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Cuff electrodes for chronic stimulation and recording of peripheral nerve activity

G.E. Loeb *, R.A. Peck

Bio-Medical Engineering Unit, Queen's University, Kingston, Ontario K7L 3N6, Canada

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Abstract

A comparative study of 5 different designs of nerve cuff electrodes was undertaken to determine their relative merits for stimulating and recording whole-nerve activity over extended periods of chronic implantation on large and small peripheral nerves in 8 cats. Four of the designs represent novel fabrication strategies, including 2 based on flexible, thin-film substrates and 2 based on dip-coating silicone elastomer on a cylindrical mandrel. Various advantages and shortcomings of these materials and designs are discussed in the context of the biophysical factors that influence these electrophysiological interfaces, particularly the problem of recording microvolt-level neurograms in the presence of millivolt-level electromyograms from adjacent muscles in freely behaving subjects. The most effective design was one in which a thin sheath of silicone rubber was wrapped around and intra-operatively sealed to a longitudinally slit, tripolar cuff made by dip-coating silicone over stranded stainless steel leads that were prepositioned on a mandrel using polyvinyl alcohol as a temporary adhesive. When properly installed, these electrodes had stable impedances, recruitment thresholds and relatively interference-free recording properties for the duration of this study (up to 9 weeks).

Keywords: Nerve cuff electrode; Electrical stimulation; Chronic recording; Neurogram; Electrophysiology; Silicone rubber

1. Introduction

Many physiological studies involve electrical interfaces with peripheral nerves to produce controlled electrical activation of particular populations of nerve fibers and to monitor spontaneous and evoked neural activity. The classical method used in acute studies on anesthetized or surgically reduced preparations is to dissect a length of the nerve (either in continuity or as a cut end), suspend it onto one or more hook-shaped wire electrodes and elevate it into a pool of nonconductive fluid (usually paraffin or mineral oil). The electrical signals are thus confined within the conductive tissues comprising the nerve trunk and isolated from surrounding tissues. The required surgical exposure and fluid pool are difficult to achieve in many preparations, particularly with short or deeply located nerves or in multiple sites in different parts of the body. The technique is obviously unsuitable for use when the preparation is moving or when repeated stimulation or measurements are needed over a long period. For such applications, physiologists have turned increasingly to nerve cuff electrodes, in which the electrode contacts are carried on the inside walls of a cylindrical polymeric sheath that can be wrapped around the nerve to approximate the biophysical relationships of the oil pool (Stein et al., 1977; Barone et al., 1979; Sauter et al., 1983). In some cases, relatively large numbers of contacts provide multiple recording and stimulation sites that can be used to determine conduction velocity (Hoffer et al., 1981a), track nerve regeneration (Krarup and Loeb, 1988), or improve selectivity of stimulation (Veraart et al., 1993).

Several basic approaches to fabrication have been described. These include stitching wires into the side walls of commercially available silicone rubber tubing (Loeb et al., 1980), wrapping wires around the nerve and molding them in situ with dental impression compound (Julien and Rossignol, 1982), threading an open spiral assembly with molded wire contacts around the nerve (McCreery et al., 1992), laminating foil contacts between prestressed sheets of silicone rubber to form a self-wrapping spiral cylinder (Naples et al., 1988), and using photolithographic metallization and machining to produce a thin-film pattern on a flexible polymeric substrate (van der Puije et al., 1993).

* Corresponding author: Abramsky Hall, Queen's University, Kingston, ONT K7L 3N6, Canada. Tel.: (613) 545-2790; Fax: (613) 545-6802; E-mail: LOEB@BIOMED.QUEENSU.CA.

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Many of these techniques are suitable for relatively large nerves (e.g., 3 mm diameter sciatic nerve of the cat) but are difficult to scale down for use with small, delicate nerves (e.g., 0.5–1 mm diameter individual muscle and cutaneous nerve branches). In this report we review the design factors that impact on the performance of such electrodes in various applications and we describe several different designs and their problems and limitations. We present a novel design and fabrication process that has achieved excellent results in a particularly demanding, chronic application.

2. Requirements

2.1. Design principles for recording

(1) In order to record the highest level of signal from a nerve inside the cuff electrode, it is necessary that the nerve be confined in a closely fitting cylindrical space with non-conductive walls and a length about 3 times the space constant of the axons (Marks and Loeb, 1976).

(2) In order to exclude extrinsic signals from sources such as muscle outside of the cuff electrode, it is necessary to distribute tripolar contacts that are equidistant from each other within a close-fitting space that is uniform in cross-sectional area along its length and that has no breaks along its side-walls (Stein et al., 1977).

(3) The electrical impedance of all contacts should be low and similar. This reduces susceptibility to noise pick-up, improves rejection of common mode noise in differential amplifiers, and facilitates the use of transformer coupling to provide noise-free pre-amplification (Stein et al., 1978).

