"The Feasibility of a Cochlear Nucleus Auditory prosthesis based on microstimulation"

Contract No. NO1-DC-5-2105

QUARTERLY PROGRESS REPORT #3

JAN 1, - March 31, 1996

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

D.B. McCreery, Ph.D.
T.G.H. Yuen, Ph.D.
W.F. Agnew, Ph.D.
L.A. Bullara, B.S.

HOUSE EAR INSTITUTE
2100 WEST THIRD STREET
Los Angeles, California 90057

SUMMARY AND ABSTRACT

The overall goal of this contract is to develop an auditory prosthesis based on multisite microstimulation within the cochlear nucleus. One portion of this work is to develop arrays of microelectrodes that can be implanted with minimal injury to the nervous tissue. During the last quarter, we have been evaluating, in the cat model, the implantation of arrays of 3 long (4 mm) closely-spaced (400 μm), discrete, activated iridium microelectrodes. The length and spacing of the electrodes are comparable to those that can be implanted into the human cochlea nucleus with the aid of a tool inserted through the translabyrinthine surgical approach to the CP angle. The electrode described in this report were manufactured with very blunt tip (approximately 15 μm in diameter) and this modification has yielded encouraging results. Based on physiologic measurements and histologic analysis, none of the 15 blunt electrodes comprising the 5 arrays implanted into the posteroventral cochlear nucleus of 5 cats induced significant microhematomas during or subsequent to implantation.

We also examined the site of three microelectrodes with rather blunt, faceted tips which had been implanted in the posteroventral cochlear nucleus of cat cn91 for 16 months. Except for small glial scars directly beneath the sites of the microelectrode tips, the surrounding tissue and neural elements appeared to be normal. There was no indication of chronic inflammation or other reaction to the electrodes or to the Epoxylite insulation. The slender glial scars deep to the electrodes tips probably resulted from slight retraction of the electrodes during the 16 months in situ, due to traction on the cables as the cat's head continued to grow. The glial sheath surrounding the electrode tips remained quite thin (20 μm or less) and this is consistent with the continued low threshold (6 to 8 μA) of the electrical evoked response from these microelectrodes.

We are continuing our investigation of whether interleaved pulsing of closely-spaced microelectrodes can moderate the stimulation-induced depression of neuronal excitability (SIDNE) that develops during prolonged pulsing with microelectrodes at high frequency. The results from one cat (cn102) are consistent with our premise that the SIDNE reflects depression of the electrical excitability of neurons, rather than

depression in the efficacy of synapses. Thus, interleaved pulsing would be expected to reduce SIDNE only when the electrodes are close enough together so that the current fields overlap significantly. The SIDNE that results from excitation of neurons by the individual microelectrodes must be managed by other means.

METHODS

Fabrication of stimulating microelectrodes.

Activated iridium stimulating microelectrodes were fabricated from lengths of pure iridium wire 50 μm in diameter. A Teflon-insulated lead wire was welded to one end of the wire, and the other end was shaped to a conical taper, by electrolytic etching. The entire shaft and wire junction was then coated with 3 thin layers of Epoxylite 6001-50 electrode varnish. The insulation was removed from the tip by electrolytic destruction of the insulation, leaving an exposed surface area of approximately 500 μm^2 +/- 5%, as determined from the electrode's double layer capacitance. The individual electrodes were then assembled into an integrated array of 2 to 4 microelectrodes spaced 300 to 400 μm apart.. The integrated array, with its closely-spaced microelectrode shafts, was designed to approximate the dimensions of an array that can be implanted into the human posteroventral cochlear nucleus using a tool inserted through the translabyrinthine surgical approach to the CP angle. The shafts of the electrodes extend 4 mm beyond the array's superstructure. Electrodes of this length, or longer, will be required to reach into the human ventroposterior cochlear nucleus.

The iridium electrodes are then "activated" to increase their charge capacities. The electrodes were then soaked in deionized water for 120 hours, and sterilized with ethylene oxide.

Implantation of stimulating and recording electrodes

Young adult cats were anesthetized with Pentothal, with transition to a mixture of nitrous oxide and Halothane. Implantation of the electrodes was conducted using aseptic surgical technique. The cat's head was placed in a stereotaxic frame, and the skull was exposed as far back as the posterior fossa by reflecting the scalp and muscles. A pair of stainless steel recording electrodes, with their exposed tips (approximately 0.4 mm in length), and separated vertically by approximately 8 mm,

was inserted by stereotaxis into the right inferior colliculus through a small craniectomy. The deeper electrode was positioned just below the central nucleus of the colliculus, and the upper electrode was placed dorsal to the surface of the colliculus. The compound action potential induced by a train of clicks delivered to the left ear was used to position the recording electrodes. The introducers surrounding the electrodes were then retracted and the shafts of the electrodes were cemented to the skull by flooding the small craniectomy with methylmethacrylate.

