"A Cochlear Nucleus Auditory prosthesis based on microstimulation"

Contract No. NO1-DC-8-2102

QUARTERLY PROGRESS REPORT #6

Oct 1, 1999- Dec 31, 1999

HUNTINGTON MEDICAL RESEARCH INSTITUTES

NEUROLOGICAL RESEARCH LABORATORY

734 Fairmount Avenue

Pasadena, California 91105

D.B. McCreery, Ph.D.

W.F. Agnew, Ph.D.

T.G.H. Yuen, Ph.D.

L.A. Bullara, B.S.

HOUSE EAR INSTITUTE

2100 WEST THIRD STREET

Los Angeles, California 90057

Robert Shannon, Ph.D

Jean Moore, Ph.D

Steve Otto. M.S.

ABSTRACT

These studies are a continuation of our program to develop an auditory prosthesis based on multisite microstimulation in the ventral cochlear nucleus. We have designed an instrument which will allow a neurosurgeon to implant the microelectrodes array through the restricted opening provided by the translabyrinthine approach to the brainstem. However, precise control of hand-held instrument is difficult to achieve and we have hypothesized that there is a correspondingly greater potential for tissue injury.

In this series, 6 arrays of iridium microelectrodes were implanted for 30 to 35 days into cat lumbar spinal cord, and 2 arrays were implanted into cat cerebral cortex. (These structures were selected as sites for evaluating tissue injury, in preference to the cat cochlear nucleus itself, due to the anatomical differences between the feline and human coclear nuclei). Histologic analysis revealed some injury in both gray and white matter adjacent to the shafts and dorsal to the tips of the shorter microelectrodes, but the neurons and neuropil immediately ventral to the tip sites (the electrodes' active stimulating sites) appeared to be normal. Longer electrodes induced more injury, especially when they penetrated into white matter. Based on these findings, we have reduced the lengths of the array's "stabilizing pins". These findings indicate that the amount of tissue injury that will be inflicted by an array of microelectrodes inserted into the human CN, using the hand-held tool, will not seriously compromise the functionality of the auditory prosthesis. In particular, there will be viable neurons and axons within 25 μm of the electrode tips.

INTRODUCTION

We have developed a microelectrode array for implantation into the human cochlear nucleus in order to restore hearing to patients who cannot benefit from a cochlear implant due to the absence of an eighth nerve. Figure 1 shows a microelectrode array and its cables. Six iridium microelectrodes ranging in length from 1.5 to 3.0 mm extend from an epoxy button (superstructure) that is 2.5 mm in diameter. In addition to the 6 electrically-functional microelectrodes, there are two stabilizing pins, each 3 mm in length. The iridium electrode shafts are 75 μm in diameter, tapering to rather blunt tips, with radii of curvature of 5 - 6 μm). The sole function of the stabilizing pins is to prevent the newly-implanted array from being dislodged by manipulations of the cable during the remainder of the surgical procedure. The cable itself is composed of 6 pure platinum leads, 50 μm in diameter. and insulated with Teflon. In the (linear) 12 mm of the cable closest to the array, the platinum leads are wound into a helix,1.1 mm in diameter in order to increase the flexibility and malleability of this terminal segment. A patch of Teflon felt is positioned 8 mm from the array button. We intend for the pad to be pre-wetted with a drop of the patient's blood, and after the array has been implanted, the surgeon can tap the pad down onto the pia so as to partially anchor and stabilize the terminal segment. Beyond the 12-mm terminal segment, the lead wires are wrapped around a multi-strand polyester suture and coated with Type A silicone elastomer, to protect the Teflon insulation from ablation. The polyester suture traverses the entire length of the cable and carries all tensional forces. To ensure that the cable is sufficiently flexible, we videotaped numerous trial implantations of the array into cat brain and spinal cord, then digitized the videotapes into a computer and analyzed the images, frame by frame, as the array was inserted into the tissue, the felt pad tamped onto the pia and then as the far end of the cable was intentionally manipulated and twisted (as may happen during the later stages of the human surgical procedure). Our criterion was that the movement of the array matrix relative to the cortex should be no greater during these manipulations than occurs during the respiratory movements of the brain surface.

We have developed an instrument for implanting the microelectrode arrays into the human cochlear nucleus (Quarterly Progress Report #1). The instrument was designed to accommodate the special requirements imposed by the translabyrinthine surgical approach to the brainstem (Figure 2). Prior to its deployment, the top of the array's superstructure is held by a vacuum against the end of a short (5 mm) sliding piece within the barrel of the array and the electrode array is protected within the end of the barrel. The angled barrel accommodates the misalignment between the translabyrinthine surgical opening and the tonotopic axis of the human ventral cochlear nucleus. The surgeon will place the orifice of the barrel onto the surface of the brain using the taenia chorodia as a landmark. When the trigger is depressed, the slide piece advances at a speed of approximately 1 m/sec, pushing the microelectrode array into the brain. At the end of the insertion stroke, a valve interrupts the vacuum, and the array is released cleanly from the slide piece. The surgeon can tamp the Teflon felt pad onto the pia, using the end of the barrel.