(4) Connective tissue will always cover all exposed surfaces of a biocompatible foreign body and will track along surfaces until it meets more connective tissue. If no provision is made to accommodate the additional volume of this connective tissue and some postoperative edema in the enclosed space, the pressure will cut off the blood supply and kill the nerve (Naples et al., 1990).

(5) Biocompatibility of a material has two components: (i) chemical — the material must not release toxic ions or compounds into the surrounding fluid or tissue; (ii) mechanical — the material must not present textures or edges that will cut adjacent tissue or excessive bulk or stiffness that will crush it.

(6) Any device that must be installed on delicate, relatively inaccessible structures by a surgeon under sterile operating conditions must be simple to manipulate and fool-proof to install correctly. Electrical signals routed to and from the device must be conveyed by ultraflexible, biocompatible leads that slide freely through the tissue to avoid tethering the device and applying mechanical tension onto the nerve.

(7) Any device that is expected to be produced commercially must be reliably manufacturable using simple, robust and repeatable processes.

2.2. Design principles for stimulation

In addition to the above-noted general mechanical and biocompatibility issues, the following additional considerations apply for electrical stimulation.

(1) The individual electrode contacts must have a sufficient surface area made from a suitable metal so that the charge-carrying capacity of reversible electrochemical processes is not exceeded during each phase of the stimulating waveform (Brummer et al., 1983).

(2) In order to recruit homogeneously all of the nerve fibers of a particular caliber, bipolar pairs of contacts should make nearly uniform circumferential contact with the nerve, with a longitudinal separation similar to the space constant of the target nerve fibers.

(3) In order to achieve selective stimulation of different sub-populations of axons or to produce unidirectional excitation of the nerve fiber, it may be desired to use multipolar contacts whose exact spacing along and around the nerve is critical (van den Honert and Mortimer, 1981; Fang and Mortimer, 1991; Grill and Mortimer, 1993; Veraart et al., 1993).

(4) Chronic application of stimulation voltages to metal electrodes tends to accelerate the ingress of fluid between the metal and the substrate or encapsulating polymers, placing greater demands on the adhesion between the two, particularly if the polymer is essential to the mechanical integrity of the electrode contact as with thin film materials.

3. Materials and methods

3.1. Electrode fabrication

Fig. 1 summarizes several different designs that we built and tested, each of which produces a similar topology: 10–15-mm-long cylindrical cuff with 3 circumferential contacts along the sidewalls and spaced at equal longitudinal intervals. In designs A and B, the contacts consisted of a photolithographically patterned thin film of sputtered platinum over titanium on a polyimide or polyesterimide substrate (van der Puije et al., 1993). A second layer of polymer was photolithographically fenestrated over the contacts and the solder pads that were located on a 30-mm-long ribbon-cable extension of the substrate, whose overall shape was also determined photolithographically. The 12-μm-thick subassembly handled like a thin but tough piece of cellophane. Conventional leads of Teflon-insulated stranded stainless steel were soldered to the pads and insulated with Silastic Medical Adhesive A (Dow Corning) to provide leads to the remote percutaneous connector (Hoffer et al., 1987); the junction

between leads and polymer ribbon cable was strain-relieved in situ by suturing to fascia adjacent to the nerve on which the cuff was installed. In design A, the section of the polymeric substrate carrying the contacts was laminated (GE silicone contact adhesive #PSA529) to a sheet of silicone rubber (Dow Corning Silastic MDX4-4210, 75–100 μm thick) that had precut windows where the contacts were to be located and that was prestretched along an axis perpendicular to the longitudinal axis of the nerve cuff. After the adhesive had cured and the assembly was cut free, the stress caused it to roll up on itself as shown in Fig. 1A. In design B, the self-spiralling roll was achieved by laminating one stretched sheet of silicone rubber to an unstretched sheet. The polymeric substrate was loose inside the roll, which held it wrapped around the nerve. For both of these designs, we experimented with various tabs and opening devices to reduce the difficulty of opening the tightly wrapped spiral for placement around the nerve in poorly accessible spaces such as the hamstring muscle recess in which the sciatic nerve resides. None of these was particularly successful mechanically and most tended to interfere with the ability of the cuff to seat itself snugly and securely around the nerve without provoking connective tissue proliferation around and into the cuff.

Design C in Fig. 1 is the conventional, hand-made nerve cuff that we have used for many years (Hoffer et al., 1987, 1981b; Pratt et al., 1991; Krarup and Loeb, 1988), which is commercially available from MicroProbe (Clarksburg, MD). A length of silicone rubber tubing is slit longitudinally and fitted with stranded stainless steel wire leads that are sewn into the side walls. The cuff is fitted with circumferential sutures that are tied over the nerve to close the opening slit. Comparative results described here are based on experience with 6 animals (3 cuffs in 1 leg of each animal) reported previously (Loeb, 1993).

