"A Cochlear Nucleus Auditory

prosthesis based on microstimulation"

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

Progress Report #6

HUNTINGTON MEDICAL RESEARCH INSTITUTES

NEURAL ENGINEERING LABORATORY

734 Fairmount Avenue

Pasadena, California 91105

D.B. McCreery, Ph.D.

A.S. Lossinsky

L.A. Bullara, B.S.

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

One of the project's objectives is to develop an array of silicon substrate stimulating microelectrodes, first for evaluation in an animal model and ultimately for implantation into the human ventral cochlear nucleus. We now have received the first shipment of silicon probes from the University of Michigan. These probes incorporate 8 iridium electrode sites on 2 silicon shanks, and at HMRI, we incorporate two probes (16 electrode sites) into each chronically implantable array. We have fabricated 2 arrays of the 3 mm probes, which are sized to place electrode sites along the entire tonotopic gradient of the human ventral cochlear nucleus. Each probe was inserted 9 times into the lower lumbar enlargement of the spinal cord of an anesthetized cat (our model for the human brainstem) using the hand-held high-speed inserter tool developed for implanting microelectrodes arrays into the human cochlear nucleus. Both arrays withstood 5 insertions into the cat spinal, but a shank on both arrays fractured during the 6th insertion and removal from the cord, and additional shanks fractured during subsequent insertions and removals. Thus, the shanks of the 3 mm probes did withstand repeated insertion and removal from the spinal cord, but they did eventually fail, probably due to accumulated stress and microfractures from the repeated insertions and removals.

As part of our evaluation of long-term implantations of microelectrodes into the cochlear nucleus, we sacrificed cat CN140 at 1125 days after implanting 3 microelectrodes into the posteroventral cochlear nucleus (PVCN). This cat had not been subjected to regimens of prolonged stimulation. The potentials evoked from the microelectrodes in the PVCN and recorded in the contralateral inferior colliculus were comparable at 17 days and at 1125 days after implantation of the array. The histologic evaluation of the microelectrode tracks and tip sites showed a thin (less than 25 μm) gliotic capsule surrounding the microelectrodes with normal-appearing neurons and neuropils immediately adjacent to the capsule. Overall, the small changes in the evoked response during the period of implantation and the histologic findings of the electrode sites were similar to those from cat CN139, which had undergone several sessions of prolonged stimulation during a comparable period *in vivo*.

I: Silicon substrate arrays for the cochlear nucleus

INTRODUCTION

The objective of this project is to develop central auditory prostheses 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 calls for the development of arrays of silicon substrate electrodes, which should allow placement of many more electrode sites into the human cochlear nucleus than is possible with discrete iridium microelectrodes. We are developing an array for implantation into the human cochlear nucleus which has 16 electrode sites distributed on 4 silicon shanks extending from an epoxy superstructure that is 2.4 mm in diameter. This is the same footprint as our first generation human arrays and is designed to be implanted using the same inserter tool (Fig. 1). The silicon probes are fabricated at the University of Michigan under the direction of Ms. Jamille Hetke. While awaiting delivery of the probes designed for the cochlear nucleus, we have developed a procedure for fabricating the arrays using probes designed for chronic implantation into the feline spinal cord (QPRs 2 & 3). We now have received the first shipment of cochlear nucleus probes, and we are fabricating arrays from these. The probe shanks are either 2 or 3 mm in length. The 2 mm probes are sized for the feline cochlear nucleus. The 3 mm probes are sized for the human ventral cochlear nucleus, based on anatomical data provided by Dr. Jean Moore, formerly of the House Ear Institute. The mechanical properties of the arrays of 3 mm probes are now being evaluated in the feline spinal cord. The 2 mm probes are being assembled into fully functional arrays, and we expect to begin implanting these into the feline cochlear nucleus in February of 2003.

