Long-Term Stimulation and Recording With a Penetrating Microelectrode Array in Cat Sciatic Nerve

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***Abstract*—We studied the consequences of long-term implantation of a penetrating microelectrode array in peripheral nerve over the time course of 4–6 mo. Electrode arrays without lead wires were implanted to test the ability of different containment systems to protect the array and nerve during contractions of surrounding muscles. Treadmill walking was monitored and the animals showed no functional deficits as a result of implantation. In a different set of experiments, electrodes with lead wires were implanted for up to 7 mo and the animals were tested at 2–4 week intervals at which time stimulation thresholds and recorded sensory activity were monitored for every electrode. It was shown that surgical technique highly affected the long-term stimulation results. Results between measurement sessions were compared, and in the best case, the stimulation properties stabilized in 80% of the electrodes over the course of the experiment (162 days). The recorded sensory signals, however, were not stable over time. A histological analysis performed on all implanted tissues indicated that the morphology and fiber density of the nerve around the electrodes were normal.**

***Index Terms*—Functional neuromuscular stimulation (FNS), implantable electrodes, neuroprosthesis, peripheral nerve.**

I. Introduction

IN SPINAL cord injury, ascending and descending nerve fibers are transected or crushed and as a result, the spinal cord is permanently damaged. Since only limited success has been achieved in regenerating the severed neuronal connections [1], [2], neuroprosthetic devices based on the activation of muscles distal to the injury [functional electrical stimulation (FES)] have been investigated for many years as an alternative method to restore motor function in paralyzed limbs. Apart from muscle stimulation, a neuroprosthetic device based on FES should also employ sensory feedback information to monitor the movement produced; this would be especially useful while generating complex movements. Several different devices have been studied as possible neural interfaces to the spinal cord [3]–[5], peripheral nerve fibers [6]–[17], and the motor end plates of the muscles directly [18]–[20]. Because peripheral nerves contain both sensory and motor fibers, electrodes implanted there could be used to stimulate motor fibers as well as to record signals from skin and muscle sensory fibers.

Desirable features of peripheral nerve interfaces are low stimulation currents, and selectivity and stability of stimulation and recording. These properties depend on the proximity of the exposed electrode surface to the target nerve fibers. In addition, intrafascicular electrodes are electrically shielded from their surroundings by the epineurium and the perineurium of the nerve. Hence it is difficult to achieve good stimulation and recording selectivity with electrodes placed around the nerve on the outside of these two neural compartments such as cuff-type electrodes. It has been shown that the stimulation selectivity and/or recording capability can be greatly enhanced by placing the electrodes within the fascicles of the nerve [6], [14].

In this study, multiple electrodes were chronically placed in different fascicles of the sciatic nerve of cats. The microelectrode array used, the Utah Electrode Array (UEA), has a grid of up to 10 by 10 electrodes at 400 μm spacing and was originally developed for recording and stimulation of cortical nervous tissue [21], [22]. This planar structure was later modified to a three-dimensional electrode arrangement, the Utah Slanted Electrode Array (USEA), to be better suited for use in peripheral nerve. In previous acute experiments, the UEA and the USEA were safely implanted into peripheral nerve [6], [23]. Different muscle groups were stimulated in a highly selective fashion employing low stimulation currents, and information was recorded from sensory fibers from the skin and muscles. However, this device has not been used chronically to date for either stimulation or recording in peripheral nerve.

There are several issues associated with the chronic implantation of a microelectrode array such as the USEA. There is substantial relative motion between the nerve and its surrounding muscles. This motion can exert forces on the electrode array and eventually could extract it from the nerve. In addition, the

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nerve might be damaged if the electrodes are unable to move with the nerve. Therefore, we suggest that some kind of containment system may be required to keep the electrodes within the nerve but yet not restrict nerve movement. Lead management and connector requirements offer additional challenges; lead wires can produce tethering forces on the array, resulting in damage to the nerve or breakage of the wires themselves. The connector system has to be able to accommodate as many electrodes in as little space as possible and should be mounted securely to the animal, close to the implant site. These issues were addressed in this study and a variety of containment systems were evaluated.

Electrical interference from surrounding muscles can be a problem in recording sensory information from peripheral nerves in an awake and freely moving animal. Ideally, the signal contamination can be eliminated by electrically shielding the electrodes and the nerve from its surroundings. Another potential solution to this problem is to filter this noise out in either the analog or digital domain.

This paper explores the USEA's long-term implantation in peripheral nerve. Electrode arrays without lead wires were implanted to test different containment systems for their ability to protect the array and nerve during contractions of surrounding muscles. The cats' ability to walk on a treadmill was monitored over the time course of about 2 mo and a histological analysis was performed on the tissue. In a different set of experiments, electrodes with lead wires were implanted for up to 7 mo and again histology was performed. The animals were tested regularly and stimulation thresholds and recorded sensory activity were identified for every electrode. Results between measurement sessions were compared to analyze possible changes in the nerve interface.

II. Methods

A. Electrode Array

In this study, different sizes of the Utah Slanted Electrode Array (USEA) were used depending on the size of the nerve [Fig. 1(a)]. The size ranged from arrays fabricated in a 7 × 10 to 10 × 10 electrode arrangement, which corresponds to a size from 2.8 × 4 mm to 4 × 4 mm; the length of the electrodes varied between 0.5 and 1.5 mm along the longer axis with 0.1 mm length difference between neighboring electrodes along this axis. The manufacturing and wiring process of the array was described in detail elsewhere [6], [21]. Each array was wired to 36-pins of each of two 40-conductor edge connector mounted in a titanium base [Fig. 1(b)] (Cyberkinetics, Inc., Salt Lake City, UT). Of the other four pins, two were wired to the connector pedestal as ground and two were wired to insulated Pt/Ir reference wires with de-insulated tips that were placed next to the electrode array.

The impedances of the electrodes were measured on a periodic basis after implantation using a WPI impedance meter which uses a 1- or 10–nA 500-Hz square wave (Omega-Tip Z, World Precision Instruments, Sarasota, FL); the average impedances at the time of implantation was 270 ± 190 kΩ(n = 453 electrodes).

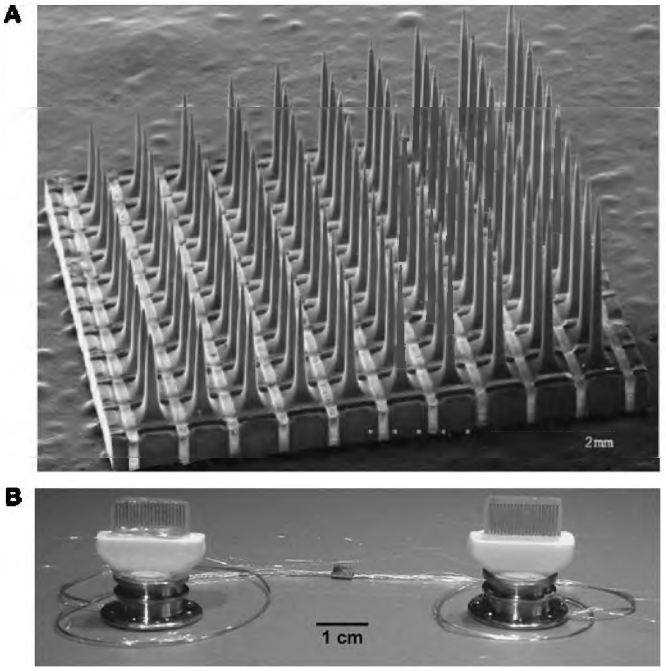

Fig. 1. Implanted device. (a) Scanning electron micrograph of the USEA). (b) Picture of the array, the lead wires and the connector system. Each connector is wired to 36 electrodes and two reference electrodes. The titanium pedestal of the connector itself is used as ground.

B. Surgical Procedure

Thirteen cats were studied of which six received nonfunctioning and seven received functioning implants. Non-functioning implants were electrode arrays that did not have lead wires connected to them. A total of 11 nonfunctioning arrays were implanted where some animals received either bilateral implants or two arrays were implanted in the same nerve. Walking behavior and histology were studied in these animals. The surgery for nonfunctioning implants was essentially the same as described below except for the implantation of the connectors. Only single functioning implants were performed in the other seven cats. All experiments were performed under sterile conditions according to the National Institutes of Health guidelines for the use of animals.