Designs D and E in Fig. 1 are based on a molded

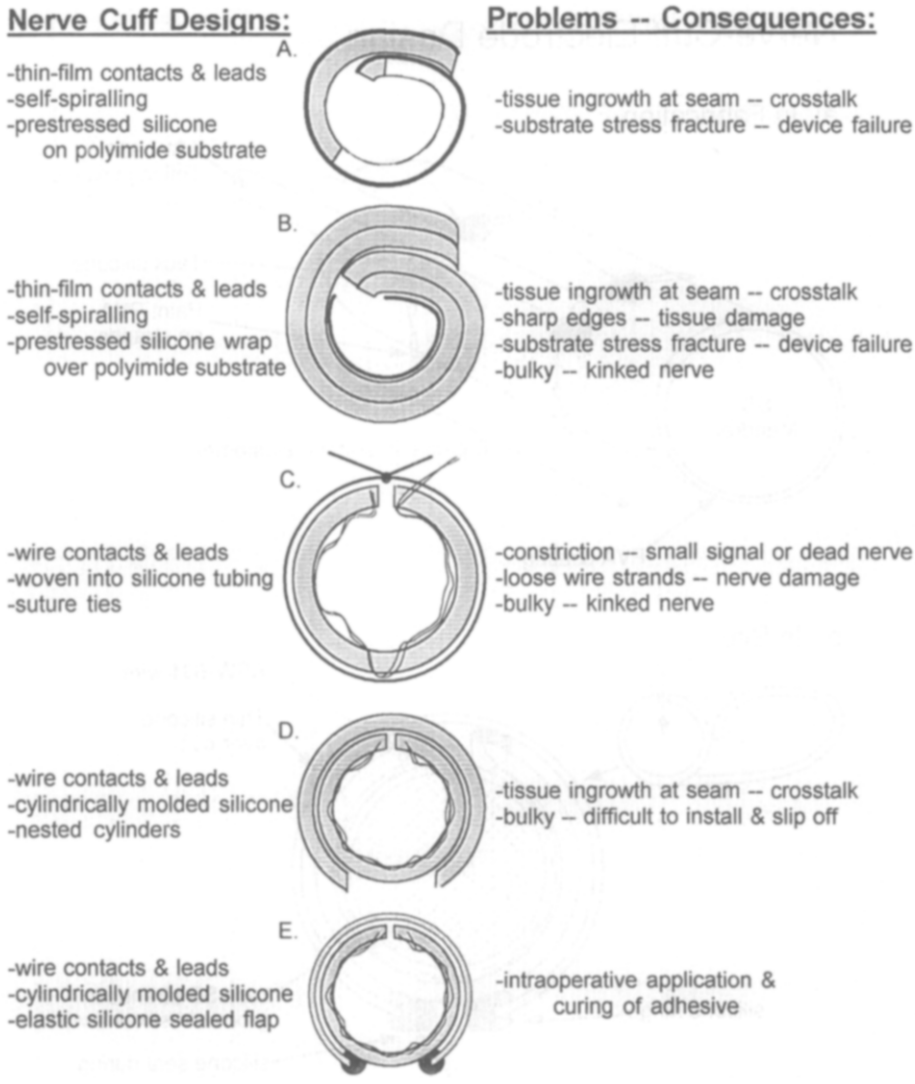

Fig. 1. Schematic cross-sectional designs of 5 different nerve cuffs based on thin-film substrates (thick black lines in A and B), woven wire in silicone tubing (C) and molded wire in silicone (D and E). Grey shading denotes silicone rubber; dotted area in (A) denotes fenestration to expose thin-film electrode contact.

cylinder constructed as shown in Fig. 2A. Individual leads were made from commercially available stranded stainless steel wire with a Teflon jacket (Cooner Wire AS-631). About 15 mm of insulation was stripped from the end of each wire and the bare strands were bent at a right angle to the insulated lead. The required number of leads were pre-assembled into a bundle by laying them out on a sheet of glass that was marked to show the desired contact spacing and overcoated with a thin layer of polvinyl alcohol (air-dried from 40% aqueous solution, PVA) to act as a mold release agent. Silicone elastomer (Dow Corning Silastic MDX-4-4210) was applied in small dabs (using a Portionaire Model PV-200VP pneumatic dispenser) along the shanks of the leads to bind them together with the correct spacing between contacts. After heat curing at 65°C for 5 min, the pre-assembled bundle of leads was tacked along the axis of a stainless steel mandrel (standard hypodermic tubing stock) whose outside diameter was equal to the desired inside diameter of the nerve cuff. The mandrel had circumferential score marks showing the desired contact positions and was similarly coated with PVA. The bare contacts were rolled completely around the mandrel and tacked with heat-cured Silastic. The excess lead length was folded back as shown in Fig. 2a and cut off close to the mandrel. A small amount of PVA was applied over the strands of the contacts on the mandrel, taking care to avoid covering the Silastic tacking. The entire mandrel assembly was dipped into uncured Silastic (may be thinned with toluene or heptane to achieve thinner cuff walls desirable for small diameter cuffs) and cured at 65°C for 1 h in a vertical position. The cuff was trimmed to length on the mandrel and a longitudinal slit was made between the ends of the contacts. The finished cuff was soaked in water to dissolve the PVA, permitting it to be removed from the mandrel.