Implanting penetrating microelectrode arrays by means of a hand-held tool does carry considerable potential for injury. We wished to evaluate the problem in a model tissue, so as to estimate the degree of tissue injury to be expected in the human cochlear nucleus, and also the determine how the neurosurgeon should be trained in the instrument's use. While the feline cochlear nucleus appears to be a satisfactory model for the investigation of the physiological effects of electrical stimulation, its physical dimension and location as a pendulous structure on the lateral surface of the cat's brainstem does not recommend it as a model for evaluating a microelectrode array that has been scaled for human use. Also, the human CN is overlaid by a tough glial pial layer (the glia limitans), which is not present in felines. The feline lumbar spinal cord appears to be a better approximation to the human brainstem and it is a good site for chronic array implantations since cats tolerate a lumbar laminectomy very well. Based on our examination of unfixed human brainstems, the thickened pia arachnoid near the dorsal roots is a fair approximation to the glia limitans. The cord has gray matter surrounded by long fiber tracks(analogous to the human cochlear nucleus) and also elongated white tracts (fiber tracts) that are

analogous to the inferior cerebellar peduncle which lie beneath the human ventral cochlear nucleus.

In Quarterly Progress Report #1, we described histologic findings from a study in which the microelectrode arrays were implanted acutely into the feline lumbar spinal cord for 4-6 hours in order to evaluate the potential for post-implantation hemorrhages. In the present series, 6 arrays were implanted into the lumbar spinal cord of 3 cats for 30-35 days. Also, two arrays were implanted into the feline parietal cerebral cortex for 30 days, to examine the consequence of implanting the arrays into a tissue that is more vascular than the spinal cord. The length of the electrodes implanted into the spinal cord range from 1.5 to 3.5 mm, and the stabilizer pins were 4 mm in length. The electrodes implanted into the cerebral cortex were shorter (1-3 mm). On the basis of recent modeling studies conducted by Dr. Jean Moore at the House Ear Institute (Quarterly Progress Report #3), it now appears that microelectrodes implanted into the spinal cord, and those implanted into the cerebral cortex were somewhat longer than will be required for the human cochlear nucleus.

RESULTS

The arrays were implanted into the lumbar spinal cord using aseptic surgical technique and with the cats anesthetized with Halothane and Nitrous Oxide. The lumbar enlargement was exposed by a standard dorsal laminectomy and the dura opened in a midline incision. The microelectrodes were inserted into the dorsal surface of the spinal cord near the dorsal root entry zone. Figure 3 is a frame from an intraoperative video showing two arrays in place in the lumbar cord (these arrays had only short cable segments). The dura was then closed loosely with 7-0 sutures. The exposed surface of the cord was then covered with a patch of fascia resected from pera-spinal muscles. The muscle layers and skin were closed and the cats were given appropriate postoperative treatment, including analgesic medication for relief of postoperative pain. Thirty to 35 days later, they were anesthetized deeply with Pentobarbital and perfused through the aorta with 1½ liters of ½-strength Karnovsky's fixative. The arrays were removed from the spinal cord, the spinal cord was resected,

cut into blocks, embedded into paraffin and sectioned to 8 µm. The sections were stained with Toluidine blue (Nissl) for visualization of cells and neuropil. The distances from the site of the electrode tips to the overlying pia were measuring using the microscope's micrometer scale. The values cited in the text have not been corrected for tissue shrinkage. Normally, brain tissue shrinks considerably when embedded into paraffin but then expands, essentially to life-size, during subsequent processing and rehydration of the histologic sections. Since our sections were cut nearly parallel to the electrode tracks, we expect that tissue shrinkage would not cause a large error in our calculation of the depths of the electrode tips.

The results from cat CNH6 are typical of those from all three animals. Figure 4 shows a histologic section cut slightly obliquely through the track of a 3 mm electrode, near its point of penetration into the dorsal surface of the lumbar cord. The track is seen passing through the axons of the dorsal column. Most of the axons adjacent to the electrode track appear to be normal. There is a small amount of gliotic scaring, particularly along the track's right margin. The injury is accompanied by proliferation of small blood vessels ("neovascularization"). The injury extends as much as 25 µm from the electrode track. The tissue injury tended to be most pronounced on same side of all of the electrode tracks in a particular array, and it is tempting to ascribe this asymmetric injury to movement of the hand-held tool as the array was being implanted. However, we have noted a similar preferential orientation of linear scars near microelectrodes that were implanted with a similar inserter instrument that was rigidly mounted to the stereotaxic frame.