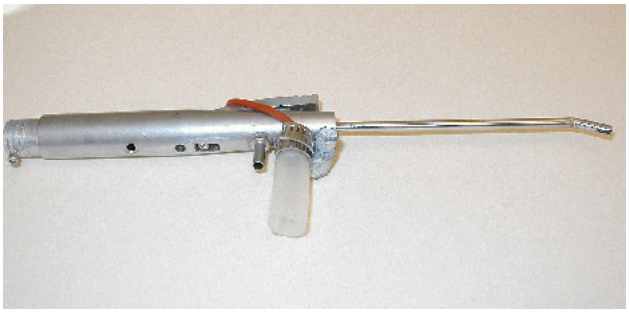


Figure 1

METHODS

The procedure for fabricating the arrays is very similar to that described previously for the spinal cord probes, with some minor modification to accommodate the different dimensions of the horizontal spine. The 8-site, 2-shank probe is first attached to a stainless steel alignment pin using EpoTeK 301 epoxy (Fig. 2A). A rectangular microscope reticule is used to align the shanks and the pins. A sturdy backing of Epotech is then formed on the rear surface of the probe's horizontal spine by floating the spine

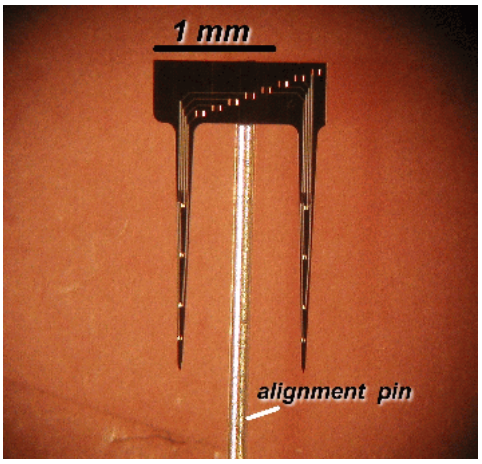


Figure 2A

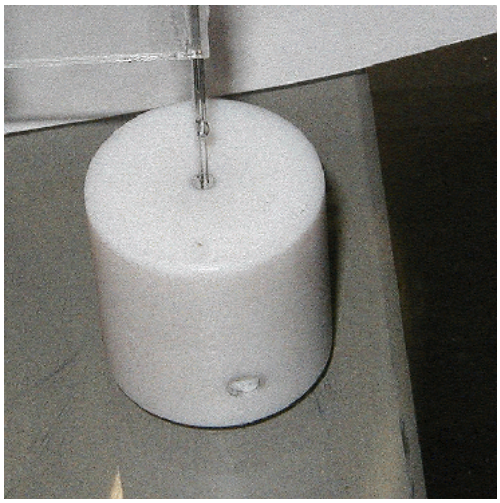


Figure 2B

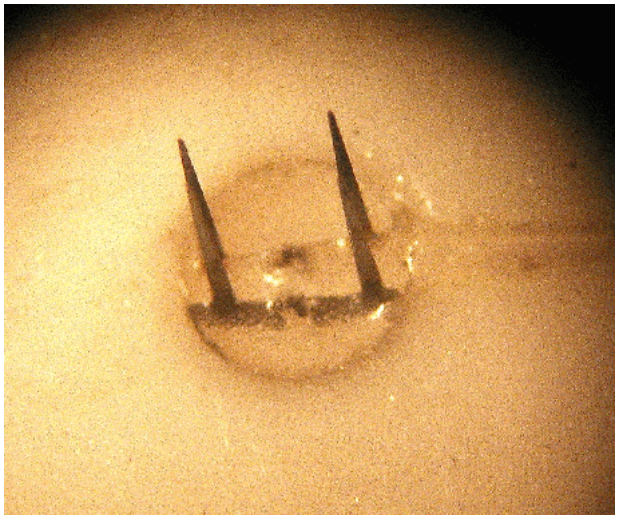


Figure 2C

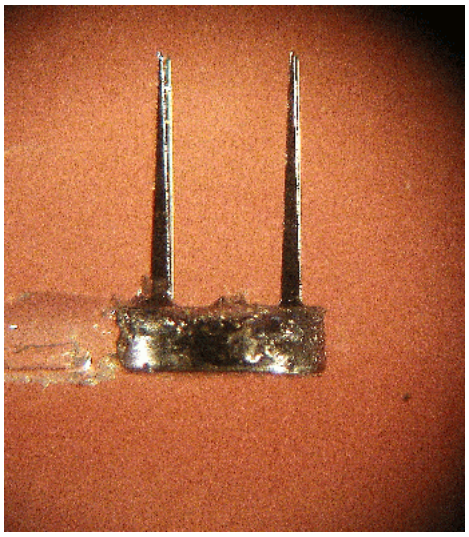


Figure 2D

in a drop of uncured Epotech, then trimming the cured Epotech around the perimeter of the spine, using an excimer laser. The lead wires are then bonded to the gold pads on the spine and the upper surface of the spine is insulated with Med-A silicone elastomer. The alignment pins of 2 of the sub-assemblies are inserted into an alignment fixture, and the probes lowered into the cavity of a mold milled from Teflon (Fig. 2B). The cavity is then filled with EpoTeK 301. When the epoxy is cured, the alignment pins are extracted (Fig. 2C) by applying gentle traction while the pin is rotated. Finally, the array is expelled from the mold by elevating the floor of the mold cavity. Fig. 2D shows an array of four 3-mm silicon shanks, with a dummy cable.