Anesthesia was induced with Telazol (10 mg/kg) and maintained with halothane (0.8%–1.5%) during the surgery. Electrocardiogram, blood pressure, expired CO_2, oxygen saturation and rectal temperature were continuously monitored. After the right leg and the lower back were shaved, a 5- to 6-cm-long incision was made from the hip to the knee and the biceps femoris and vastus lateralis muscles were separated to gain access to the sciatic nerve. The array was positioned on the nerve and the wires on both sides of the array were sutured to the epineurium of the nerve. Then, the array was inserted into the nerve using a pneumatically actuated impulse inserter [24] (Cyberkinetics, Inc., Salt Lake City, UT).

We put a containment system around the nerve and the array to improve the stability of the array in the nerve and to facilitate gliding of surrounding muscles over the structure without exerting major shear forces on the array. Fig. 2 shows three of the four different containment systems used: Fig. 2(a) a Gore-Tex

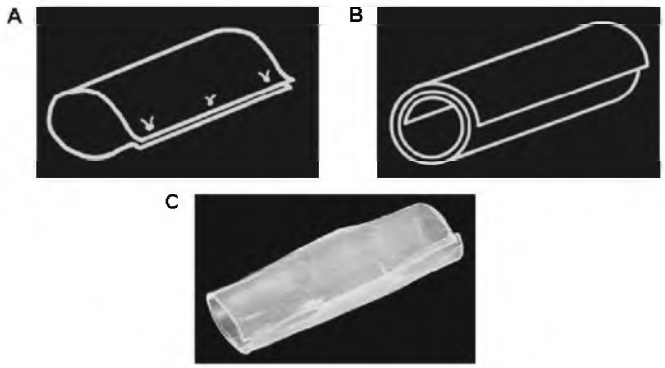

Fig. 2. Three of the four different containment systems used in the study: (a) a sheet of GoreTex wrapped around the nerve, (b) a self-sizing spiral cuff, and (c) a silicone custom cuff (here oval shaped).

sheet sutured around the nerve, Fig. 2(b) spiral cuffs (Axon Engineering Inc., Garfield Heights, OH), and Fig. 2(c) custom cuffs made of silicone in a dip process. Similar silicone cuffs were used by Hoffer and Haugland [25], [26]. The fourth containment system (not shown) consisted of Kwik-Cast (World Precision Instruments, Inc., Sarasota, Florida), a two component silicone elastomer. The two-component elastomer was applied on the nerve and allowed to flow around the nerve at the implant site. The Gore-Tex sheet was about 3 cm × 1.5 cm in size and had a thickness of 0.1 mm. It was wrapped around the nerve and the implanted array and sutured on the side. The commercially available spiral cuffs had an inner diameter of 2.7 or 3.5 mm depending on the size of the nerve. They were 1.5 cm long and fully wrapped around the nerve and array twice. The spiral cuffs were sutured to the nerve with a fine suture proximally to prevent the cuff from sliding away from the implant site.

To produce the custom made cuffs, a Teflon rod was modified to have the shape of the nerve with the array implanted in it. This replica was then chemically cleaned and dipped in medical-grade silicone (MED-1037, NuSil) multiple times until the desired thickness of up to 0.5 mm was reached. The resulting cuff was then cut to a length of about 15 mm and cut open on one side. There were two versions of custom cuffs; the early ones used a circular diameter model of the nerve whereas later ones were more realistically oval shaped. After implantation of the array, the containment system being studied was put around the nerve with the array, a Pt/Ir reference wire (20IR2T, Medwire) was placed inside and the containment system was closed using polypropylene sutures.

For functional implants, an additional incision was made on the animals' back orthogonal to the vertebral column and spanning the two iliac crests. Both connectors were routed under the skin from the incision on the leg to the one on the back. The iliac crests and the L7 spinal process were partially exposed. In the first experiments, holes were drilled through all three bones and either silk sutures or stainless steel sutures were used to secure the connectors. In the more recent experiments, a stainless steel suture was put through the spinal process but each connector was attached to the iliac crest using two bone screws. Finally, the skin was closed at the implantation site and around the two connectors on the back.

C. Experimental Procedures

After implantation, the animals were tested about once every 1–4 weeks and light Telazol anesthesia was applied when necessary. Three different kinds of tests were performed: behavioral tests of the animal's walking ability on a treadmill, measurement of the stimulation threshold of each electrode and recording of sensory activity.

1) Behavioral Tests: The cats' ability to walk on a treadmill was monitored one to two times per week. We categorized the extent of walking impairment into four different classes: 1) no visible discomfort or walking deficit; 2) some discomfort but no walking deficit; 3) unable to put weight on ankle and discomfort; and 4) no use of the leg. This scale was used as a measure of nerve damage after implantation.

2) Stimulation: For stimulation, biphasic, cathodic-first, constant-current stimuli with 200 μs per phase and a 100-μs interphase interval were delivered using a computer-controlled WPI Linear Stimulus Isolator (A395, World Precision Instruments, Sarasota, FL). To determine the stimulation threshold on each electrode, the stimulation was started at the expected threshold level, increased in 5-μA steps until a muscle twitch could be detected and then decreased in 1-μA steps until threshold was reached. The twitch and the type of muscle groups activated was detected using visual inspection and palpation around the ankle joint, foot and toes as described in more detail in the results section. A similar method has been used by Mushahwar *et al.* [27]. Although the stimulated muscle could sometimes be clearly identified, often only the direction of movement and location of muscles could be identified, rather than specific muscle groups.

3) Recording: Sensory activity was recorded using a 100-channel amplifier and data-acquisition system (NSAS, Cyberkinetics, Inc., Salt Lake City, UT). Recording was either under Telazol anesthesia to avoid EMG contamination or in alert animals resting or walking on a treadmill. With the animal under anesthesia, sensory activity was evoked by mechanical stimulation consisting of brushing of the animal's paws and digits or limb rotation around a joint. We determined the amplitude of the activity and the movement that evoked it and compared responses at different recording sessions.

D. Histology

Each animals was sacrificed after periodic experimentation that ranged anywhere from 5–31 weeks. They were deeply anesthetized and transcardially perfused with 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4) at room temperature. After perfusion the sciatic nerves and surrounding tissues were removed and kept overnight in the same fixative at 4 °C before being rinsed in phosphate buffer. The nerves were then cut into two pieces at the midpoint of the implant. The proximal portion was washed in distilled water, dehydrated in graded concentrations of ethanol and embedded in paraffin. Light microscopy observations were performed on 5-μm serial sections stained with either haematoxylin and eosin (H&E) or TriChrome methods to reveal the position of the electrodes, the thickness of the connective tissue around the electrode shanks and signs of axonal degeneration. Distal portions of the nerves were postfixed for 1 h in

2% OsO_4, dehydrated in graded concentrations of ethanol and embedded in Epon 812. Serial 0.5-μm semithin sections were stained with toluidine blue and examined with a Leica DMB Microscope.

Connective tissue thicknesses were calculated for five implants. More detailed morphometrical analysis was performed on six nerves (two unimplanted control nerves, two nonfunctioning and two functioning implants). The morphometrical evaluation was performed in 8–10 randomly selected microscopic fields for each nerve. The image fields were evenly distributed over the nerve's cross-section (not restricted to fascicles with electrodes in them). Each field spanned approximately 200 × 200 μm, and represented approximately 15%–20% of the cross-sectional area of the nerve.

The image fields were digitized using a high-resolution Olympus DP-11 digital camera and analyzed using the computer-assisted image analysis program (NIH Image, developed and maintained by the National Institutes of Health, Bethesda, MD) and a modified version of software designed to study axonal morphometry [28]. Because it was difficult to automatically select the boundary between the nerve fibers and the surrounding background for small axons and thinly myelinated fibers using standard image analysis techniques, each digitized image was analyzed using a semiautomatic method. The axonal contour and the external contour of the myelin sheath (fiber contour) were manually traced on enlarged images. A set of custom macros allowed the calculation of the length of a line, the cross-sectional area, and the lengths of the major and minor axes of the best fitting ellipse. Fiber diameters and axonal diameters were deduced from the fiber and axonal perimeters assuming a cylindrical shape of axons. These basic data were used to derive the myelin sheath thickness [28]. Axonal counts were performed using the Cavalieri 3.0 macros (G. MacDonald, Virginia Merril Bloedel Hearing Research Center, University of Washington, Seattle, WA).