Figures 5A & 5B show the sites of the tips of two microelectrodes in the medial grey matter, lateral to the cord's central canal. Both tips are approximately 1,250 µm beneath the surface of the cord (a typical depth for the human cochlear nucleus, based on the most recent modeling studies conducted at the House Ear Institute). The distal part of the electrode tracks and the electrode tip sites are surrounded by gliotic sheaths up to 25 µm in thickness, but the neurons and neuropil immediately adjacent to the sheaths appear to be quite normal. Figure 6 shows a somewhat deeper microelectrode tip site (1,675 µm) in the same array. The tip was in the grey matter of

the ventral horn, just dorsal to the ventral funiculus. There is some gliotic scarring and neovascularization, with most of the latter restricted to the right of the tip site. The tip site is surrounded by a gliotic sheath approximately 25 μm in thickness. The white matter of the ventral funiculus just ventral to the tip site appears quite normal, as does the neuropil of the ventral horn to the left of the tip.

A consistent finding in all 3 animals was that the longest electrodes (those 3 mm or more in length and also the 4.5 mm stabilizer pins) inflicted more tissue injury than did the shorter electrodes. However, the injury was confined to the vicinity of the tips and the damage adjacent to the electrode shafts closer to the superstructure was not more severe than was the case for the shorter microelectrodes. Figure 7A & 7B show the tracks of two long (4.5 mm) stabilizing pins in the grey matter of the ventral horn. The tracks are surrounded by thin gliotic sheaths less than 25 μm in thickness. There is some neovascularization adjacent to the tracks but the neurons and neuropil appear to be quite normal. Figure 8 shows a section just lateral to the track of one of these stabilizer pins as it passed through the white matter of the ventral funiculus. There is extensive vacuolation of the axons of the funiculus. (Note that this micrograph spans a much wider field than in previous figures). All of the stabilizer pins in the 6 arrays implanted into the lumbar spinal cords inflicted similar injury in the ventral funiculus. On the basis of this finding, we reduced the length of the stabilizer pins to 3 mm and we redesigned the electrode cable so as to accommodate the reduced stability that would be afforded by the shorter pins.

It is inevitable that there will be some movement of a hand-held instrument during insertion of the electrodes. Also, the extent to which the brain is dimpled by the tip of the instrument's barrel is difficult to control . With these points in mind, we wish to examine the consequences of implanting these electrode arrays into the feline cerebral cortex which is more vascular than the spinal cord. We assume that this will afford a good test of the risk of injuring parenchymal blood vessels during electrode insertion. Two arrays were implanted into the parietal cortex of cat CNH7. The 6 working microelectrodes in each array were somewhat shorter than those implanted into the spinal cord, and they ranged in length from 1.5 to 3 mm. As noted below,

even these electrodes may have been longer than necessary for a human array. Each array also contained two uninsulated iridium stabilizer pins, each 3 mm in length.

The cat was anesthetized with Halothane and Nitrous Oxide. Using aseptic surgical technique, a craniectomy was made over the parietal cortex, the dura opened, and the arrays implanted into the gyrus suprasylvius. The arrays were covered with a patch of fascia resected from the temporalis muscle, and the muscle and skin closed over the craniectomy. The bone flap was not replaced. The cat was given appropriate postoperative care. Thirty-two days later, it was sacrificed for histologic evaluation of the electrode site. The perfusion with histologic fixative, tissue preparation and sectioning were essentially as described for the spinal cord. The tissue was sectioned in the frontal plane, slightly obliquely to the axis of the electrode tracks.

Figure 9A shows the site of the tip of one of the microelectrodes from the rostral array 1,225 µm beneath the pia. The tip of the electrode appears to be abutted against a blood vessel, but there is no indication of hemorrhaging. A poorly defined gliotic scar extends to the left of the tip site. Neurons ventral to the tip are slightly flattened but otherwise appear to be normal. The neuropil ventral to the tip site also appears to be compressed in the direction of the axis of the electrode. We have consistently observed this curious phenomenon near electrodes that have been implanted in the cat cerebral cortex and in the cat cochlear nucleus, the latter for more than 18 months. The configuration of the cochlear nucleus array makes it very unlikely that the tissue compression is due to shrinkage of the tissue around the rigid electrodes during fixation. Figure 9B shows the site of the tip of another microelectrode from the same array, also calculated to be 1,125 µm beneath the pia. The linear gliotic scar extending to the left of the tip site is better defined than in Figure 9A, and there are scattered deposits of hemosiderin along the length of the scar, indicating a microhemorrhage or at least some extravasation of red blood cells from a nearby vessel. In addition to the linear glial scar and hemosiderin, there was some vascular hyperplasia dorsal to the tip site. Neurons ventral to the tip site are mechanically flattened but otherwise appear normal and healthy. There were normal-appearing neurons and neuropil immediatly beneath (within 5 µm) all 12 of the electrode tips in the two arrays that terminated in

the cortex (gray matter). In all cases, there was some gliotic scarring dorsal to the tip site, but in no case was it more severe or more spatially expansive than the example in Figure 9B.

As in the spinal cord, the longest electrodes inflicted more injury. Figure 10 shows the site of an electrode tip that was 2,050 µm deep in the grey matter. There is a globular gliotic scar dorsal to the tip site. However, no hemosiderin was present and there were no other indications that the scar had evolved from a healed hemorrhages. Neurons ventral to the tip site appear to be normal, except for some mechanical flattening.