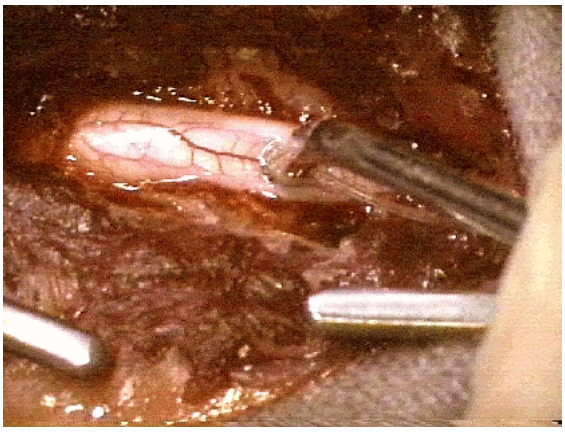


Figure 3A

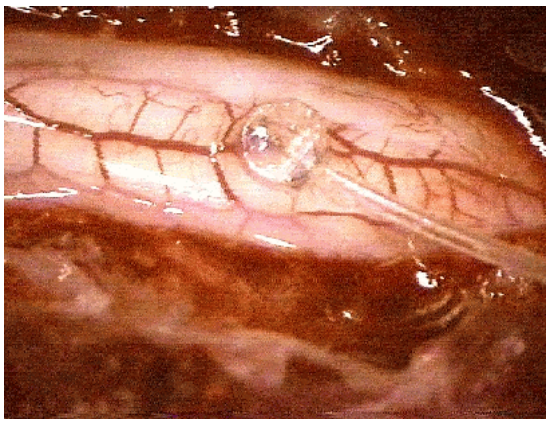


Figure 3B

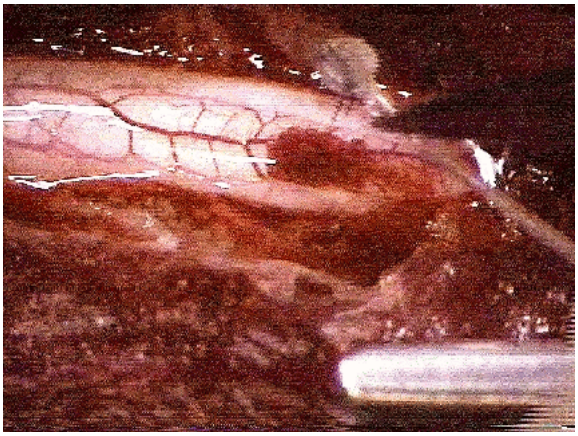


Figure 3C

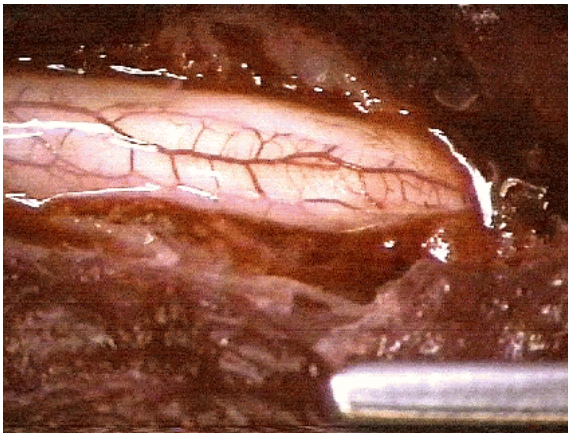


Figure 3D

RESULTS

We have selected the feline lumbosacral cord as a model for the human auditory brainstem because of its many anatomical similarities including a thickened glial membrane and some large blood vessels over its dorsal surface. The 3 mm probes are somewhat longer than those that we have previously implanted into the feline cord so we evaluated 2 of these arrays for mechanical integrity. A cat (CN140) that was scheduled to be sacrificed was anesthetized with Halothane and the lumbosacral cord was exposed by a standard dorsal laminectomy. The 2 arrays were inserted into the cord's dorsal surface a total of 18 times using the handheld electrode inserter tool developed for the human cochlear nucleus (Fig. 1 & 3A). Fig. 3B shows the barrel of the tool resting on the surface of the cord prior to the implanting the array. Fig. 3C shows array #1, after implantation. We attempted to impale the large midline artery, and we achieved this a total of 6 times with the 2 arrays. The impaled artery did not bleed while the array was *in situ* (Fig. 3B), but it did bleed profusely but momentarily after the array was removed (Fig. 3C);

However, in all cases, bleeding ceased about 10 seconds after removal of the array, and blood continued to flow through the artery (Fig. 3D).

Array #1 was implanted and removed 9 times. On the 6th implantation and removal, one of the shanks fractured at the level of the epoxy superstructure. On the 9th insertion and removal, a second shank fractured midway between the tip and the superstructure. One shank fractured from array #2 during the 6th insertion and removal. It is not certain if the shanks fractured during implantation or during the subsequent removal, but the mechanical stresses probably are greater during removal and it is likely that failure occurred at this time. Thus the shanks of the 3 mm probes did withstand insertion and removal from the spinal cord, but they did eventually fail, probably as a result of accumulated stress and microfractures from the repeated insertion and removal.

II: Long-term implantation of an electrode array in the ventral cochlear nucleus of cat CN140

On Nov 23, 1999, three iridium microelectrodes were implanted by stereotaxis into the left posteroventral cochlear nucleus of cat CN140. 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.

Over the next 37 months, the electrodes were checked periodically, but unlike cat CN139, the electrode were not subjected to regimens of prolonged stimulation. This cat appeared to have been startled and mildly distressed by the intranuclear microstimulation, and therefore she had not been subjected to regimens of prolonged stimulation. The cat's adverse reaction to the stimulation may have been due to the somewhat anterior and medial location of the microelectrodes, which placed them close to the nucleus and nerve root of the 7th nerve. This is a limitation of the cat model, due to the proximity of the PVCN and the 7th nerve root. Thus cat CN139 was used to access the integrity of the tissue around the implant sites. 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 to obtain averaged evoked responses (AERs). The "probe" stimulus applied to the intranuclear microelectrodes was a train of cathodic-first, biphasic current pulses, 150 μs/ph in duration and at a rate of 50 Hz. Approximately 2 years after implantation of the array, the connection to electrode 2 failed within the percutaneous connector, but electrode 1 and 3 continued to function. The responses evoked from electrodes 1 and 3, recorded at 17 and 1125 days after implantation, are plotted in Figure 4. The value listed above each trace is the amplitude of the 150 μs/phase probe stimulus that was used to evoke the response in the IC.