A small craniectomy was made in the posterior fossa over the cerebellum, through which the integrated array of 2 or 3 iridium stimulating electrodes was inserted by stereotaxis into the left (and in one case, also into the right) posteroventral cochlear nucleus (pvcn). Since the feline cochlear nucleus lies on the lateral surface of the brainstem and the human cochlear nucleus is buried behind the middle cerebellar peduncle, the new feline array was inserted through a portion of the overlying cerebellar flocculus, so that we could evaluate electrodes whose length was appropriate for use in humans. The microelectrodes were positioned first by stereotaxic coordinates and the final positioning was achieved by observing the potential evoked in the inferior colliculus while stimulating with the microelectrode.

Stimulation protocols and data acquisition

At intervals after implantation, the recruitment curves of the evoked responses were recorded in the inferior colliculus. Stimulation and data acquisition was conducted using the two-way radiotelemetry stimulation and data acquisition system described previously (QPR # 4, Contract NO1-NS-2-2323). This telemetry system and its companion software allows continuous monitoring of the voltage waveform across the stimulating microelectrodes, and of the compound evoked potential induced in the inferior colliculus by the stimulating microelectrodes. The responses evoked by 1024 to 4096 consecutive charge-balanced, controlled-current stimulus pulses applied to the stimulating microelectrodes were averaged to obtain an averaged evoked compound action potential (AECAP). For each AECAP, the amplitude of the first or second

component was measured after the averaged response is filtered through a low-pass filter with a bandwidth of 250 to 2.5 kHz. The amplitude of the early and second components is measured from the peak of the positivity on the leading edge to the trough of the subsequent negativity. The response growth function (recruitment curve), which representing the recruitment of the excitable neural elements surrounding the microelectrode, is generated by plotting the amplitude of the first or second component of each of several AECAPs against the amplitude of the stimulus pulse .

In one cat (cn102) , the chronically implanted stimulating microelectrodes were pulsed continuously for 7 hrs per day using charge-balanced, symmetric, cathodic-first pulse pairs (150 μsec/phase) at a pulse repetition rate of 500 Hz. During the 7 hours of continuous stimulation, the interpulse potential of the iridium stimulating electrodes was held at an anodic bias of approximately 350 mV with respect to the implanted Ag/AgCl reference electrode, in order to increase their charge capacity (Beebe and Rose, 1988). During the 7- hour test stimulation, the amplitude of the 500 Hz pulse train was amplitude-modulated according to the envelope of a rectified and logarithmically-compressed "artificial voice" signal. This computer-generated artificial voice signal was developed by the International Telephony Consultive Convention (CCITT) for testing telecommunication equipment. The artificial voice reproduces many of the characteristics of real speech, including the long-term average spectrum, the short-term spectrum, the instantaneous amplitude distribution, the voiced and unvoiced structure of speech, and the syllabic envelope.

For histologic evaluations of the implant sites, the cats were deeply anesthetized with pentobarbital and perfused through the aorta with ½ strength Karnovsky's fixative (2.5% glutaraldehyde, 2% paraformaldehyde and 0.1M sodium cacodylate buffer). The cochlear nucleus and adjacent portion of the brainstem were resected, embedded in paraffin, sectioned serially in the frontal plane (approximately parallel to the shafts of the stimulating microelectrodes) at a thickness of 8 μm, and stained with Cresol Violet (Nissl stain) or with hematoxylin and eosin.

RESULTS

I. RESULTS WITH BLUNT-TIPPED IRIDIUM ELECTRODES

We have been evaluating methods of reducing tissue injury caused by insertion of arrays of discrete iridium microelectrodes into the ventral cochlear nucleus. In our cat model, the results with blunt-tipped microelectrodes have been very encouraging. These electrodes terminate in a conical taper to a final diameter of 12-15 μm at the very tip. This tip size was selected because it is comparable to that of the smallest venules and arterioles in the brain. We hypothesized that the blunter tips would push the small blood vessels aside during implantation, rather than piercing or severing these vessels. Electrodes with sharp tips (3-6 μm in diameter) easily pierced through the glial limitans overlying the human cochlear nucleus but have yielded a high incidence of interstitial hematomas when implanted into the cat ventral cochlear nucleus (QPR #1).

In the current series, 5 arrays of 3 microelectrodes (15 probes in all) were implanted chronically into 5 young adult cats. Four arrays (12 probes) whre impalnted during the 3rd quarter of the contract period (cn107, cn108, cn109, cn110.) Two weeks after implantation, the threshold of the evoked response recorded in the inferior colliculus was 6-8 μA for all 12 electrodes, indicating that neurons very close to the tips were healthy and functional. One array of 3 electrodes (cn111) was implanted after the end of the quarter, and at 7 days after implantation, all three electrodes are functioning well, with evoked response thresholds below 6 μA.