III. Results

A. General Observations

The four different kinds of containment systems tested were Kwik-Cast, a simple Gore-Tex sheet wrapped around the nerve, self-sizing spiral cuffs, and custom-built silicone cuffs that were molded to the shape of the array in the nerve. Kwik-Cast was only used in one animal; it was difficult to apply around the nerve in a uniform fashion and it seemed to partially interpose between the array and the nerve. Because the Gore-Tex used in two animals was relatively loose around the nerve and because of its flexible nature, connective tissue growth inside as well as outside of the cuff was extensive and, as will be seen later, stimulation thresholds and recordings were not stable over long periods of time.

Self-sizing cuffs work better in terms of keeping the array in the nerve but since the inner diameter of the cuff was defined by the diameter of the nerve and the array at the implantation site, there were big pockets for connective tissue growth proximally and distally within the cuff and the cuff could easily slide along the nerve and away from the implantation site. We tried to prevent this by suturing the cuff to the nerve proximally. However,

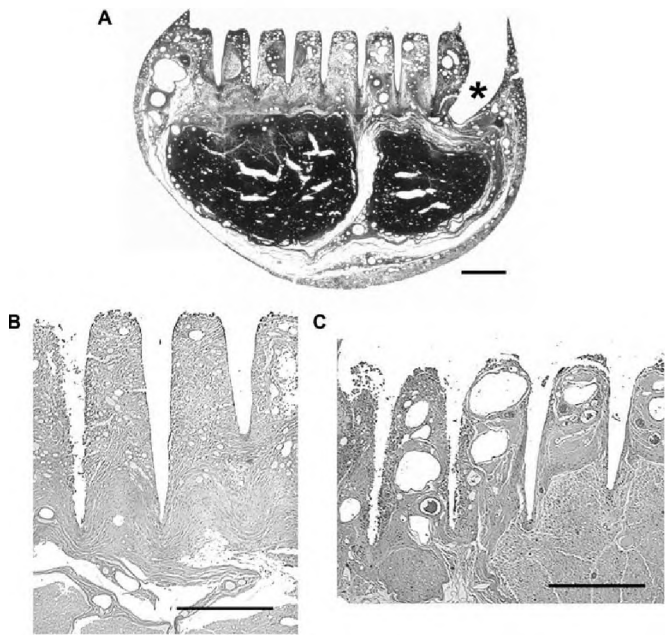

Fig. 3. Light microscopic pictures of cat sciatic nerve cross sections illustrating incomplete insertions of electrode arrays. The section thickness was 1 μm. The bars are 0.5 mm long. (a) A spiral cuff was used as a containment system. This particular row of electrodes does not reach the fascicles. The cuff seems to have pulled the array out of the nerve ("*" region where the spiral cuff penetrated the nerve). (b), (c) "Round" silicone custom cuffs were used. The connective tissue could reach a thickness of 1.5 mm and be heavily vascularized.

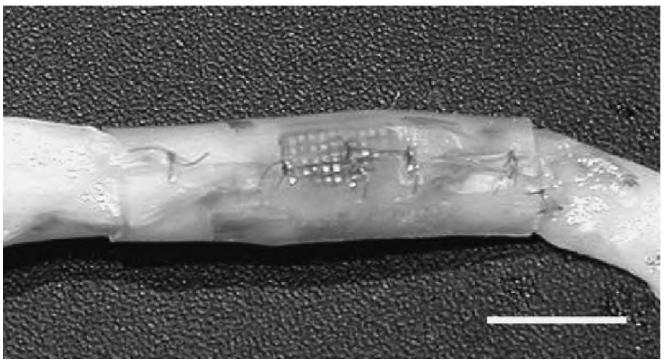

Fig. 4. Photograph of cat sciatic nerve implant with an "oval" custom containment system. The bar is 5 mm long.

that limited the self-sizing capabilities of the cuff. In addition, the inner end of the cuff easily got caught under the base of the array, which did sometimes partially pull the array out of the nerve [Fig. 3(a)]. Consequently, spiral cuffs were not used in the functioning implants.

The most effective containment system used was the custom-made silicone cuff. The round cuffs left too much room for connective tissue to grow between the array and the nerve and the connective tissue layer reached a thickness of 0.5–1.5 mm [Fig. 3(b), (c)] and was sometimes highly vascularized. The later version of this cuff could easily be placed around the nerve; it did not leave much room for connective tissue growth and could not slide along the nerve if it fit well to the nerve (Fig. 4).

In summary, all different containment systems developed some connective tissue ingrowth after a few weeks and all electrode arrays stayed within the nerve cuff but the electrodes

TABLE I
SUMMARY OF THE ANIMALS' WALKING BEHAVIOR ON THE TREADMILL AFTER SURGERY (SEE SECTION II FOR CLASSIFICATION OF WALKING DEFICIT)

Animal # - Implant #	Containment	Week after surgery									Duration (weeks)
		1	2	3	4	5	6	7	8	>9	
1+	GoreTex	-†	-	-	-	1	1	1	1	1	10
2+	GoreTex	2	2	1	1	1	-	-	-	-	14
3*	KwikCast/Round	1	2	3	3	2	2	1	1	1	11
4	Round	2	3	3	2	1	1	1	1	1	17
5-1	Round	1	1	1	1	1	1	1	1	1	18
5-2	Round	1	1	1	1	1	1	1	1	1	14
6-1	Round	1	2	1	1	1	1	1	1	1	24
7*	Round/Spiral	2	1	2	2	2	2	2	2	2	9
6-2	Spiral	1	1	1	1						5
8	Spiral	1	1	1	1	1	1	1	1	1	16
8	Oval	1	1	1	1	1	1				7
9+	Oval	1	1	1	1	1	1	1	1	1	31
10+	Oval	1	1	1	1	1	1	1	1	1	10
11+	Oval	1	1	1	1	1	1	1	1	1	26
12+	Oval	1	1	1	1	1	1	1	1	1	20
13+	Oval	1	1	1	1	1	1	1	1	1	24

+ Fully functional implants
* Two arrays were implanted in the same nerve.
† No measurements were taken.

themselves did not necessarily remain in the nerve and its fascicles. This macroscopic and histological evaluation of the implant systems gave an indication of the extent of the tissue response as a result of array implantation and the success of the containment system to hold the array in position.

Behavioral tests were conducted to analyze gross nerve damage that might be manifest in walking impairment after implantation. Each cat's ability to walk on a treadmill was monitored one to two times a week and placed in one of four categories (see Section II). Two cats showed substantial walking impairment for up to a month after surgery (Table I). One had two electrode arrays implanted in the same nerve and the other developed a strong inflammatory response in the leg; the reason for this is unknown. The other cats showed little or no walking deficit on the treadmill and any deficit disappeared within 2–3 weeks after implantation. These results were independent of the containment system used.