In design D, the cuff electrode was closed by nesting it into a second cuff that was a similarly sized 'blank' of silicone rubber with no electrodes. In design E, the 'over-

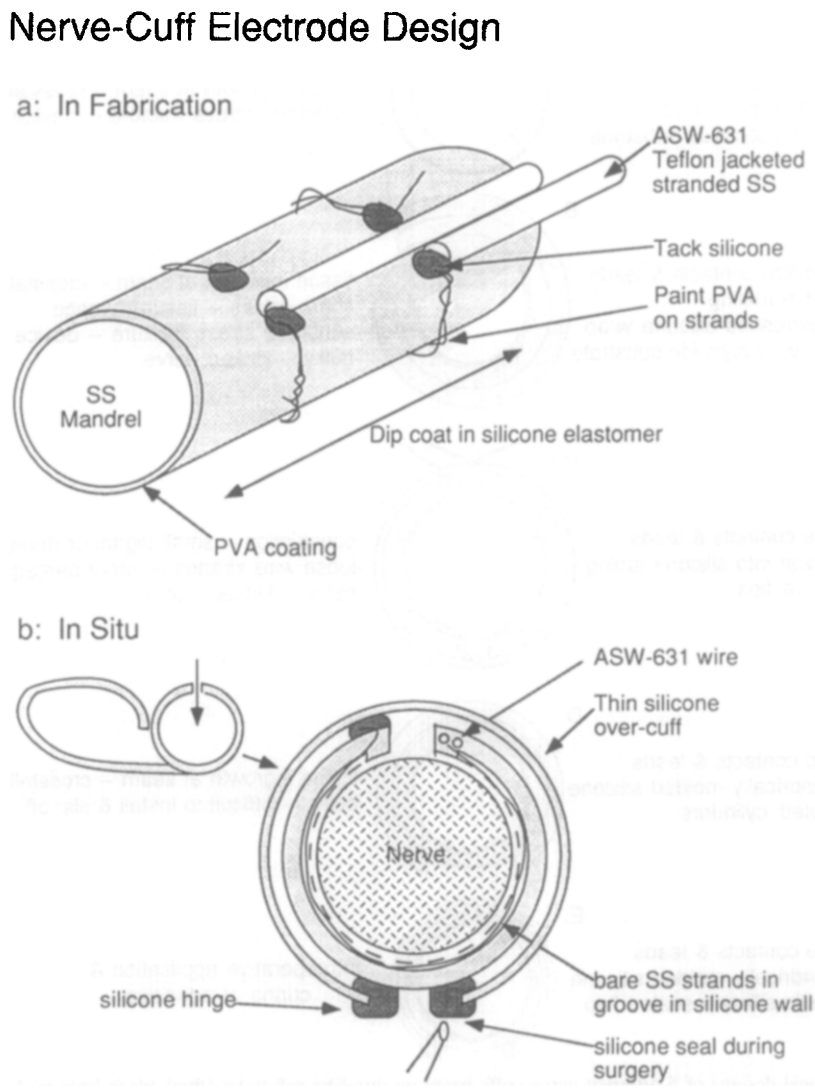

Fig. 2. A: Materials and fabrication sequence for molded cuff designs (D,E). SS, stainless steel; PVA, polyvinyl alcohol (see Section 2 for details). B: Surgical handling and in situ configuration of design (E).

cuff' was much thinner and attached to one edge of the cuff electrode, as shown in Fig. 2b. This overcuff was made by dip-coating thinned, uncured Silastic on a bare mandrel of the same or slightly larger diameter than the cuff mandrel and trimming and slitting after heat curing. The overcuff was set in place on the nerve cuff and a small bead of Silastic was applied along one edge to bind the two together. The overcuff could be displaced to one side to open the main cuff and then dropped back into place covering the slit after the nerve was inserted. In preliminary experiments, we found that it was necessary to seal the trailing edge of the over-cuff by applying a small bead of Silastic Medical Adhesive A during surgery to prevent eventual ingrowth of connective tissue along the longitudinal seam. Medical Adhesive A was autoclaved in its original dispensing tube and was loaded into the back end of a small, sterile syringe equipped with a fine needle for dispensing by hand under the operating microscope. It cured reliably within 1 h even in contact with body fluids.

3.2. *In vivo testing*

Eight young adult cats were each implanted in both hind legs with a 3-mm-diameter tripolar cuff on the common sciatic nerve, a 1-mm-diameter tripolar cuff on each of the sural and superficial peroneal nerves, and 6 bipolar epimysial electrodes on various muscles adjacent to the various nerve cuff sites. Two animals were used for each of designs A, B, D and E, for a total test of 48 cuffs (12 of each design). All leads were routed subcutaneously to a 40-pin back-pack connector described previously (Hoffer et al., 1987). Surgery was done under pentobarbital anesthesia, using aseptic conditions and prophylactic antibiotics. Postoperatively, monopolar electrical impedances from each of the electrode contacts were measured using a 1 μA, 1 kHz sine wave (Bak Electronics IMP-1 impedance tester, modified to provide a lower impedance range).