Between the 17th and 1125 day, there was a small increase in the threshold of the earliest positive-negative potential (P1) evoked from microelectrode #1(from approximately 8 μA to 10 μA, Figure 4A, 4B)). The threshold of the early component of the response evoked from microelectrode #3 increased from approximately 8 μA to approximately 13 μA (Figure 4C,4D). The overall configuration of the evoked response also changed slightly between the 17th and 1125th day, the most noticeable change being the increase in the latency of the late components. This suggests that the position of the microelectrodes in

the ventral cochlear nucleus had changed slightly over the 1,125 days *in situ*. However, the changes in the evoked responses were very similar to those seen in cat CN139, which received 31 days of stimulation over a period of 28 months (QPR #3).

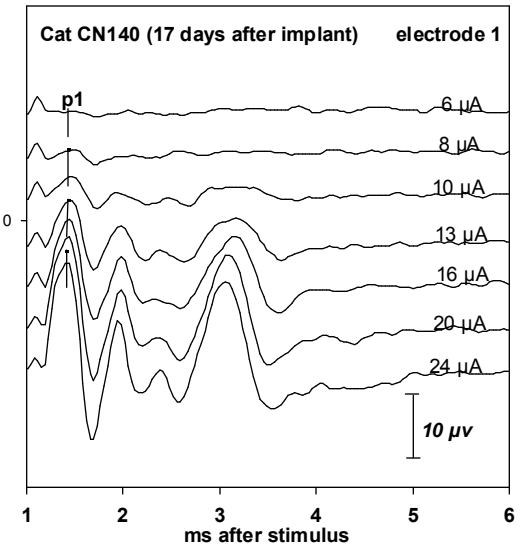
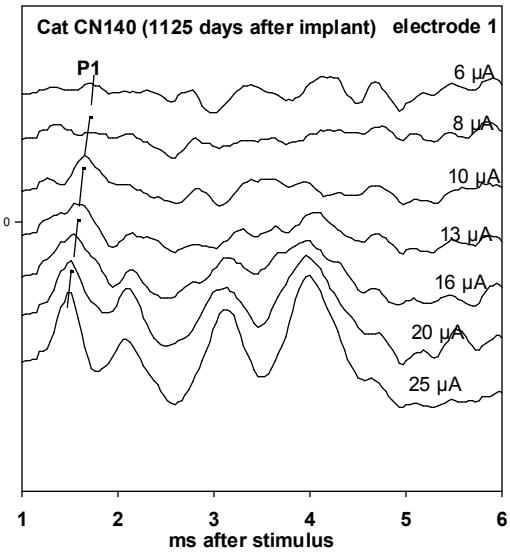


