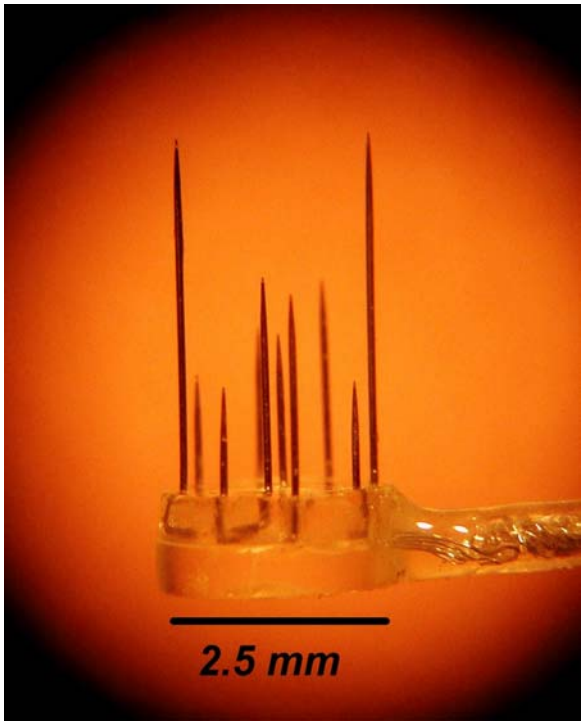

Figure 7

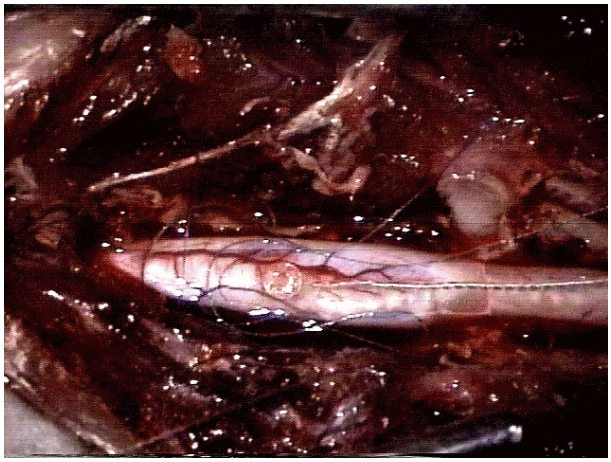
Figure 8

the hinge of Parylene was torn (Figure 6B). This indicates that 4 ：m of Parylene-C will not yield a reliable tether. One options is to increase the thickness of the Parylene layer, to approximately 10 ：m (The maximum that is practical). Another is to coat the entire rear surface of the probe with a layer of casting epoxy (EpoTek 301) then encapsulate the EpoTek and the probe in Parylene. We expect that the Parylene will mechanically bind the epoxy to the silicon shank even if the epoxy does delaminate from the silicon surface during an extended period *in vivo.*

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 the electrodes into arrays, using the dimensional specifications developed at HMRI and HEI.

Cochlear has now supplied us with 3 prototypes of the human arrays. The first version contains some flaws which have been corrected in the most recent sample (Figure7). As a test of the biocompatibility of the arrays fabricated in Sydney, one of the prototype arrays was implanted into the lumbar spinal cord of a cat, using the hand-held inserter tool. Figure 8 shows the array immediately after implantation, and before closure of the spinal dura.

Twenty-nine days after implantation, the cat was deeply anesthetized with pentobarbital, given i.v. heparin and perfused through the aorta for 30 seconds with a prewash solution consisting of phosphate-buffered saline, and 0.05% procaine HCl. This was followed by perfusion with ½ strength Karnovsky's fixative. Tissue blocks containing both the microelectrodes and areas rostral and caudal to the electrodes were resected and processed into paraffin. The slides were stained for Nissl, for routine light microscopy. Histologic sections were photographed using a digital microscope camera with 1600 x 1200 pixel resolution.

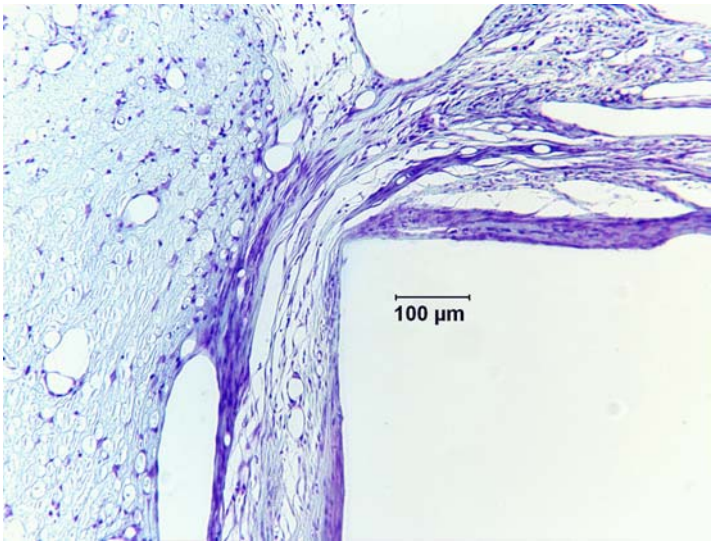

Figure 9

Figure 9 shows the capsule of connective tissue surrounding the epoxy array matrix. The capsule beneath the array is approximately 200 : m in thickness. The neural tissue (dorsal column of the spinal cord) immediately beneath the capsule appears healthy.