B. Stimulation

In functioning implants, we analyzed which muscle groups could be stimulated, what currents were required to evoke a muscle twitch and what sensory information could be recorded for each electrode. The animals were subdivided into three different groups based on the techniques used to fix the connector on the back and the cuffs used around the sciatic nerve. For part

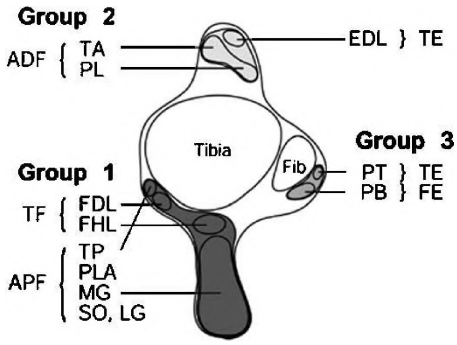

Fig. 5. Drawing of a cross-section of the cat hindlimb just above the ankle joint. Muscle groups and their tendons (seen in figure) are divided into three groups based on their location (shades of gray) and further subdivided by the kind of movement produced (abbreviation). The following muscle groups are listed: Extensor and flexor digitorum longus (EDL, FDL), flexor hallucis longus (FHL), lateral and medial gastrocnemius (LG, MG), peroneus brevis, longus and tertius (PB, PL, PT), plantaris (PLA), soleus (SO), tibialis anterior and posterior (TA, TP). Movement categories: ADF, APF, FE, TE, and TF.

of this analysis: 1) the connectors were sutured into the skin and heavy silk sutures were put through holes in the spinal process and the iliac crest and a GoreTex sheet was put around the nerve (two animals), 2) the same connector fixation as the first group but the oval shaped custom silicone cuff was put around the nerve (two animals), and 3) the connectors were rigidly attached to the iliac crest with bone screws and the oval shaped custom silicone cuff was put around the nerve (three animals). Because the connectors were not secured to bone in the first four animals, lead wires frequently broke and one animal lost both connectors overnight after 2 1/2 mo. Connector problems this severe only occurred in one animal (Animal #10) where the connectors were rigidly fixed to the iliac crest. The reason for this failure after 4 mo is not known.

The muscles that were excited through stimulation of sciatic nerve were organized in three different groups based on the location of the muscle tendons around the ankle (groups 1, 2, and 3) (Fig. 5). Within these groups muscles were further subdivided by the movement produced [ankle dorsiflexion (ADF), ankle plantarflexion (APF), toe extension (TE), toe flexion (TF), and foot extension (FE)]. We used both criteria, direction of movement and tendon location, to establish which muscle was stimulated; however, in awake animals location of the tendon was easier to determine. In Fig. 5 and in the following stimulation maps (Fig. 6), groups are indicated by different shades of gray and the corresponding number; the letter abbreviations specify a subsection of a group organized by the movement produced. If a movement could not be assigned to one group alone, the two groups involved were noted by both numbers and an intermediate shade of gray.

As was already seen in a previous publication [6], maps showing the target muscles and stimulation threshold can be generated for each measurement day. Each row in the stimulation maps indicated a row of equal-length electrodes. The data for the shortest and most proximal electrodes are shown at the top of the graph. These stimulation maps were compared at different times to analyze potential movement or changes of the electrodes with respect to the nerve fibers. In most cases, axons targeting similar muscle groups had the

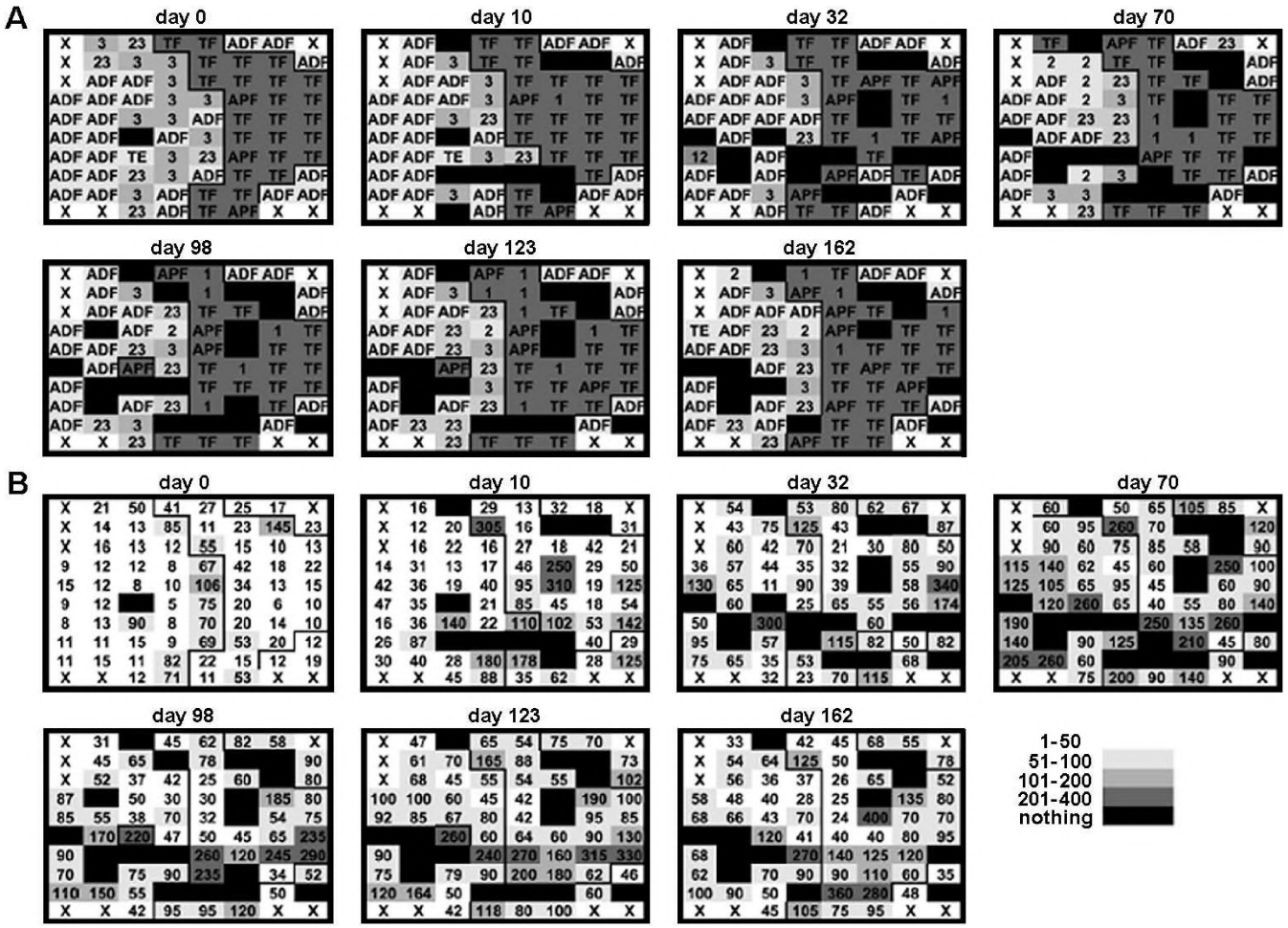

Fig. 6. Functional stimulation maps of the USEA implanted in sciatic nerve and monitored at different times after implantation. The presumed boundaries between fascicles are indicated by black lines. An X indicates electrodes that were not connected, a black square indicates electrodes that do not produce a movement. Shortest and most proximal electrodes are on the top row of the figures and most distal electrodes on the bottom row. (a) Map of muscles activated at threshold by each electrode of the USEA. (b) Single biphasic pulse, twitch current thresholds for each electrode in μA.

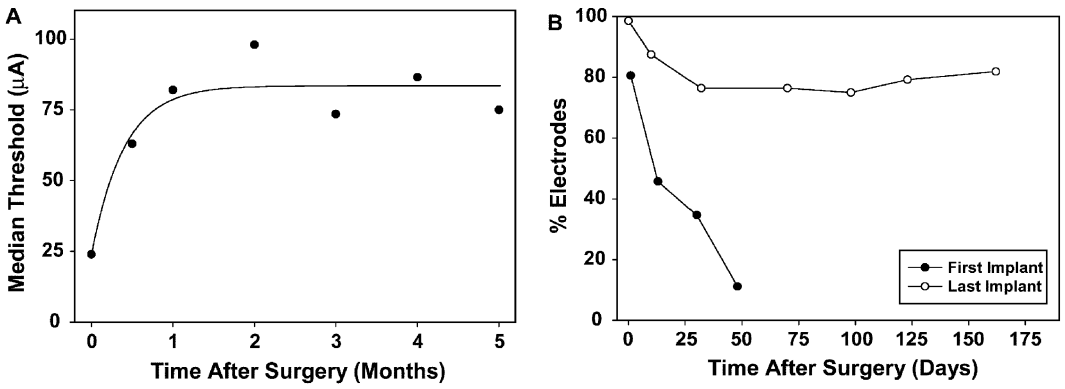

Fig. 7. Summary of the stimulation data of seven implants. a) Median stimulation threshold over time and (b) percentage of electrodes in the first and last implant that can produce a muscle twitch over time. In (a) the data was only plotted for the first 5 months because only two animals were left with active electrodes afterwards.

tendency to run together in the nerve [Fig. 6(a)], potentially in the same fascicle. The motor nerve fibers were divided into two major groups of fascicles (a line was drawn between them in Fig. 6): 1) the fascicles of the tibial nerve fibers (APF and TF; muscle group 1 in Fig. 5) and 2) the fascicles of the common peroneal nerve fibers (mainly ADF, TE and FE; muscle groups 2 and 3). Each group might contain more than one fascicle but the classification scheme used did not allow us to make that distinction.