In the two arrays, a total of 6 microelectrodes and stabilizer pins entered the white matter underlying the cortex. In all cases, the tissue injury and sequelae of scarring was more severe than in the grey matter. Figure 11A shows a tip site in the white matter just beneath the cortex, and at a depth of 2,200 µm. The gliotic scar extends for up to 500 µm, dorsal and lateral to the tip site. We have speculated that the greater injury in the white matter is due to the accentuated lateral motion of the longer electrodes, both during insertion and possibly during residence in the brain . However, the axons of white matter may be particularly vulnerable to this type of injury. This premise is supported by Figure 11B which shows the site of the tip of a microelectrode located 2,750 µm below its point of entry into the pia. (The tip site is in the grey matter only because the electrode had penetrated into the bank of the gyrus as it traverses down into the sulcus). There is a small gliotic scar dorsal to the tip site, but the severity of the scarring is comparable to that which accompanied the shallower electrodes (Figure 9).

DISCUSSION

The histologic evaluations of the chronically-implanted microelectrode arrays indicates that the hand-held insertion tool can be used to implant microelectrodes into the human cochlear nucleus. The tool was used to implant microelectrode arrays into the feline lumbar spinal cord and also into the cerebral cortex. Recent modeling

studies conducted by Jean Moore at the House Ear Institute depicts the human ventral cochlear nucleus as a flattened structure, approximately 1 mm in thickness, overlaid by a glial-pial layer approximately 0.5 mm in thickness. Based on this model, and allowing for individual variations and for the growth of a connective tissue capsule up to 0.5 mm in thickness beneath the electrode array, we estimate that the microelectrodes of the human array should range in length from 1 to 2 mm. In the cat's cerebral cortex and spinal cord, tissue injury was quite minimal near the tracks and near the tips of the shorter microelectrodes (those less than approximately 2 mm in length). There was more injury near the tips of the longer electrodes and stabilizing pins, both in the spinal cord and in the cerebral cortex. For this reason, we have reduced the length of the stabilizing pins from 4.5 to 3 mm. In order to compensate for the reduced stability afforded by the shorter pins, we have redesigned the distal portion of the array cable so as to reduce its spring constant and increase its malleability. Based on the results presented in this report, we expect that even these shorter stabilizer pins will inflict some local injury in the white matter deep to the human cochlear nucleus. These are the fibers of the middle cerebellar peduncle. The gliotic scars will probably be on the order of 0.5 mm in diameter and will be localized to the vicinity of the tips of the stabilizer pins.

It is not possible to control the mechanical contact between a hand-held tool and the surface of the brain to the extent that is possible with an inserter that is rigidly mounted on the stereotaxic head frame. As part of the workscope of another contract, we have been systematically examining the consequences of varying the amount by which the inserter tool dimples the surface of the spinal cord, prior to inserting the array, and the type and severity of the resulting tissue injury . These studies indicate that it is quite important to control the amount by which the inserter tool dimples the tissue prior to releasing the array. In this respect, it may be fortunate that the human cochlear nucleus is covered by a glia limitans, since this tough membrane should make it more difficult for the end of the inserter instrument's barrel to dimple the surface of the brainstem excessively.

WORK FOR NEXT QUARTER

Although the current array design appears to be acceptable, it would be desirable to reduce the amount of gliotic scarring dorsal to the tip sites. It is our experience that microelectrodes with larger shafts tend to inflict more tissue injury. The iridium microelectrodes comprising the cochlear nucleus array are 75 µm in diameter. This shaft diameter was selected on the basis of earlier anatomical studies of human material performed at the House Ear Institute, which indicated that the working electrodes should range in length from 1.5 to 3.5 mm, in order to access the entire tonotopic axis of the ventral human CN. The most recent studies of the human brainstem indicate that 1 to 2 mm will be a more appropriate range of lengths. On this basis, we plan to reduce the diameter of the 6 working electrodes, to 50 µm. The diameter of the 3 mm stabilizing pins will be maintained at 75 µm, (or perhaps reduced slightly, to 65-70 µm. This modification should retain sufficient mechanical strength to tolerate moderate handling errors in the operating room, as might occur while loading the array into the inserter instrument. These arrays and their cables will be evaluated for post-implantation stability in acute studies in cat cerebral cortex, and then will be implanted chronically (for 30 days) into feline cerebral cortex and feline spinal cord.