These animals required this particular set of implants to study the electromyogram (EMG) activity of various muscles during unrestrained behavior and in response to precisely controlled electrical stimulation of large diameter cutaneous afferents in the sural and superficial peroneal nerves. As young kittens (10–14 days old), each of these animals had undergone transfer of tendons between two small ankle muscles in one leg with a sham operation in the contralateral leg. The sciatic nerve cuffs were used to monitor the threshold and growth of evoked potentials at various latencies in response to current-regulated, symmetrically biphasic stimulation of the cutaneous nerves (0.1 ms/phase, 1–3 pps, delivered by A-M Systems Model 2100 transformer-isolated stimulus generator). Neurograms were pre-amplified by a transformer-coupled headstage (transformer step-up gain of 10 times differential amplifier gain of 10; Micro Probe, Model ADT-1) followed by an additional gain of 400 (1–10 kHz) before taping along with EMG signals on a 14-track FM tape recorder (10 kHz bandwidth). Thresholds and suprathreshold responses were quantified on-line by peristimulus averaging of 8 successive sweeps of the neurogram (Hitachi digitizing oscilloscope). EMG signals were differentially amplified (gain of 500–4000 depending on source; 50–5000 Hz bandwidth; Bak Electronics MDA-1 amplifier).

4. Results

Before coming to the preferred design E described in Figs. 1 and 2, we invested a substantial effort in the development of thin-film designs A and B (van der Puije et al., 1993). This approach was abandoned after encountering severe biocompatibility problems. Briefly, the relatively hard, stiff substrate material had to be made quite thin to flex adequately, resulting in sharp edges that evoked a severe foreign body reaction in adjacent tissue and that seemed to encourage connective tissue ingrowth along the longitudinal seam. Within a few days in vivo, both substrate materials (polyimide and polyesterimide) tended to develop stress cracks where they were flexed in tensile or compressive strain, usually resulting in broken leads. Interestingly, there was no loss of adhesion of the metallization at the edges of the crack nor was the tensile strength of the adjacent, unstressed portions of the substrate noticeably reduced; a similar failure in polyester films (Mylar) has been reported (Loeb et al., 1977). Finally, wafer fabrication processes severely limit the length of the thin film cable from the nerve cuff, requiring a relatively bulky

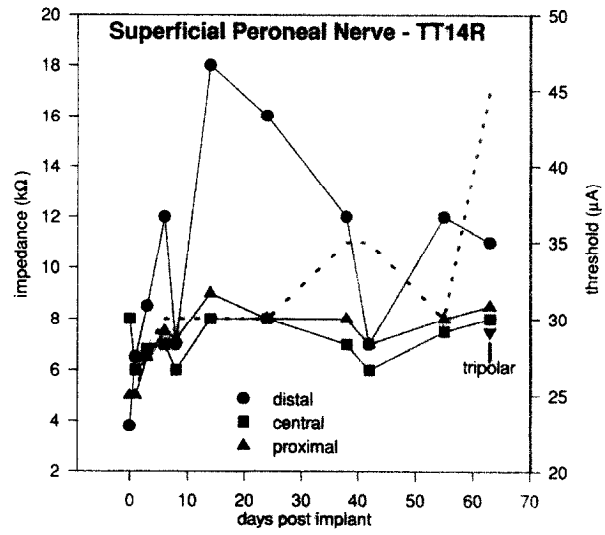

Fig. 3. Monopolar impedances (solid lines) vs. time for each of 3 contacts (symbols in key) in a tripolar cuff electrode (E) on the superficial peroneal nerve, measured at 1 kHz with respect to remote indifferent electrode; tripolar value indicates impedance of center with respect to distal and proximal end contacts in parallel. Dashed line (right abscissa) indicates threshold for eliciting just-detectable volley in the sciatic nerve cuff with biphasic, bipolar stimulation through the superficial peroneal nerve cuff (100 μs/phase, cathode-first on proximal contact, anode-first on central contact).

junction to conventional wire leads. The junction region had to be strain-relieved to nearby tissue (usually muscle), sometimes resulting in tethering damage to nerve and leads.

By contrast and as expected from previous experience, the molded wire and silicone rubber cuffs were easy to handle and install and performed reliably over the several weeks required in the present application. Fig. 3 shows impedances recorded over time from each contact of a 1-mm cuff of design E on the superficial peroneal nerve. The fluctuations immediately after implantation are consistent with the expected sequence in which trapped air bubbles are absorbed and replaced by fluid followed by loose connective tissue, while the nerve reacts to the surgical handling with edematous swelling followed by some resolution. Subsequent fluctuations such as shown for the distal contact in Fig. 3 may be associated with slight changes in the tightness of the encapsulating tissue that tends to invade the open ends of the cuff. At the ends of their periods of implantation, the impedances of all contacts in the 1-mm cuffs of design E had a mean impedance of 6.6 ± 2.3 (SD) kΩ. The impedances of all contacts in the 3-mm cuffs of design E were 1.7 ± 0.7 kΩ.