For the majority of animals, the most substantial changes took place during the first 1 to 3 weeks after implantation likely due to nerve damage and/or degeneration and other tissue responses such as connective tissue growth. Thus, there was poor stability in terms of what muscles could be stimulated and especially

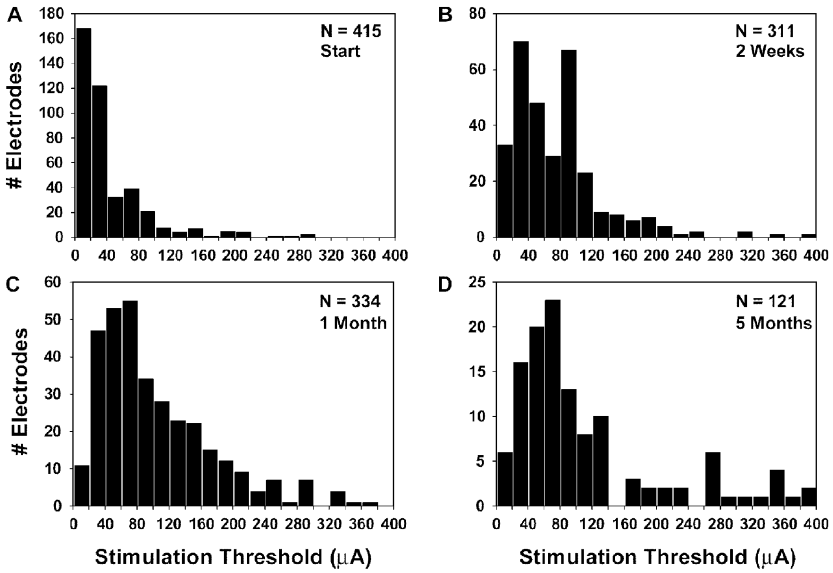

Fig. 8. Histograms of stimulation thresholds at different times after implantation: (a) the surgery day, (b) 2 weeks, (c) 1 month, and (d) 5 months after implantation. The data was taken from all seven implanted animals. The total number of electrodes available for analysis is indicated in the upper right corner of each graph.

TABLE II
SUMMARY OF FUNCTIONING CHRONIC IMPLANTS

Animal	1	2	9	10	11	12	13
Containment	GoreTex	GoreTex	oval	oval	oval	oval	oval
Attachment	skin	skin	skin	skin	iliac	iliac	iliac
# Electrodes	72	72	72	72	65	72	72
Duration (days)	48	98	220	59	138	100	98
	% Electrodes						
Start	81	79	68	83	85	90	99
0.5 Months	46	54	60	96	43	89	88
1 Month	35	68	92	43	69	88	76
2 Months	11	49*	49*	47	78	85	76
3 Months	–	25	43	–**	55	88	75
4 Months	–	–	40	–	57	65	79
5 Months	–	–	–	–	40*	50	82
6 Months	–	–	35	–	46	–	–
7 Months	–	–	26	–	–	–	–
	Median Stimulation Threshold (μA)						
Start	25	22	13	20	75	27	15
0.5 Months	32	73	38	93	160	63	35
1 Month	110	65	89	170	165	52	60
2 Months	100	120	40	273	157	60	90
3 Months	–	178	47	–	183	55	68
4 Months	–	–	80	–	195	63	80
5 Months	–	–	–	–	183	70	66
6 Months	–	–	65	–	163	–	–
7 Months	–	–	57	–	–	–	–

– Cat had been sacrificed
* One connector failed (up to 36 electrodes)
** Two connectors failed (up to 72 electrodes)

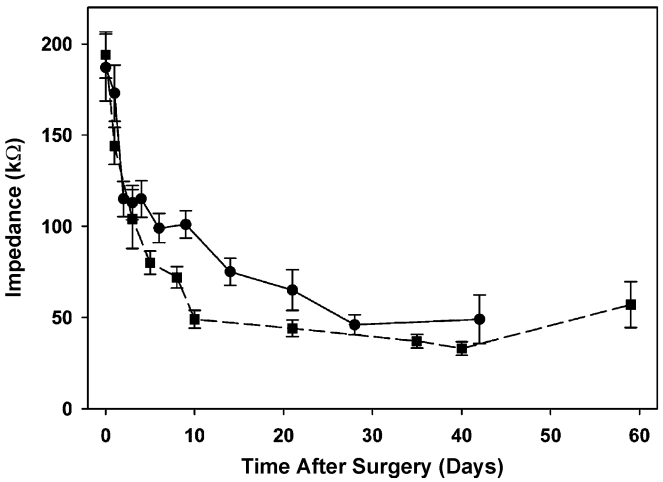

Fig. 9. Average electrode impedance over time for two animals (with standard error of mean).

what currents were required for threshold stimulation in some animals (not shown here). The stimulation maps suggest that the location of the electrodes within the nerve stabilized after 3–6 weeks mainly due to completion of connective tissue growth that holds the array in place. The maps did not show a clear trend of electrode movement. If the electrodes had slowly moved out of the nerve due to connective tissue proliferation between the array base and the nerve, shorter electrodes would have failed first and the longer electrodes would have stimulated the same muscles as the shorter ones did earlier but in general this was not seen. Electrodes failed randomly not dependent on length or position and stimulation of the shortest electrodes could often still evoke muscle twitches [Fig. 6(a)]. Stimulation thresholds for these short electrodes were also between 50 and 100 μA indicating that the electrode tips were still located in close proximity to motor fibers [Fig. 6(b)]. In agreement with previous experiments [6], stimulation thresholds at the edge or between presumed fascicles had a tendency to be higher than within fiber groups producing similar motor activity.

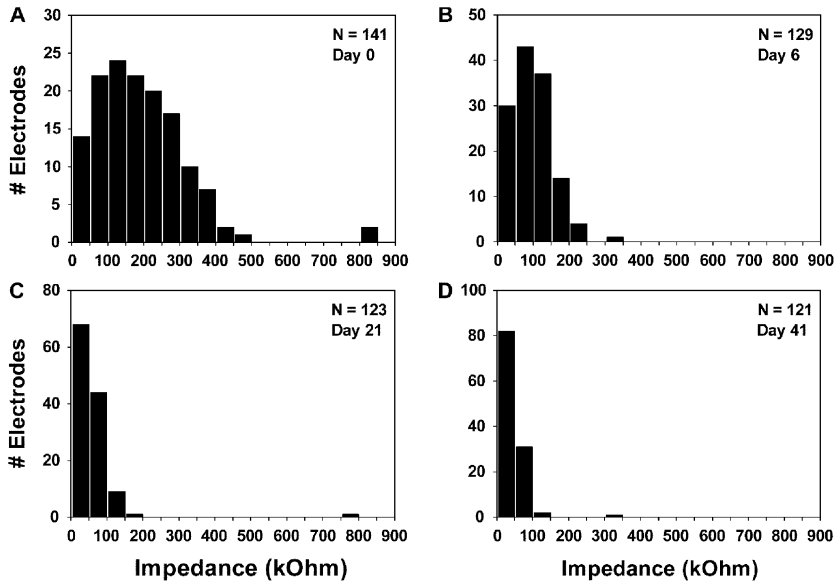

Fig. 10. Histograms of electrode impedances at different times after implantation: (a) the surgery day, (b) 6 days, (c) 21 days, and (d) 41 days after implantation. The data were taken from two implanted animals. The total number of electrodes available for analysis is indicated in the upper right corner of each graph.