Figure 4A



F

Figure 4B

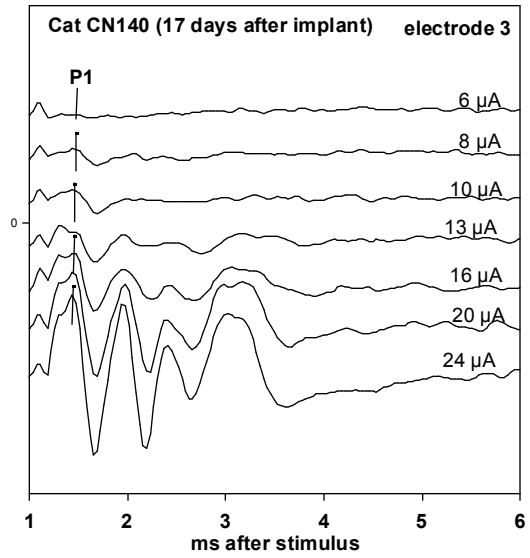


Figure 4C

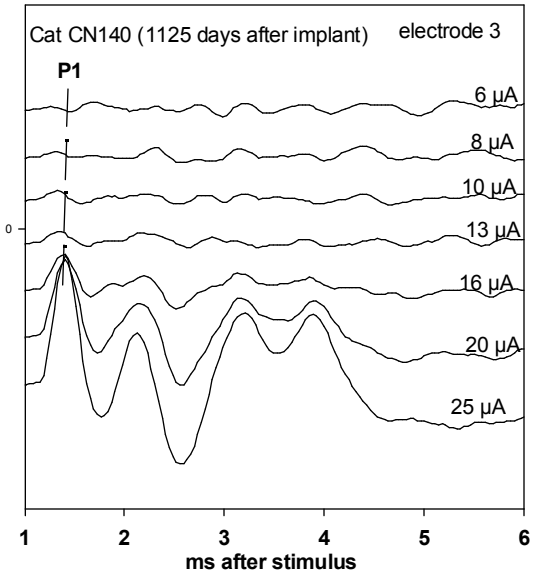


Figure 4D

Histologic evaluation of the microelectrode sites from cat CN140

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 µm in the frontal plane (parallel to the electrode tracks) and stained with Nissl. The sections were photographed with a digital microscope camera at a resolution of 1600 x 1200 pixels.

Figure 5A shows the tracks of microelectrodes #1 and #2, in the medial-anterior part of the posteroventral cochlear nucleus. The microelectrode's medial and rostral placement afforded an opportunity for the stimulation spread into the root of the facial nerve and may explain why the cat appeared to find the stimulation uncomfortable. Figure 5B shows the region of the tip of microelectrode #1. The sheath of connective tissue lining the electrode track is very thin (< 25 µm in thickness) and the surrounding neuropil appears quite normal.

Figure 6A shows the track of microelectrode #3, also in the medial part of the PVCN. Figure 6B shows the lower part of the microelectrode's track, which is surrounded by a thin capsule of connective tissue. The surrounding neuropil and neurons appear normal. Figure 6C shows the tips region of microelectrode #3, at higher magnification. The connective tissue sheath is not more than 25 µm in thickness, and neurons with 50 µm of the lower part of the tract appear normal.

Overall, the small changes in the evoked response during the period of implantation and the histologic findings of the electrode sites were similar to those from cat CN139, which had undergone several sessions of prolonged stimulation during a comparable period *in vivo*.