Fig. 4A,B shows the typical histological appearance of

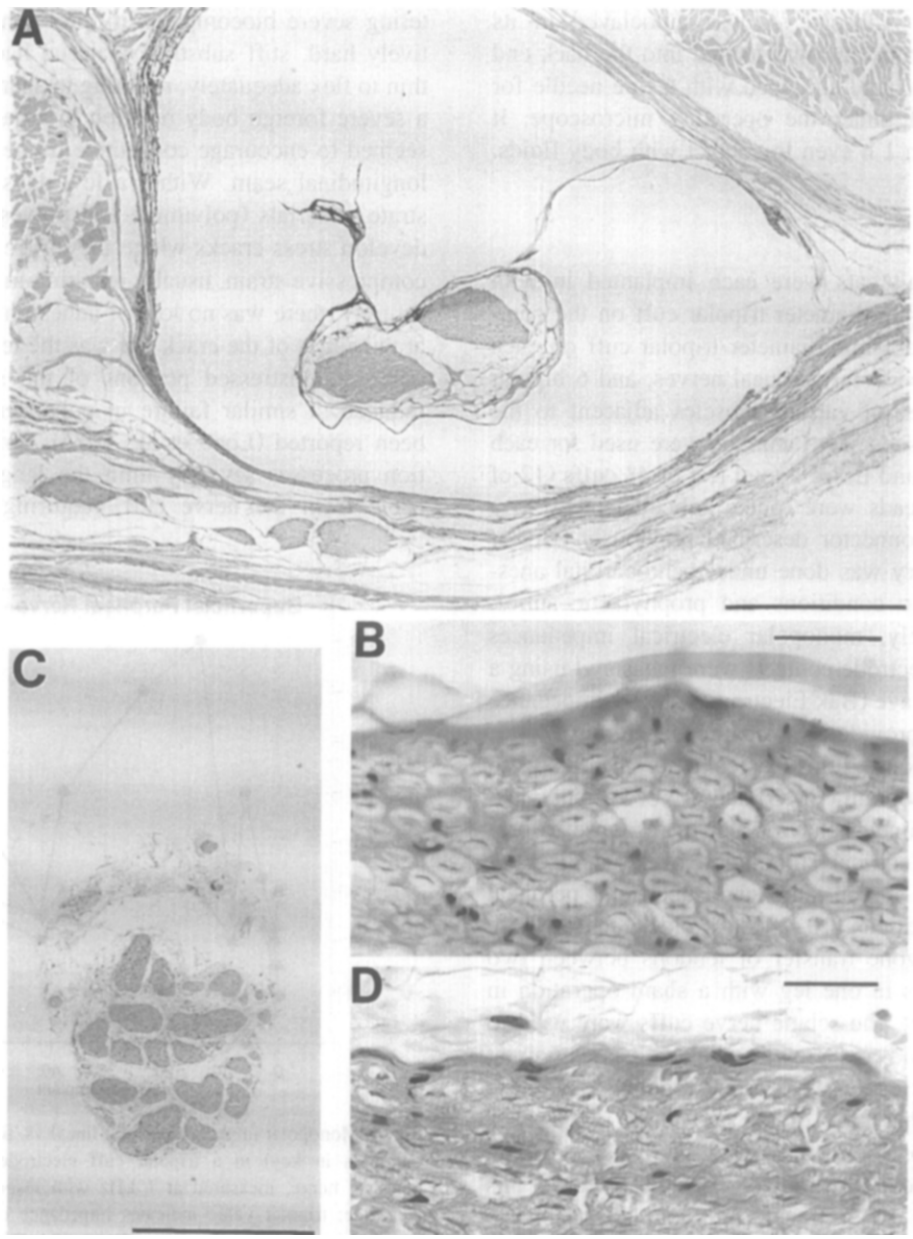

Fig. 4. Histological cross-sections of superifical peroneal nerves fixed by immersion in formalin, then embedded in paraffin and stained with hematoxylin and eosin. A,B: from within nerve cuff after 9 weeks. C,D: from control nerve in another cat (cut more obliquely). A: thin, organized connective tissue capsule around outside and inside surfaces of cuff, with tendrils extending into the seams between the two layers of silicone (which have fallen away from the section). Scale bars: (A,C) 500 μm; (B,D) 50 μm.

the superficial peroneal nerve and connective tissues within and around its nerve cuff, which is consistent with such a benign foreign body reaction in a longitudinally closed cylindrical space. Note the tendency for tendrils of connective tissue to form in the narrow spaces between the closely apposed silicone tubes where they are not actually glued together. A control superficial peroneal nerve from another animal (Fig. 4C,D) shows a different fascicular pattern but similarly thin perineurium with an absence of inflammatory cells.