[

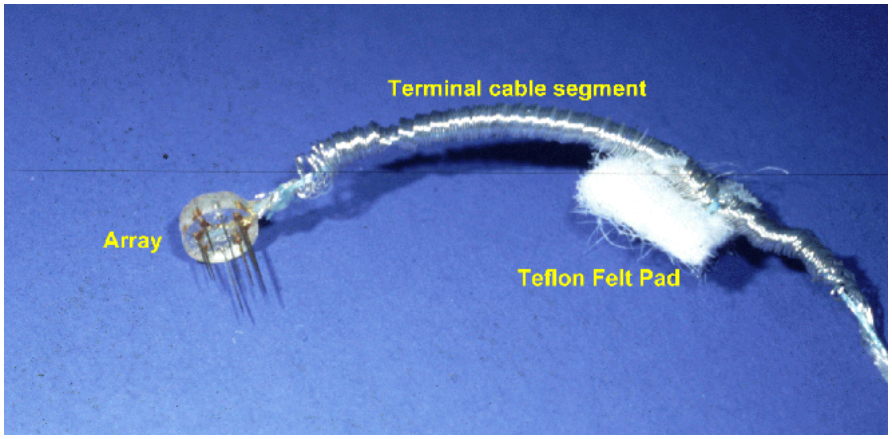


Figure 1. The microelectrode array and cable. Six iridium microelectrodes and 2 stabilizing pins extend from the 2.5 mm Masterbond Epoxy button (superstructure). The Teflon felt pad is attached to the flexible spiral terminal segment of the cable.

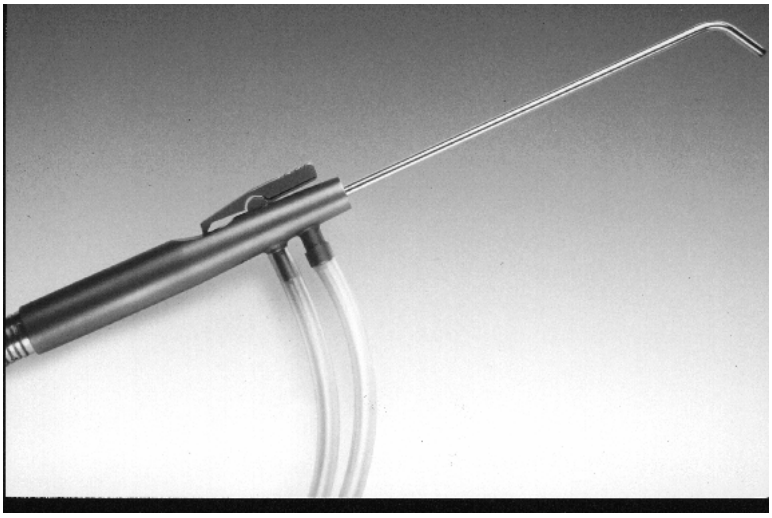


Figure 2. The hand-held instrument for inserting the microelectrode array into the human cochlear nucleus. Prior to insertion, the electrode array is protected within the end of the tool's barrel which is curved so that the surgeon can insert the array into the cochlear nucleus through the translabyrinthine surgical opening.

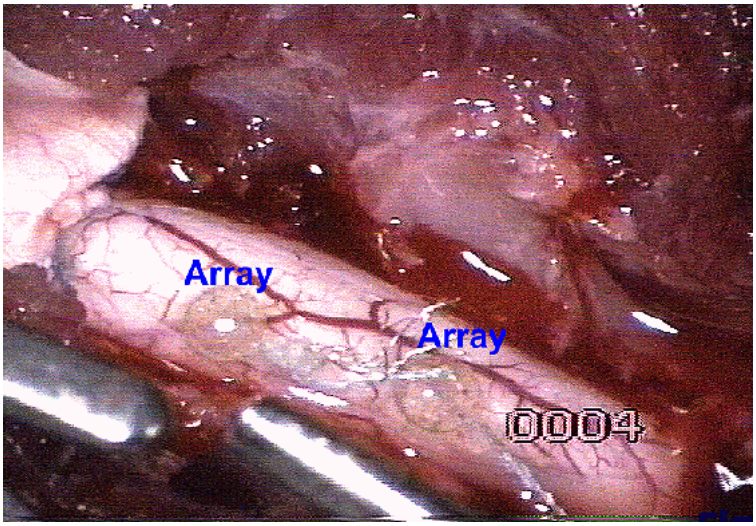
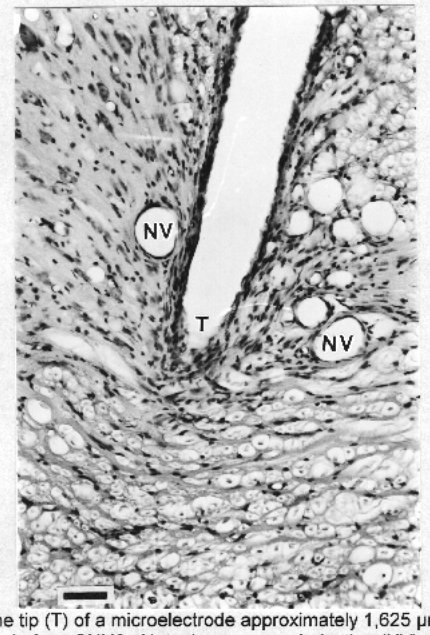


Figure 3. The dorsal surface of the lumbar enlargement of the spinal cord of cat CNH6, showing 2 microelectrode arrays implanted near the dorsal root entry zones.