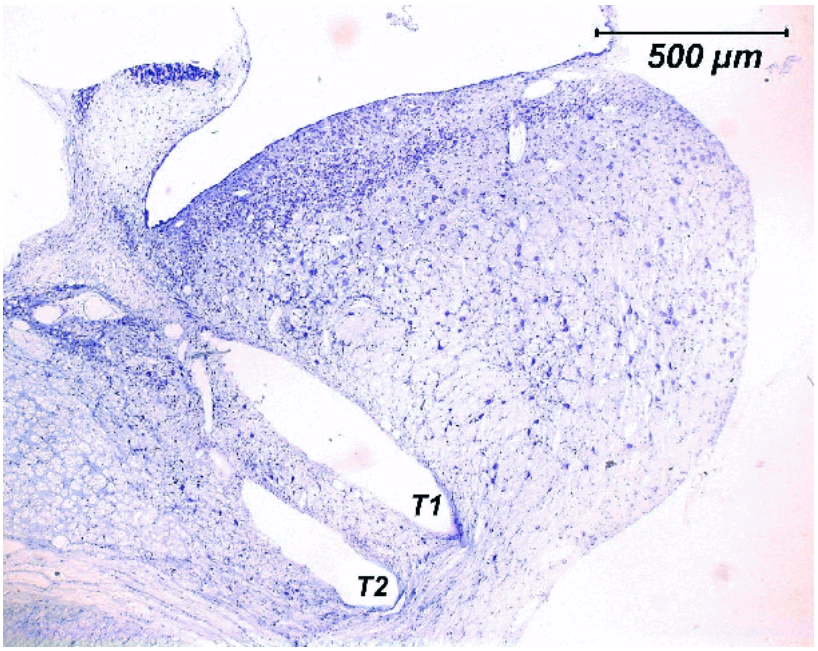


Figure 5A-Cat CN140. The tracks of microelectrodes 1 & 2. Nissl stain.