4.1. Stimulation and monitoring of evoked potentials

The bilateral protocol of this experiment was designed specifically to test for and exclude differences in the electrical recruitment of cutaneous nerve fibers so that differences in the reflex pathways could be identified. All of the threshold current values were reasonably low (typically 20–50 μA), but the individual values tended to increase in the first week and to fluctuate randomly over subsequent weeks (Fig. 3, dashed line and right abscissa). This was likely due to differences in the sizes of the individual nerves (both initially and as a result of postoperative edema), thickness of connective tissue developed in the cuff and in the snugness of closure of the overlying cuff. The threshold should be related to the current density in the cuff, so all other things being equal, it should vary directly with the square of the actual inside diameter to which the cuff settled in situ. More importantly, the amplitude of the evoked potentials recorded in the sciatic nerve grew briskly and consistently as the stimulation intensity was increased in multiples above absolute threshold (Fig. 5, top) and was highly symmetrical between the two sides when normalized to the threshold recorded on any particular day.

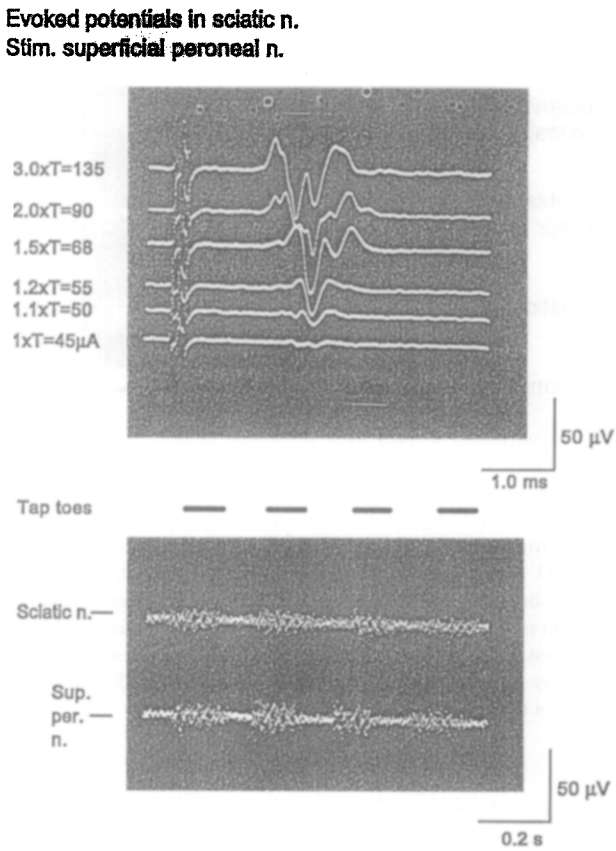

Fig. 5. Top: Series of evoked potentials recorded in the sciatic nerve cuff following stimulation at progressively higher levels via the superficial peroneal nerve cuff (same nerve, last day of testing from Fig. 3); each trace is a stimulus triggered average (artefact at left) of 8 presentations during treadmill locomotion; note shift to shorter latency for earliest components of the compound waveform at stimulus levels about 1.5 × T, which probably reflects proximal shift in point of spike initiation for largest diameter fibers. Bottom: Activity recorded from tripolar configurations in sciatic and superficial peroneal nerve cuffs for light taps to toes in recumbent, alert animal (same day as top).

4.2. Recording sensory activity

Perhaps the most sensitive test of the functional integrity of the nerve in the cuff is the ability to detect a brisk discharge within the multiunit 'hash' that can be heard on an audio monitor when light cutaneous stimuli are applied to the innervated region of the skin. Only the largest myelinated fibres, which are most susceptible to damage from compression and hypoxia, contribute action currents large enough to be so detected above noise without signal averaging. Such activity was consistently detectable in all nerve cuffs of design E (including the small cuffs on the cutaneous nerves and the large cuffs on the whole sciatic nerves) for the 2–9 week duration of their implantation (Fig. 5, bottom). It was lost in cuff designs A and B when electrical leads broke and in designs A, B and D when proliferating connective tissue opened the longitudinal seam, eventually creating a thick tongue of tissue that partially avulsed the nerve from the cylindrical space in some cases.

Perhaps the most sensitive test for the electrical integrity of the circumferential seal is the amplitude of the EMG cross-talk from active contraction of the adjacent muscles. In a perfect tripolar electrode (uniform cross-sectional area, completely closed cylinder, equidistant tripolar spacing of electrically identical contacts and infinite common-mode signal rejection in the pre-amplifier), the EMG cross-talk would be zero. While recording the cuff neurograms during unrestrained treadmill walking, we monitored the amplitude of the EMG in the muscles directly adjacent to the various nerves (Fig. 6). With a well-sealed cuff of design E, there was no EMG apparent in the nerve cuff signals when filtered with only a simple single-pole bandpass filter (1000–10000 kHz, 6 dB/octave). The actual values of the typical EMG signals were 100–1000 uV peak-to-peak outside the cuff and undetectable to 10 uV peak-to-peak inside the cuff, i.e., an attenuation factor of at least 10–100. In a few cases, the seal was not well-seated after surgery and the cuff was infiltrated later-