parallel to

Figure 6. The site of the tip (T) of a microelectrode approximately 1,625 µm beneath the dorsal surface of the spinal cord of cat CNH6. Note the neovascularization (NV) adjacent to the electrode track. The tip site is surrounded by a thin gliotic sheath. The neurons and axons ventral to the tip site appear quite normal. Bar =50 µm

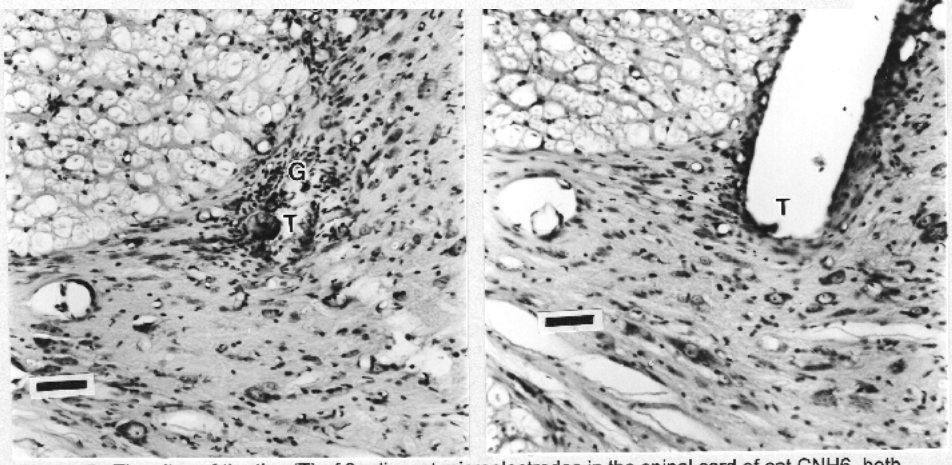


Figure 5. The sites of the tips (T) of 2 adjacent microelectrodes in the spinal cord of cat CNH6, both approximately 1,250 µm beneath the pia, and both just lateral to the central canal. The histologic section in **A** passes though the tips's glia sheath, while in **B,** it transects the sheath, about 16 µm dorsal to the absolute tip. Dorsal to the tip site shown in **A,** there is a focus of gliosis, approximatly 100 µm in width, surrounding the distal electrode shaft. Adjacent neurons and neuropil appear normal. Bar = 50 µm

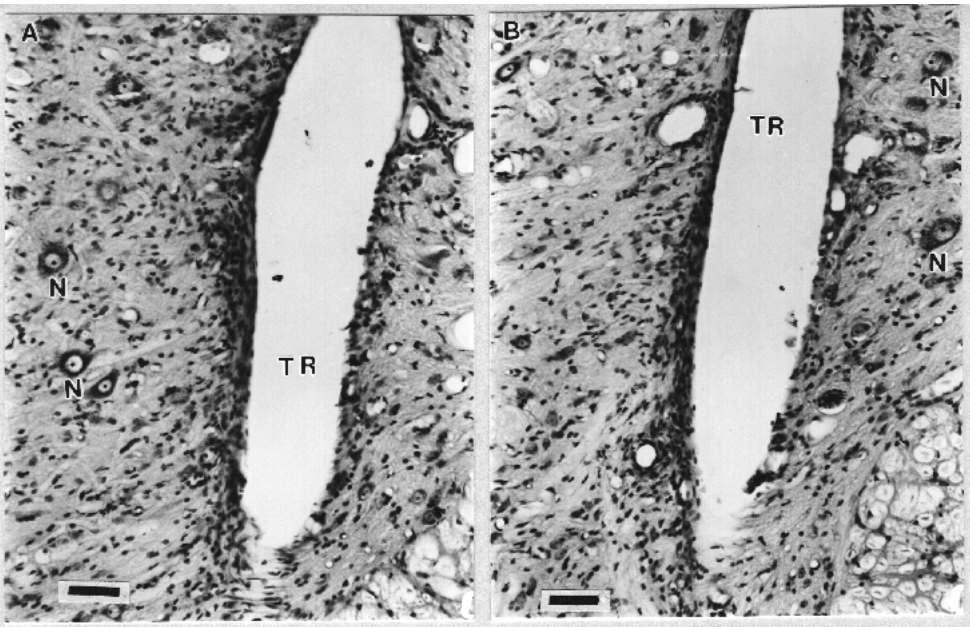


Figure 7. The tracks (TR) of 2 stabilizing pins traversing the intermediate grey of the lumbar spinal cord of cat CNH6. Lateral to the track and the thin gliotic sheath, the neurons (N) and neuropil appear normal. The labels "TR" mark a depth of approximately 1700 µm below the cord's dorsal surface. Bar = 50 µm.