The median stimulation threshold increased by a factor of 3.5 within the first month [Fig. 7(a)] and changed less drastically thereafter. Median threshold values were chosen to summarize the data because the threshold distribution was not symmetrical as seen in Fig. 8. Some electrodes' thresholds were very stable over time, but changing numbers of electrodes influenced the median threshold values and there was a large variability between animals (Table II). Histograms of the stimulation threshold values of all electrodes in all seven implants were plotted immediately, 2 weeks, 1 mo, and 5 mo after implantation (Fig. 8). Initially, most stimulation thresholds were in the 1–40 μA range. The threshold distribution broadened and shifted toward higher values shortly after implantation and changed little thereafter. It should be noted that stimulation thresholds in excess of 400 μA were not measured in these experiments. There were only small differences between groups of animals implanted using different containment systems or connector fixation techniques in terms of stimulation thresholds (Table II). During the first 2 mo when most electrodes were active, there was no statistical difference between the "skin/GoreTex" and "iliac/oval" groups [One-way analysis of variance (ANOVA), $p < 0.05$].

Not counting electrodes lost due to wire breakage or connector loss, we were still able to stimulate motor fibers using low stimulation currents (mostly under 100 μA) in 50% of the electrodes after 7 months in our longest running animal (Animal #9, Table II). In the animal with the greatest percentage of surviving electrodes (Animal #13), 82% of all electrodes (59 electrodes) were still able to evoke motor responses after 162 days with 70% (49 electrodes) evoking the original movement [Fig. 6 and 7(b)]. This represents an improvement over the first implant were most electrodes failed three months after implantation [Fig. 7(b)]. Although one connector attached to the iliac crest did fail after about 4 months (Animal #11, Table II), there still is a significant difference in the number of electrodes lost over time between animals with different connector fixation techniques (One-way ANOVA, $p < 0.05$) with iliac crest fixation being superior to skin fixation. The results of one implant (Animal #11) were fairly variable and slowly degraded over time and visual inspection of the array after explantation showed that many electrodes were broken at the tip.

C. Recording

Recording using the electrodes in the array was not as successful as stimulation and data were only taken from the first five implants. On average 8% of the electrodes could record single unit activity during the first few days after implantation. Individual single units could sometimes be recorded for several weeks but in general the recording stability was poor in these experiments. Recording of neural activity was usually not possible for more than a month after implantation.

The electrode impedance can be influenced by chemical or physical changes of the recording surface. We observed a rapid drop of the electrode impedances within the first couple of weeks after implantation (Fig. 9) but we did not do an in-depth analysis of the surface of the electrodes' tips after the array was removed from the tissue. The distribution of electrode impedances taken from two animals was broad on the surgery day with values ranging from less than 50 up to 500 kΩ (Fig. 10). Six days after implantation electrode impedances had already dropped in half, three weeks after implantation most impedances were below 100 kΩ and they settled down around 50 kΩ.

Whereas nervous and muscle activity around the sciatic nerve are not an issue for stimulation, recordings can be seriously influenced if the electrodes and the reference electrode are not well shielded from this activity. In most cases, we attempted to place the reference electrode within the containment system surrounding the electrode array but they frequently did not stay

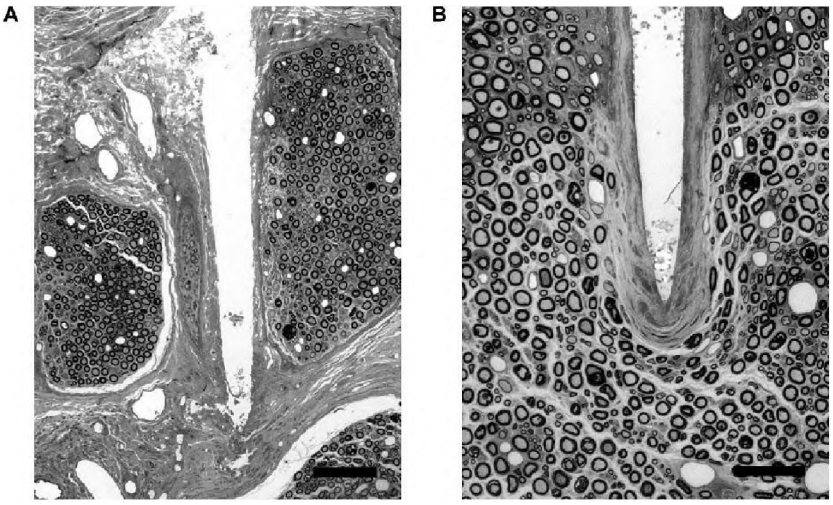

Fig. 11. Light microscopic pictures of a cross section of the same cat sciatic nerve. (a) One electrode misses the nerve's fascicles. The bar is 100 μm long. (b) Another electrode tip is inside a fascicle and close to viable neurons. The bar is 50 μm long.

there. Although some single units could be recorded in anesthetized animals, EMG activity and other noise contamination were so large when the animals were freely moving on the treadmill that the signal was not easily detectable. However, neuronal spikes have a higher frequency content than the noise contamination. Most signal contamination can be removed using appropriate filtering and single units can be revealed but this is difficult to implement online.

D. Histology and General Observations After Explantation

At the time of sacrifice, a visual inspection and histological analysis were performed on all implanted functioning implants. There did not appear to be any large displacements of the array, the containment system and the nerve in all cases from their original implant positions but connective tissue around the containment system and the condition of the electrode arrays varied. Later experiments showed considerably less tissue response than earlier implants possibly due to the use of the custom cast containment system. Some electrode arrays had a lot of broken electrodes whereas the majority did not have any broken electrodes; this most likely was influenced by the quality of implantation. Surprisingly, even electrodes with broken tips sometimes had good stimulation properties. In five earlier implants, the thickness of the connective tissue between the base of array and the epineurium was 436.7 $\pm$ 62.3 μm (Mean $\pm$ Standard Error) whereas its thickness from the electrode shanks to the nerve fibers was only 30.4 $\pm$ 3.8 μm (mean $\pm$ standard error). This means that some of the shorter electrodes did not reach inside the fascicles after a few months. Other electrodes were implanted between fascicles [Fig. 11(a)]. In general, however, the electrodes were still located inside the nerve and its fascicles [Fig. 11(b) and 12]. There were signs of neuronal degeneration in some implants, characterized by reduction of the cross-sectional area of the axoplasm, while the cross-section of the myelin either remains constant or increases [29]. However, viable neurons could oftentimes be found around the electrode tips [Fig. 13(a)].

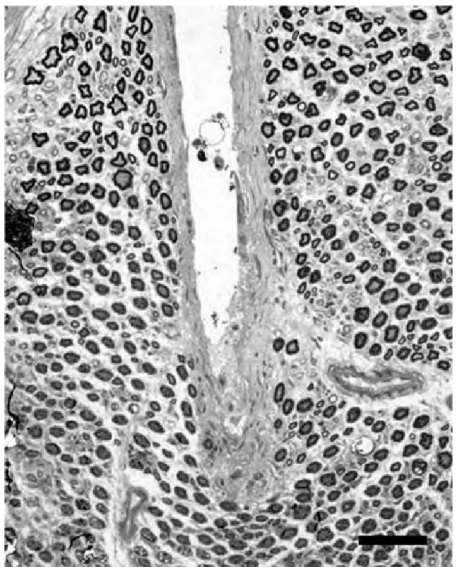

Fig. 12. Light microscopic picture of a cross section of cat sciatic nerve. Many viable neurons can be seen in close opposition with an electrode. The bar is 50 μm long.

Transverse semithin sections studied under light microscopy showed that the density and the estimated total number of myelinated fibers were similar in unimplanted control nerves and nerves from nonfunctioning and functioning implants (Table III). Axonal fibers with an abnormally thin myelin sheath (Hypomyelinated fibers) and axonal degeneration were rarely observed beneath nonstimulated electrodes, although it was consistently seen in fibers after chronic stimulation (Fig. 13). The histogram distribution of axonal diameters and the scatter plots of the myelin area versus axonal area are shown in Fig. 14. There were an increasing number of thinly myelinated axons (approximately 12% of the fibers) especially close to the electrode tracks in stimulated arrays that probably represent axons attempting to regenerate its distal segment after mechanical or electrical trauma.