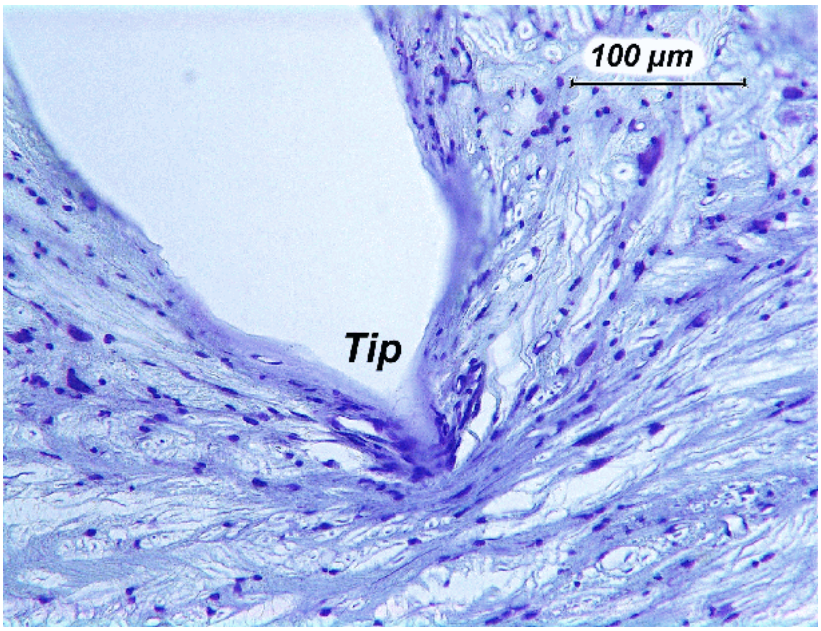


Figure 5B-The tip region of microelectrode 1

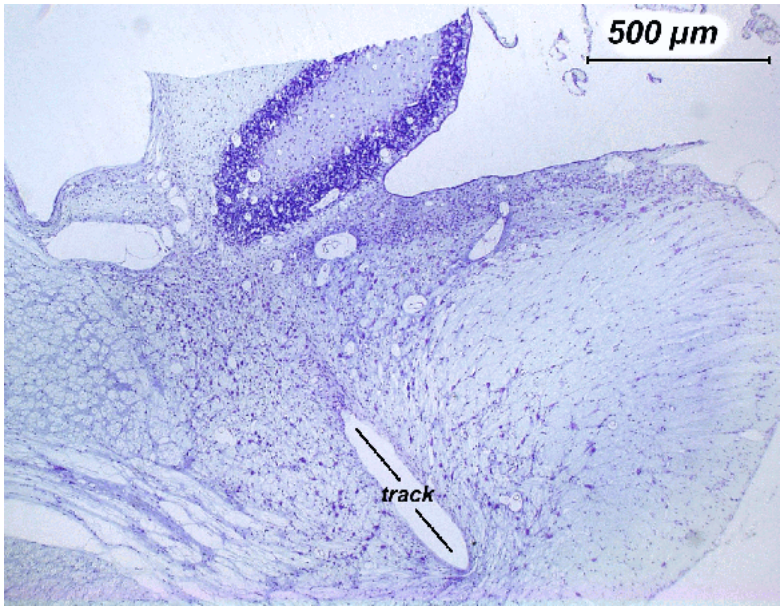


Figure 6A-The track of microelectrode 3 through the PVCN