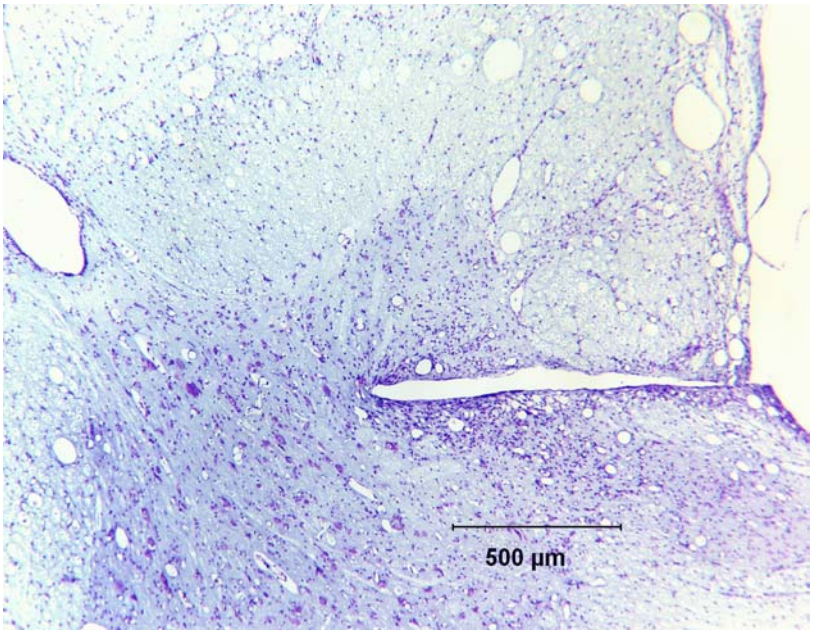

Figure 10

Figure 10 shows the track of one of the 1 mm electrodes, through the dorsal column and into the medial margin of the dorsal horn. There are some vacuolations in the fiber tract, which probably represent degenerating axons, and some associated inflammatory changes. These changes are commonly seen when microelectrodes of this type penetrate through fiber tracts.

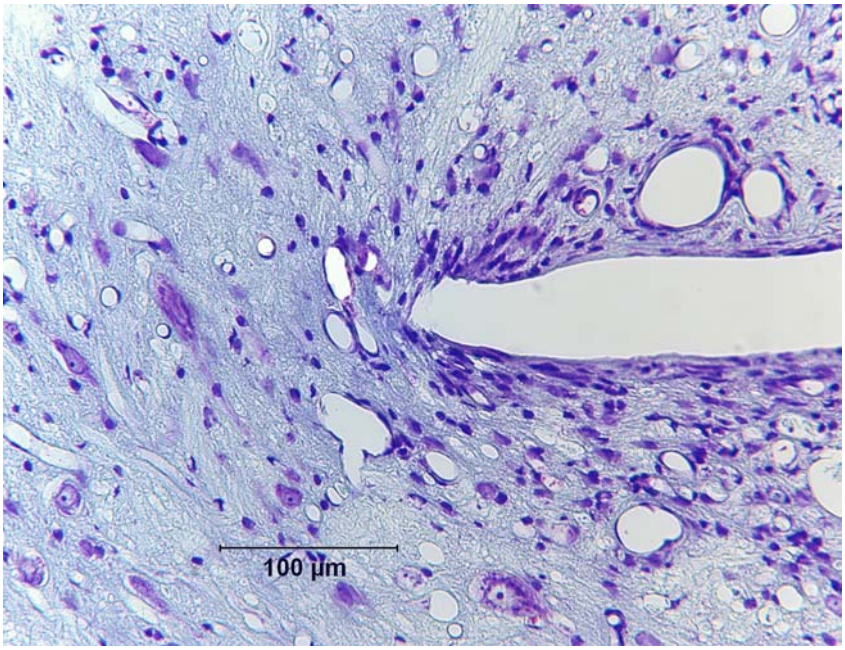

Figure 11

However, the capsule surrounding the electrode tip site in the dorsal horn is thin, and the surrounding neuropil and neurons appear healthy (Figure 11).