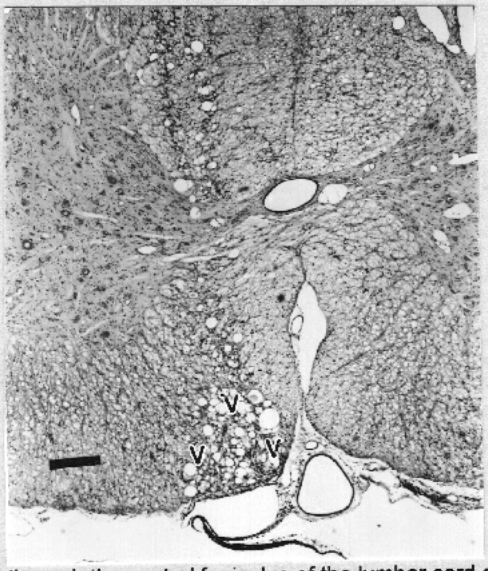


Figure 8. A section through the ventral funiculus of the lumbar cord of cat CNH6. The section is just lateral to the track of the stabilizer pins, showing a region of vacuolations (V) of the myelinated axons, spanning more than 400 µm of the ventral funiculus. Bar = 250 µm

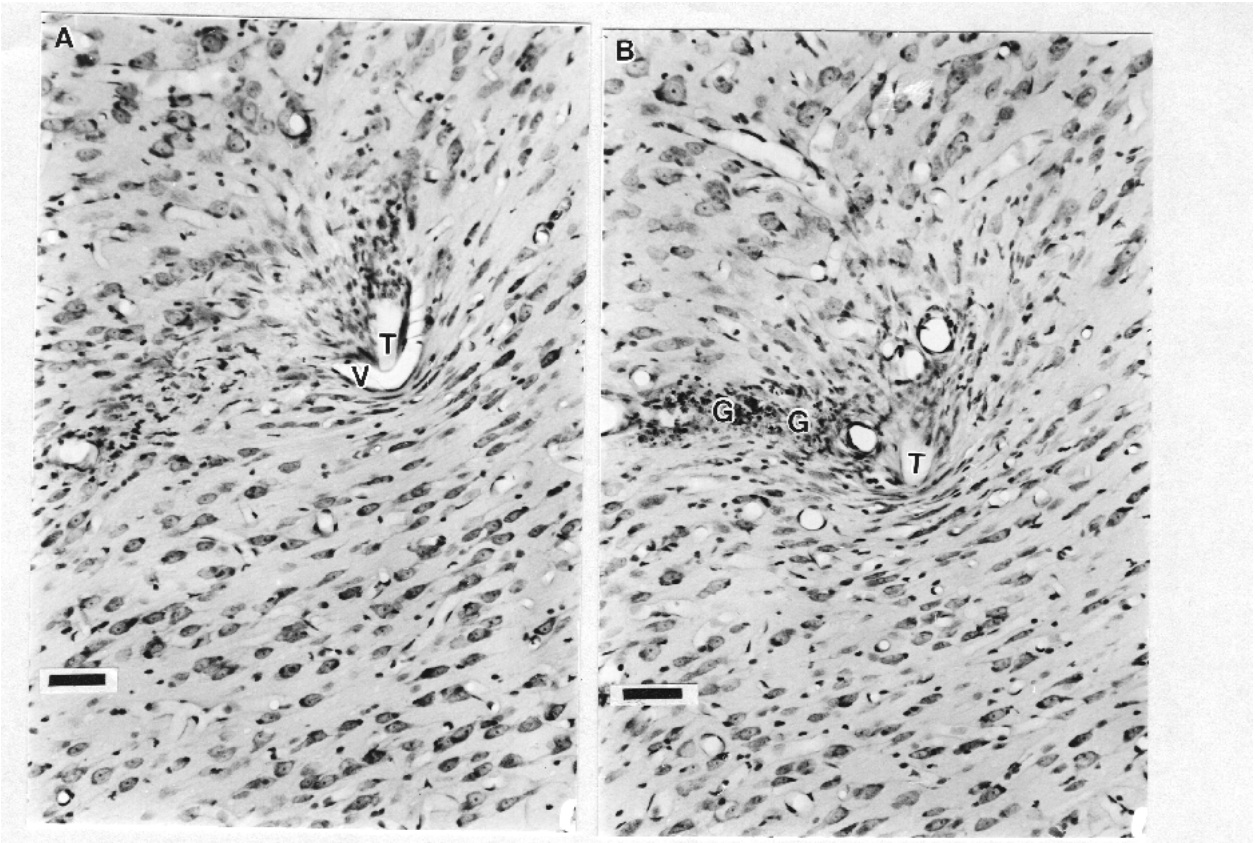


Figure 9. A. The site of the tip (T) of a microelectrode implanted in the cerebral cortex of cat CNH7. The site is approximately 1,125 µm beneath the pia. The microelectrode is impinging against a large blood vessel (V) which appears undamaged. **B.** The tip site of another electrode from the same animal, also approximately 1,125 µm beneath the pia. An elongated glial scar (G) extends to the left of the tip site and contains scattered deposits hemosiderin, but there is no space-occupying hematoma. Neurons and neuropil ventral to the tip site are somewhat flattened and compressed but otherwise appear to be normal. Bar = 50 µm.