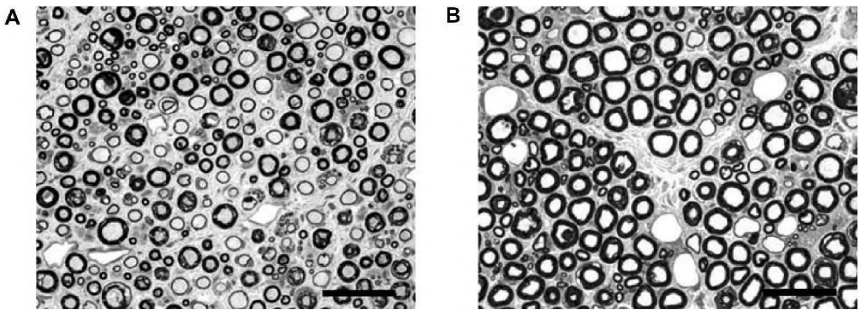

Fig. 13. Light microscopic picture of cross sections of nerve fibers (a) in a radius of 400–500 μm around stimulated electrodes and (b) about 2 cm proximal to the implant site. Regenerating fibers can be seen in the section close to stimulated electrodes. The bars are 40 μm long.

TABLE III
PROPORTION OF HYPOMYELINATED AXONS AND AXONS UNDERGOING AXONAL DEGENERATION AFTER ELECTRICAL STIMULATION OF SCIATIC NERVE. "CLOSE TO" REPRESENTS A RADIUS OF 400–500 μm AROUND THE ELECTRODES AND "FAR FROM" REPRESENTS THE PERIPHERY OF THE NERVE

	Density of myelinated fibers (/mm^2) [1]	Percentage of hypomyelinated fibers	Percentage of degenerated fibers
Unimplanted nerves	7747 ± 822	0.2%	0.5%
Non-functioning arrays	7880 ± 693	3.46%	0.52%
Stimulated arrays			
Close to electrode tracks	7875 ± 710	11.95%	4.55%
Far from electrode tracks	7548 ± 549	3.40%	9.90%

[1] Mean ± Standard Error

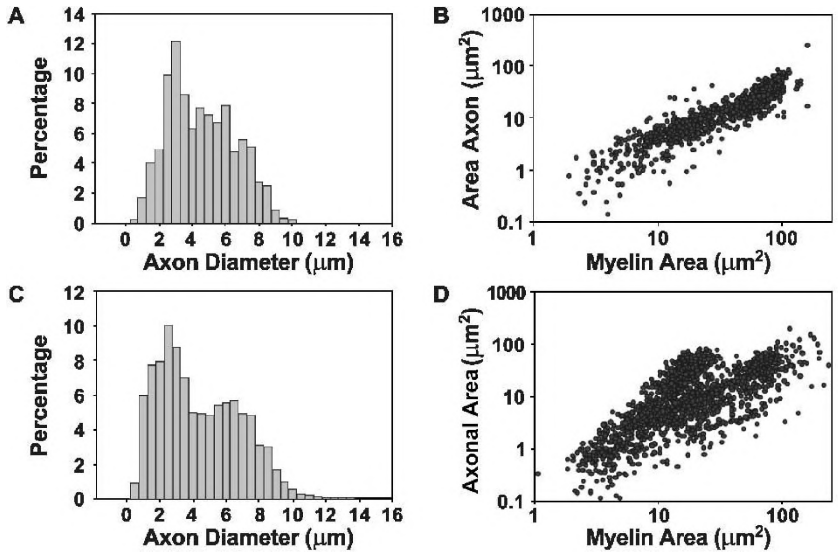

Fig. 14. Comparison of nerve morphology in a control (a), (b) versus an implanted nerve (c), (d). (a), (c) Histogram distribution of axonal diameters. (b), (d) Scatter plots of myelin area versus axonal area.

IV. DISCUSSION

A general motor neuroprosthesis will use electrical stimulation to produce movement and sensory feedback signals to control the movement. For such a device to be useful, it has to be safe for the neural tissue and able to stimulate synergistic muscle groups selectively and consistently on a chronic basis. The feedback signal has to be easily analyzable and the kind of information that is encoded on each recording channel should be stable over time. The device should also be durable. In the present study we tested the USEA for its stimulation and recording properties over the time course of 4–7 mo post implant.

We demonstrated that the USEA can be implanted into peripheral nerve on a chronic basis and that selective stimulation of motor fibers can be performed over long periods of time. Improvements such as the fixation of the connectors on the iliac crest greatly helped to maintain the integrity of the lead wires from the connector to the array. We have shown that a con-

tainment system that surrounds the array and the nerve with a design that incorporates the shape of the array in the nerve reduced connective tissue growth around the electrodes and their surroundings.

After recovery from surgery, the animals did not behaviorally react to the presence of the connectors on the iliac crest or the array in the nerve; even when monitoring cables were plugged into the connectors and measurements were taken. Whereas stimulation thresholds did consistently increase within the first few weeks, they often remained constant after the first month; only a few electrodes through which a muscle twitch could be evoked were lost after the first month. We believe that some axonal degeneration has taken place by this time but the damage to the nerve is not extensive enough to visibly affect the animal's movement or behavior. This was confirmed by the fact that the density of myelinated fibers was normal around the implanted electrodes with about 10% of the fibers regenerating. Because of the significant difference in the number of electrodes lost over time between animals with different connector fixation techniques and because electrodes do fail at random locations or, occasionally, by the entire set of electrodes connected to one connector, the loss of electrodes is most likely due to lead breakage or connector failure.

Smaller, lower aspect ratio and safer connectors will become available with improvements in micromaching techniques in the future and more flexible, permeable and/or potentially partially dissolvable containment systems can be implemented in the future to further improve the stability of the system. Even though there was variability in the stimulation response, changes were seldom drastic and there were generally multiple electrodes that could be used to evoke a particular muscle movement. In contrast to most techniques, this could potentially enable us not only to stimulate muscles selectively, but to do so in a fatigue resistant manner by interleaving stimulation between several electrodes as suggested by others [30] and provide us with backup electrodes if others should fail. Previously, it was shown in acute experiments that muscle selectivity could be maintained for stimulation currents slightly above threshold level for most electrodes [6]. At higher current, agonist but not antagonist muscles were sometimes co-activated.

In terms of a neuroprosthetic application, the stimulation results shown here are encouraging, but the same is not true for recording of sensory activity. Neural recordings were either contaminated with noise such as EMG activity or could not be picked up at all after a few days. Three factors can influence the quality of recordings: 1) the distance of the recording surface to the sensory fibers; 2) the electrode impedance; and 3) the magnitude of the recorded noise in relation to the desired signal. The distance of the electrode tip to the recorded fibers is negatively influenced by the formation of connective tissue around the shaft of the electrodes; the greater the fibrotic buildup, the smaller will be the recorded signal. The increase in stimulation thresholds suggests that a formation of connective tissue or degeneration of nerve fibers around the electrode tips took place within the first month after implantation. In contrast to the connective tissue growth that would normally result in an electrode impedance increase [31], the electrode impedances dropped in the weeks after implantation. This suggests physical changes on the electrode surface that might have been due to the fact that currents were passed through the electrodes for stimulation but this was not studied here.

Recorded signals can be recovered with digital filtering techniques but the number of recorded units was generally not satisfactory. Better electrical shielding of the nerve and coating the electrode shanks with an agent designed to minimize tissue reaction might improve results but recording sensory activity from a different location, such as the dorsal root ganglia, holds more promise. The cell bodies of sensory nerve fibers, which produce larger electrical activity, are located there and the site is better protected from sources of signal contamination such as large muscles. Acute experiments have shown that sensory signals can be recorded in the DRG with very high yields and with large signal-to-noise ratios [32].

In summary, whereas many problems related to the electrode interface and its chronic implantation have yet to be solved, this study shows that the long-term implantation of a penetrating microelectrode array in peripheral nerve is possible. While the time frame of our chronic study (5 to 31 weeks) did not allow studying very long-term consequences of array implantation, the study does provide "proof-of-concept" that there can be very little permanent nerve damage. Peripheral nerve interfaces of similar design can mediate stable and selective chronic activation of several different muscle groups. Devices of this architecture may provide an effective neural interface for various motor neuroprosthetic applications.