By 18 days after implantation, the threshold of the evoked response from 2 of the 3 electrodes in cat CN-110 had increased markedly. Figure 1 shows the recruitment (growth) of the second component of the AECAP evoked from 2 of the stimulating microelectrodes and recorded in the contralateral inferior colliculus. Electrode 3 continued to function well, but the recruitment curve of the response from Electrode 2 became very flattened near threshold, and the threshold of the response from electrode 2 exceeded 24 microamps . The animal was therefore sacrificed and a histologic analysis of the implant sites was conducted. The histologic evaluation

showed that the array had been inserted deep into the posteroventral cochlear nucleus and that 2 of the 3 electrodes had begun to protrude through the ventral surface of the nucleus. Although this animal was sacrificed sooner than we had planned, it did provide an opportunity to examine the sites of the blunt-tipped microelectrodes at an early stage (18 days after implantation). Figure 2 shows the site of the tip of the one microelectrode that did remain completely within the PVCN. There was some accumulation of lymphocytes and/or loosely consolidated glial cells near the tip, due to the relatively short period of implantation. However, the neurons and other tissues surrounding the tip appear to be healthy. No hematomas were found anywhere within the cochlear nucleus. This is especially encouraging in light of the fact that during the implant surgery, the array was inserted 3 times into the cochlear nucleus in order to obtain a good evoked response in the inferior colliculus.

Figures 3A and 3B show the recruitment curves of the AECAPs evoked by 3 blunt-tipped microelectrodes implanted into another cat (CN-107). The data were acquired 15 and 70 days after implantation. The threshold of the evoked response remained quite stable over the 55-day interval. The slight increase in the threshold (from 5 to 6 μA at day 15, to 6 or 7 μA at day 70) and the accompanying linearization of the growth of the recruitment curve probably reflects the formation of a thin sheath of connective tissue around the site of the tips.

These results with the blunt-tipped microelectrodes are very encouraging. The problem encountered in cat CN-110 illustrates one relatively minor problem attendant to the used of the blunt-tipped probes in the cat cochlear nucleus; namely, that they cause the cochlear nucleus to be displaced somewhat as the electrodes are being inserted. This would not be a problem in the human cochlear nucleus which is embedded in the anterolateral wall of the pons. The cat cochlear nucleus is a pendulous structure on the lateral aspect of the brainstem and is therefore easily displaced by pressure on its dorsal surface. Recently, we have determined that these blunt microelectrodes will penetrate into unfixed human brainstem, if the velocity of insertion is relatively high (approximately 5 cm/sec). These studies will be described in

detail in the next Quarterly Progress Report.

II. HISTOLOGIC EVALUATION OF LONG-TERM IMPLANTS (CAT CN-91).

Cat CN-91 was sacrificed 16 months after implantation of 3 activated iridium stimulating electrodes into the posteroventral cochlear nucleus. The tips of these electrodes had been beveled into ellipsoidal facets set at an angle of approximately 45° relative to the long axis of the shafts. In general, our experience with these electrodes has been quite good, although they are rather difficult to manufacture (particularly when the electrode shafts are several millimeters in length, as is necessary for electrodes intended for implantation into the human cochlear nucleus). The leading edge of the facet is rounded and quite blunt, and this may have been fortuitous in view of our good results with the blunter conical tips, as described above.

Figure 4A-4C are photomicrographs of the sites of the 3 electrode tips. Figure 4A is an oblique section that shows the lowermost 200 μm of the track of electrode 1. The sheath surrounding the electrode track is rather poorly defined but is at most 15 μm in thickness. The neurons near the tip are surrounded by thin haloes (probably artifacts of fixation) but otherwise appear to be normal. A tear in the tissue just to the left of the tip probably occurred when the electrode was withdrawn from the fixed tissue.

Figure 4B shows the site of the tip of Electrode #2 near the medial margin of the posteroventral cochlear nucleus and within 250 μm of the middle cerebellar peduncle. The track, which is 500 μm in width, is lined by a sheath of connective tissue up to 20 μm in thickness. Several glial cells have become incorporated into the small scar below the site of the tip. Neurons near the tip are surrounded by thin haloes but otherwise appear to be normal. There is no hemorrhage or inflammation in the surrounding tissue.