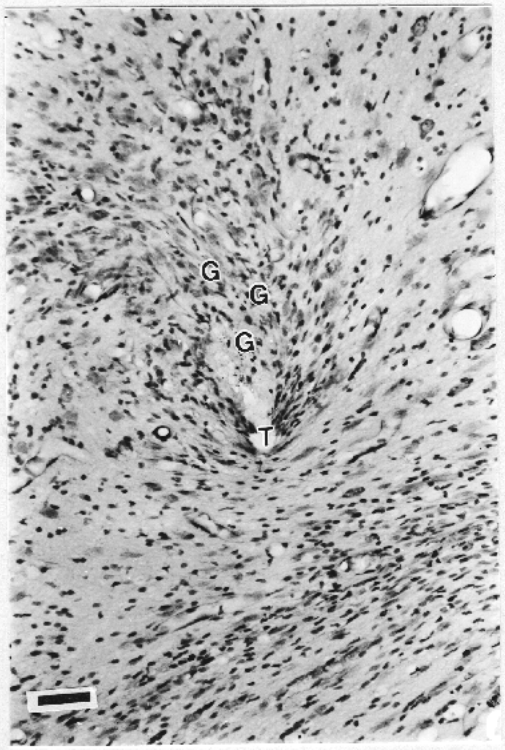


Figure 10. The site of an electrode tip, somewhat deeper (2,050 µm) in the cortex of cat CNH7, and near the boundary between the cortex and the white matter. There is gliotic scarring (G) dorsal to this tip site, but neurons and neuropil ventral to the tip appear to be normal. Bar=50 µm

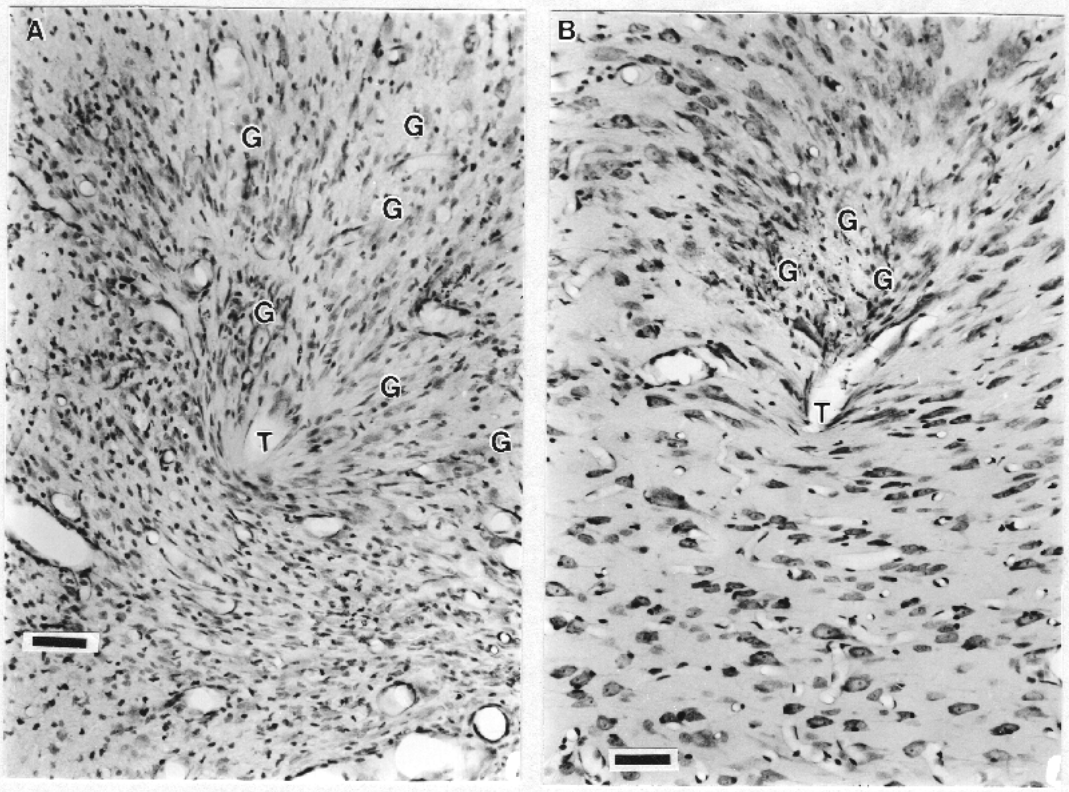


Figure 11. A. The tip site (T) of a microelectrode which had penetrated into the white matter deep to the cortex. The estimated depth of the tip site is 2,200 µm. The site is surrounded by an extensive glial scar (G) at least 500 µm in width. **B.** The site of the tip of another microelectrode from the same array as depicted in **A**, but within the grey matter in the bank of the gyrus rather than in the white matter. The estimated length of the electrode track is 1,750 µm. The gliotic scarring (G) is considerably less expansive than near the tips sites in the adjacent white matter. Bar = 50 µm.