ACKNOWLEDGMENT

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REFERENCES

[1] M. B. Bunge, "Bridging areas of injury in the spinal cord," *Neuroscientist*, vol. 7, pp. 325–339, 2001.

[2] L. L. Jones, M. Oudega, M. B. Bunge, and M. H. Tuszynski, "Neurotrophic factors, cellular bridges and gene therapy for spinal cord injury," *J. Physiol.*, vol. 533, pp. 83–89, 2001.

[3] W. M. Grill, "Electrical activation of spinal neural circuits: application to motor-system neural prostheses," *Neuromodulation*, vol. 3, pp. 97–106, 2000.

[4] V. K. Mushahwar, D. F. Collins, and A. Prochazka, "Spinal cord microstimulation generates functional limb movements in chronically implanted cats," *Exp. Neurol.*, vol. 163, pp. 422–429, 2000.

[5] B. J. Woodford, R. R. Carter, D. McCreery, L. A. Bullara, and W. F. Agnew, "Histopathologic and physiologic effects of chronic implantation of microelectrodes in sacral spinal cord of the cat," *J. Neuropathol. Exp. Neurol.*, vol. 55, pp. 982–991, 1996.

[6] A. Branner, R. B. Stein, and R. A. Normann, "Selective stimulation of cat sciatic nerve using an array of varying-length microelectrodes," *J. Neurophysiol.*, vol. 85, pp. 1585–1594, 2001.

[7] A. Q. Choi, J. K. Cavanaugh, and D. M. Durand, "Selectivity of multiple-contact nerve cuff electrodes: a simulation analysis," *IEEE Trans. Biomed. Eng.*, vol. 48, pp. 165–172, Feb. 2001.

[8] M. A. Crampon, M. Sawan, V. Brailovski, and F. Trochu, "New easy to install nerve cuff electrode using shape memory alloy armature," *Artif. Organs*, vol. 23, pp. 392–395, 1999.

[9] W. M. Grill and J. T. Mortimer, "Stability of the input-output properties of chronically implanted multiple contact nerve cuff stimulating electrodes," *IEEE Trans. Rehabil. Eng.*, vol. 6, pp. 364–373, Dec. 1998.

[10] G. T. Kovacs, C. W. Storment, M. Halks Miller, C. R. Belczynski Jr., C. C. Della Santina, E. R. Lewis, and N. I. Maluf, "Silicon-substrate microelectrode arrays for parallel recording of neural activity in peripheral and cranial nerves," *IEEE Trans. Biomed. Eng.*, vol. 41, pp. 567–577, June 1994.

[11] F. J. Rodriguez, D. Ceballos, M. Schuttler, A. Valero, E. Valderrama, T. Stieglitz, and X. Navarro, "Polyimide cuff electrodes for peripheral nerve stimulation," *J. Neurosci. Methods*, vol. 98, pp. 105–118, 2000.
[12] J. Rozman and M. Trlep, "Multielectrode spiral cuff for selective stimulation of nerve fibers," *J. Med. Eng. Technol.*, vol. 16, pp. 194–203, 1992.
[13] P. J. Slot, P. Selmar, A. Rasmussen, and T. Sinkjaer, "Effect of long-term implanted nerve cuff electrodes on the electrophysiological properties of human sensory nerves," *Artif. Organs*, vol. 21, pp. 207–209, 1997.
[14] J. P. Smit, W. L. Rutten, and H. B. Boom, "Endoneural selective stimulating using wire-microelectrode arrays," *IEEE Trans. Rehabil. Eng.*, vol. 7, pp. 399–412, Dec. 1999.
[15] K. D. Strange and J. A. Hoffer, "Restoration of use of paralyzed limb muscles using sensory nerve signals for state control of FES-assisted walking," *IEEE Trans. Rehabil. Eng.*, vol. 7, pp. 289–300, Sept. 1999.
[16] J. S. Walter, P. Griffith, J. Sweeney, V. Scarpine, M. Bidnar, J. McLane, and C. Robinson, "Multielectrode nerve cuff stimulation of the median nerve produces selective movements in a raccoon animal model," *J. Spinal Cord Med.*, vol. 20, pp. 233–243, 1997.
[17] K. Yoshida and K. Horch, "Closed-loop control of ankle position using muscle afferent feedback with functional neuromuscular stimulation," *IEEE Trans. Biomed. Eng.*, vol. 43, pp. 167–176, Feb. 1996.
[18] T. Cameron, T. L. Liinamaa, G. E. Loeb, and F. J. Richmond, "Long-term biocompatibility of a miniature stimulator implanted in feline hind limb muscles," *IEEE Trans. Biomed. Eng.*, vol. 45, pp. 1024–1035, Aug. 1998.
[19] G. E. Loeb, C. J. Zamin, J. H. Schulman, and P. R. Troyk, "Injectable microstimulator for functional electrical stimulation," *Med. Biol. Eng. Comput.*, vol. 29, pp. Ns13–Ns19, 1991.
[20] B. Ziaie, M. D. Nardin, A. R. Coghlan, and K. Najafi, "A single-channel implantable microstimulator for functional neuromuscular stimulation," *IEEE Trans. Biomed. Eng.*, vol. 44, pp. 909–920, Oct. 1997.
[21] C. T. Nordhausen, E. M. Maynard, and R. A. Normann, "Single unit recording capabilities of a 100 microelectrode array," *Brain Res.*, vol. 726, pp. 129–140, 1996.
[22] P. J. Rousche and R. A. Normann, "Chronic intracortical microstimulation (ICMS) of cat sensory cortex using the Utah intracortical electrode array," *IEEE Trans. Rehabil. Eng.*, vol. 7, pp. 56–68, Mar. 1999.
[23] A. Branner and R. A. Normann, "A multielectrode array for intrafascicular recording and stimulation in sciatic nerve of cats," *Brain Res. Bull.*, vol. 51, pp. 293–306, 2000.
[24] P. J. Rousche and R. A. Normann, "A method for pneumatically inserting an array of penetrating electrodes into cortical tissue," *Ann. Biomed. Eng.*, vol. 20, pp. 413–422, 1992.
[25] J. A. Hoffer, G. E. Loeb, and C. A. Pratt, "Single unit conduction velocities from averaged nerve cuff electrode records in freely moving cats," *J. Neurosci. Methods*, vol. 4, pp. 211–225, 1981.
[26] M. Haugland, "A flexible method for fabrication of nerve cuff electrodes," in *Proc. 18th Annu. Int. Conf. IEEE Engineering in Medicine and Biology Society*, vol. 42, 1996, pp. 2.2.3–2.2.10.
[27] V. K. Mushahwar and K. W. Horch, "Selective activation of muscle groups in the feline hindlimb through electrical microstimulation of the ventral lumbo-sacral spinal cord," *IEEE Trans. Rehab. Eng.*, vol. 8, pp. 11–21, Mar. 2000.
[28] E. Fernandez, N. Cuenca, and J. De Juan, "A useful programme in BASIC for axonal morphometry with introduction of new cytoskeletal parameters," *J. Neurosci. Methods*, vol. 39, pp. 271–289, 1991.
[29] W. F. Agnew and D. B. McCreery, "Considerations for safety with chronically implanted nerve electrodes," *Epilepsia*, vol. 31, pp. S27–S32, 1990.
[30] K. Yoshida and K. Horch, "Reduced fatigue in electrically stimulated muscle using dual channel intrafascicular electrodes with interleaved stimulation," *Ann. Biomed. Eng.*, vol. 21, pp. 709–714, 1993.
[31] R. B. Stein, D. Charles, T. Gordon, J. A. Hoffer, and J. Jhamandas, "Impedance properties of metal electrodes for chronic recording from mammalian nerves," *IEEE Trans. Biomed. Eng.*, vol. BME-25, pp. 532–537, 1978.
[32] Y. Aoyagi, R. B. Stein, A. Branner, and R. A. Normann, "Single unit recording capabilities from dorsal root ganglia using a multielectrode array," *Soc. Neurosci. Abstr.*, vol. 27, 2001, Program no. 392.15.

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Yoichiro Aoyagi, photograph and biography not available at the time of publication.

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