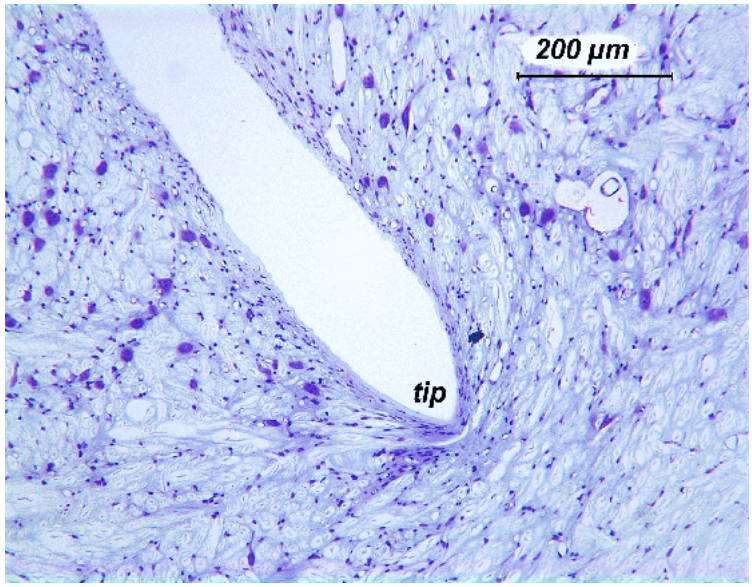


Figure 6B-The tip region and track of microelectrode 3

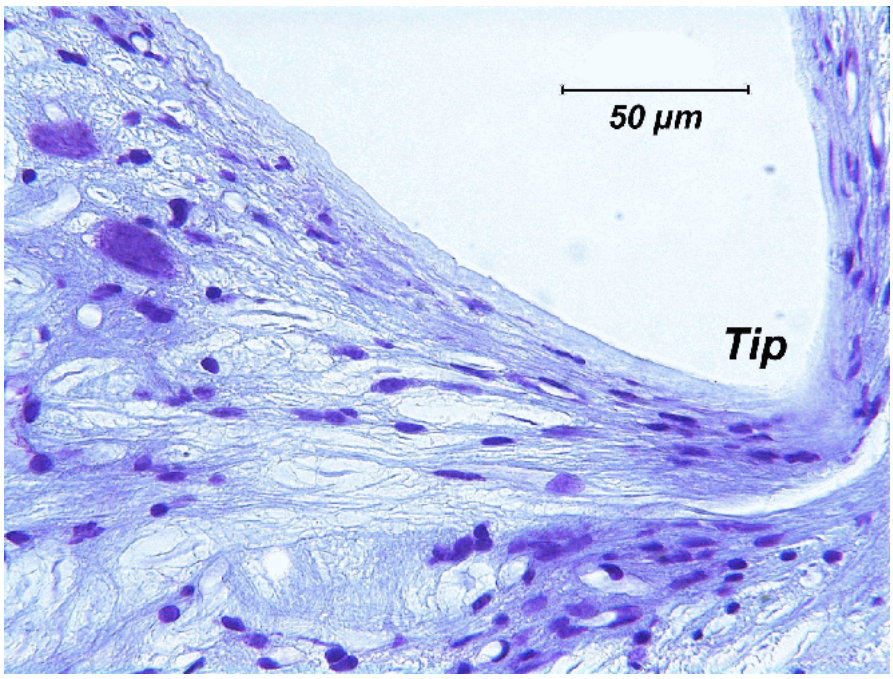


Figure 6C-High magnification view of the tip region of microelectrode 3