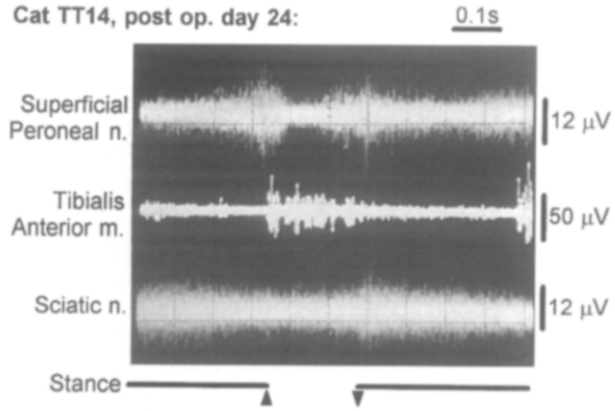

Fig. 6. Simultaneous records from superficial peroneal (top trace) and sciatic (bottom trace) nerve cuffs and an epimysial electrode on the adjacent tibialis anterior muscle (middle trace) during 1.5 cycles (bar at bottom) of treadmill locomotion. Transients in superficial peroneal neurogram occurring at footlift (↑) and footfall (↓) were modulated differently from EMG activity in tibialis anterior and all other nearby muscles. Whole sciatic nerve activity showed a smaller but consistent transient at footfall but more tonic activity during stance, probably reflecting the sum of cutaneous and proprioceptive activity from ankle extensors; a similar pattern was seen in both nerves during sustained dorsiflexion applied manually in the recumbent, alert cat.

ally by a tongue of connective tissue. This was immediately detectable by EMG cross-talk that was comparable to the amplitude of the neural hash but still could have been filtered out by high-roll-off, high-pass filters that transmit most of the much higher frequency neurogram signal while attenuating the lower frequency EMG. This problem seems to be stable for designs C and E when the intra-operative seals (sutures and adhesive, respectively) are not properly made. For designs A, B and D, the cross-talk tended to get progressively larger as the connective tissue bridge inexorably thickened, as revealed by correlating the recording quality with the postmortem examination of all of the cuff sites.

5. Discussion

Most of the devices of all designs worked sufficiently well for the first 3–5 postoperative days required for the limited purposes of this physiological study. They were then tracked at occasional intervals to identify the various long-term problems summarized in Fig. 1. The thin-film designs A and B failed rapidly because of the apparent unsuitability of the polyimide and polyesterimide materials for long-term use in vivo. More mechanically robust substrates such as Teflon are being explored by others (Cogan and Walter, personal communication) and might prevent gross lead breakage. However, all of the designs that relied on the apposition of surfaces under spring-like pressure to produce wedge-shaped seals seem to be susceptible to penetration by at least some connective tissue, as shown in Fig. 4. If the surfaces of the materials provoke only a thin foreign body encapsulation (e.g., silicone but not polyimide), then the cuff electrode may still be suitable for stimulation and perhaps even recording of large, synchronous evoked potentials. However, anything less than a perfect seal seriously degrades the recordability of asynchronous, naturally occurring activity in the face of extrinsic interference from naturally and electrically produced muscle activity. These problems will be particularly troublesome for attempts to use nerve cuff electrodes as sensors of skin contact or joint angle in neural prosthetic systems (Haugland and Hoffer, 1994; Haugland et al., 1994), in which microvolt levels of naturally occurring activity must be recorded for many years.

Design E described in this report represents a useful improvement over previously described designs because it provides a method of closure that can accommodate postoperative edema and connective tissue envelopment of the nerve without risking constriction or resorting to an excessively large caliber. The elastic flap thus retains one of the major advantages of self-spiralling designs (Naples et al., 1988) but in a form that is easier to build reliably and to handle intra-operatively, particularly for small sizes ($\leq$ 1 mm diameter). Most importantly for long-term recording applications, the seal can be topologically closed against the invasion of connective tissue, which defeats the common-mode rejection of cross-talk from extrinsic EMG sources. The recessed but cleanly exposed stranded-wire contacts in our design provide uniformly low contact impedances without risking dislodging of the wire strands during surgical handling. Loose strands projecting from the sidewall of cuffs made by stitching wires into preformed tubing tend to act like a garrote on the nerve in the cuff.

The method of manufacture still requires manual dexterity rather than offering the precise reproducibility of photolithographic fabrication, but the mandrel-based assembly and dip-coating greatly facilitated efficient production of multipolar cuff electrodes with sufficiently precise tolerances for our rather demanding applications. With no particular effort to automate any processes, a batch of 6 such electrodes required for one of our animals required 9 man-hours. The postassembly required to incorporate thin-film substrates with printed electrodes into a functional nerve cuff plus attachment of supplemental leads also required about 9 man-hours for a similar batch of six. The cost of materials for wire and silicone rubber electrodes is negligible ($< \$6$/electrode), whereas the cost of producing thin-film substrates tends to be dominated by the yield problems inherent in producing large footprint devices on silicon wafers (estimated at \$100–500/substrate depending on economies of scale).

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