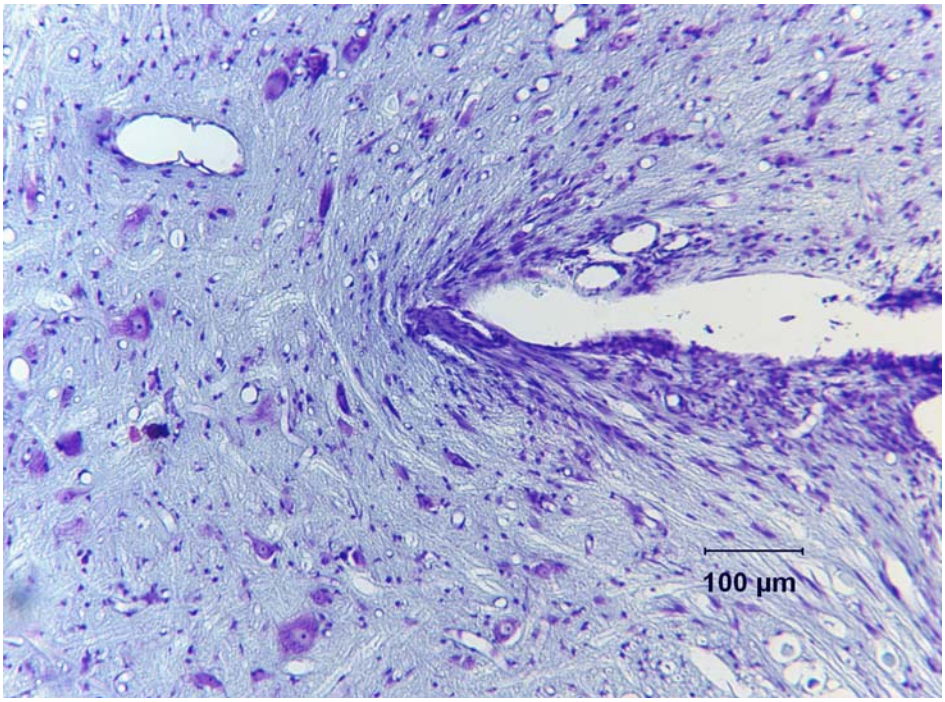

Figure 12

Figure 12 shows the tip site of one the long (2mm) electrodes. The tip is in the dorsal part of the ventral horn. The electrode track is surrounded by a capsule approximately 50 ：m in thickness. Neurons near the cell bodies are somewhat flattened, a phenomenon that we have observed in the feline cochlear nucleus up to 2 years after implanting the arrays. However, the neuropil

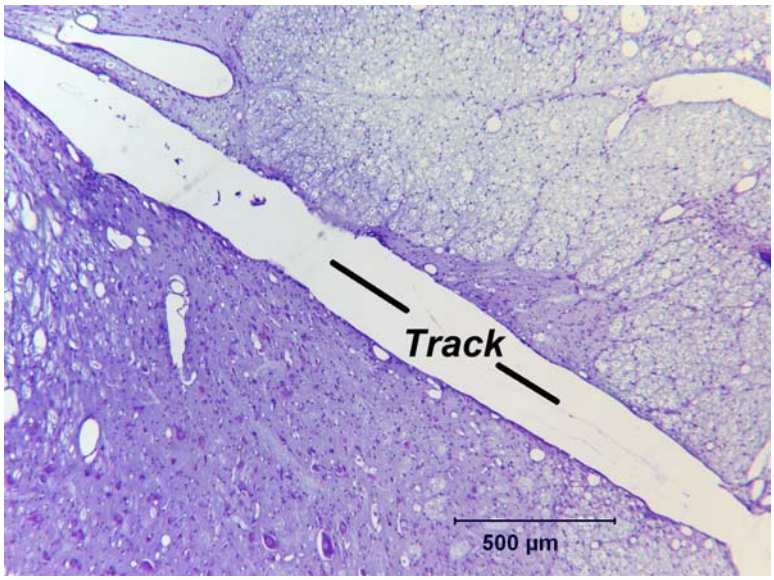

Figure 13A

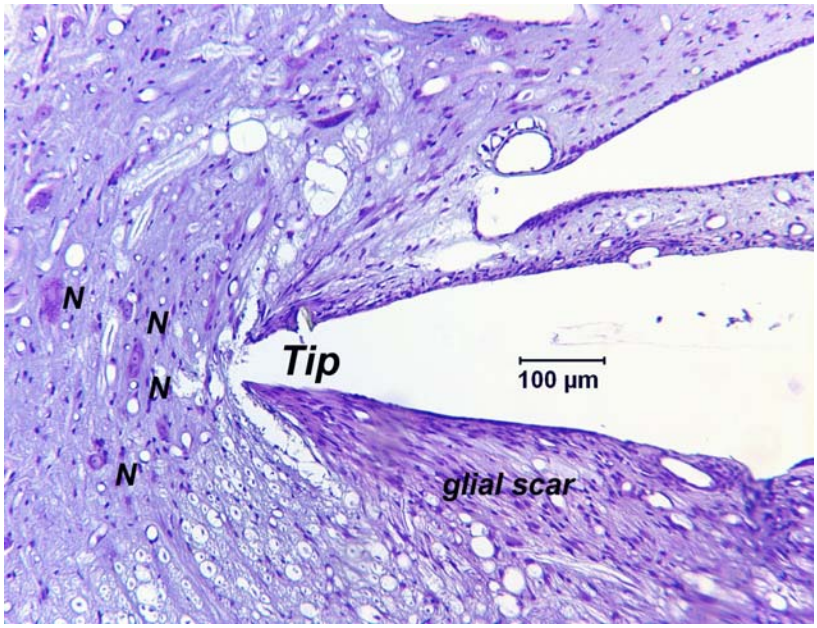

Figure 13B

surrounding the capsule appears normal, with no inflammatory changes.

Figure 13A shows nearly the entire track of one of the 3.5mm stabilizer pins. The pin had penetrated deep into the ventral horn. The wide “track” is partly artifactual, as the histologic section spread open. However, there are no inflammatory changes along the track and the surrounding tissue appears healthy. Figure 13B shows the tip site of the stabilizer pin, at higher magnification. There is a glial scar on one side of the tip, and some spongy changes in the neuropil. These probably occurred when the array was tipped to the left as the dura was closed over it (see below). However, the neurons (N) and neuropil surrounding the tip appear quite normal. None of the large blood vessels, including the large one that can be seen above the tips site, were damaged.

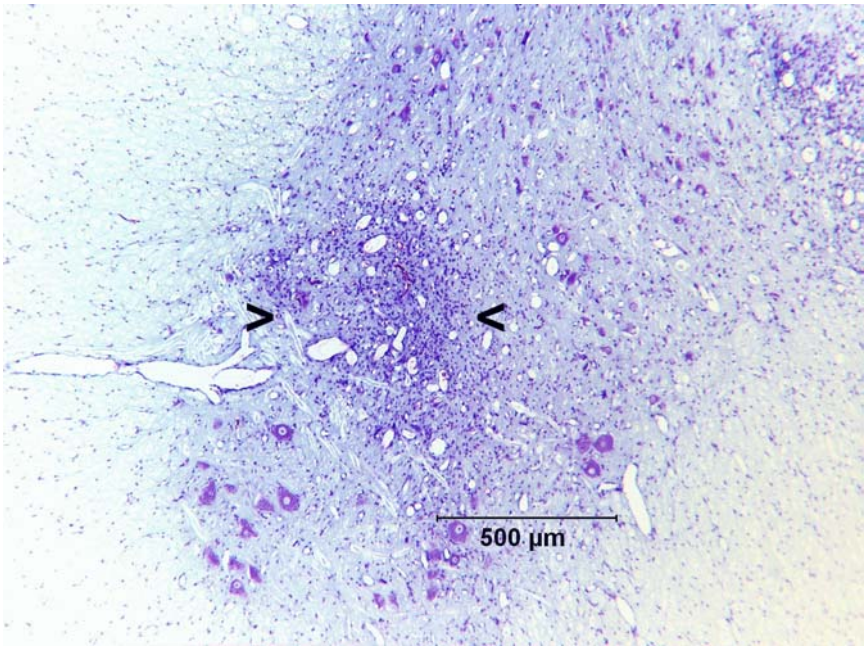

Figure 14

Figure 14 shows an infarcted area approximately 0.5 mm in diameter in the ventral horn. The site is below, but lateral to the array button and is at least 1 mm from the track of any of the electrodes. It is not contiguous with any of the electrode tracks. There is infiltration of inflammatory cells and neo-vascularization, as is typical of sub-acute injury in the CNS. The infarct does not appear to be a resolved micro-hemorrhage associated with implantation of the array since there is no hemosiderin visible, as would be expected with a 29-day old hemorrhagic infarct. It is possible that the infarct was associated with the closure of the dura over the rather thick array button, and the compression of the spinal cord.

In summary, the histologic features of the implant site of the prototype human array were typical of those seen in the feline cochlear nucleus and spinal cord after implantation of microstimulating arrays fabricated entirely at HMRI, and inserted either by stereotaxis or with the high-speed inserter tool. The micro-infarct seen in Figure 14 may represent a limitation of the feline lumbar spinal cord as a site for evaluating these arrays, which have rather large and thick epoxy superstructures.