Figure 4C shows an oblique section through nearly 1,000 μm of the track of Electrode #3. This microelectrode was in the extreme posterior margin of the PVCN

near the boundary of the dorsal cochlear nucleus, and this probably accounts for the low amplitude of the evoked response (see below). The track is lined with a sheath of compact connective tissue, 5 to 10 μm in thickness. Neurons adjacent to the tip appear normal, and there is no evidence of inflammation, interstitial hematoma or microcavitations. Figures 5A and 5B show the recruitment curves of the AECAPs evoked from each of the 3 microelectrodes and recorded in the contralateral inferior colliculus. The curves were acquired 16 days and 16 months respectively after implantation of the electrodes. Sixteen days after implantation, the threshold of all of the electrodes was approximately 6 μA, although the amplitude of the response of Electrode #3 was very low, probably due to its location in the extreme posterior aspect of the PVCN. The recruitment curves acquired 16 days and 16 months after implantation were generally quite similar, and at 16 months after implantation, the threshold of the evoked response remained at about 6 μA. This low threshold is consistent with the very favorable histologic findings, including healthy axons and neurons within 20 μm of the sites of the tips, and the absence of chronic inflammation or other reaction to the electrodes or to the Epoxylite insulation. The slender glial scars deep to the electrodes tips probably resulted from slight retraction of the electrodes during the 16 months in situ, due to traction on the cables as the cat's head continued to grow. This animal was not quite mature when the electrodes were implanted. The glial sheath surrounding the electrode tips remained quite thin (20 μm or less in thickness) and this is consistent with the continued low threshold (6 to 8 μA) of the electrical evoked response from these microelectrodes.

III. EFFECTS OF INTERLEAVED PULSING ON STIMULATION-INDUCED DEPRESSION OF NEURONAL EXCITABILITY.

Long-lasting stimulation-induced depression of neuronal excitability (SIDNE) is a consequence of prolonged (e.g., 7 hours) of high-frequency (e.g., 500 Hz) stimulation with implanted microelectrodes. This phenomenon, which occurs in the absence of histologically-detectable tissue injury, may persist for several days after termination of

the stimulation and may be more severe when several closely-spaced microelectrodes are pulsed simultaneously. We have been investigating methods of ameliorating the severity of SIDNE during prolonged pulsing.

An array of 2 iridium microelectrodes were implanted into the left and right posterioventral cochlear nucleus of cat CN102. Approximately 3 months after implantation, the pair of microelectrodes in the left cochlear nucleus (Electrodes #3 and #4) were pulsed simultaneously, and the electrodes in the right PVCN (Electrodes #1 and #2) were pulsed in the interleaved mode (pulsed alternatively). In both cases, the stimulation was a charge-balanced, 500 Hz pulse train, amplitude modulated over the range of 6-20 μA according to the rectified, logarithmically-compressed artificial voice signal. The duty cycle of the stimulation was 50% (15 seconds of the artificial voice followed by 15 seconds of stimulation at the base amplitude of 6 μA, which is very close to the threshold of the neural response).

Figure 6 shows an AECAP recorded in the right inferior colliculus when Electrode #3 in the left cochlear nucleus was pulsed at 50 Hz. The recruitment curves described below were constructed from the peak-to-trough amplitude of either the first component (e) or the late component (l) as illustrated in the figure. Figure 7A shows the recruitment curves of the third component of the evoked response, before and after 7 hours of simultaneous pulsing of the two microelectrodes. Figure 7B shows the recruitment curves from the second half of this study in which the two electrodes were pulsed in the interleaved mode. The two parts of the study were conducted 6 weeks apart. After 7 hours of stimulation in either mode, the threshold of the evoked response increased to approximately 10 μA, but the growth of the response was not affected. This shift in the recruitment curve corresponds to a marked depression of the electrical excitability of the neurons very close to the stimulating microelectrode. Figure 7C shows the recruitment curves of the early component of the evoked response. The recruitment curve of the early component was shifted to the right in virtually the same manner as the recruitment curve of the late component. The early component represents the activity of neurons excited by the electrical stimulation and projecting

directly to the inferior colliculus, without passing through an intervening synapse. The late component almost certainly represents neuronal activity which must pass through at least one interposed synapse. The fact that the SIDNE is manifested in a virtually identical fashion for both components supports our premise that this phenomenon is due to suppression of the direct electrical excitability of neurons near the stimulating microelectrodes rather than to an accommodation in the synaptic pathways of the auditory system.

Figure 8 shows the recruitment curves of the evoked response from the other pair of microelectrodes (# 3 & 4) when these were pulsed simultaneously (Figure 8A) or in the interleaved mode (Figure 8B). In this case, the recruitment curve was shifted markedly to the right after 7 hours of simultaneous pulsing, but the shift was much less severe when the two electrodes were pulsed in the interleaved mode. In this animal, both pairs of electrodes are spaced about 400 μm apart, but the lengths of electrodes #1 and #2 are slightly different, so that the distance between the tips is actually slightly greater than 400 μm. These results are consistent with our premise that the SIDNE reflects depression of the electrical excitability of neurons, rather than depression in the efficacy of interposed synapses. Thus, interleaved pulsing would be expected to reduce SIDNE only when the electrodes are close enough together so that the current fields overlap significantly. The SIDNE that results from excitation of neurons by the individual microelectrodes must be managed by other means.

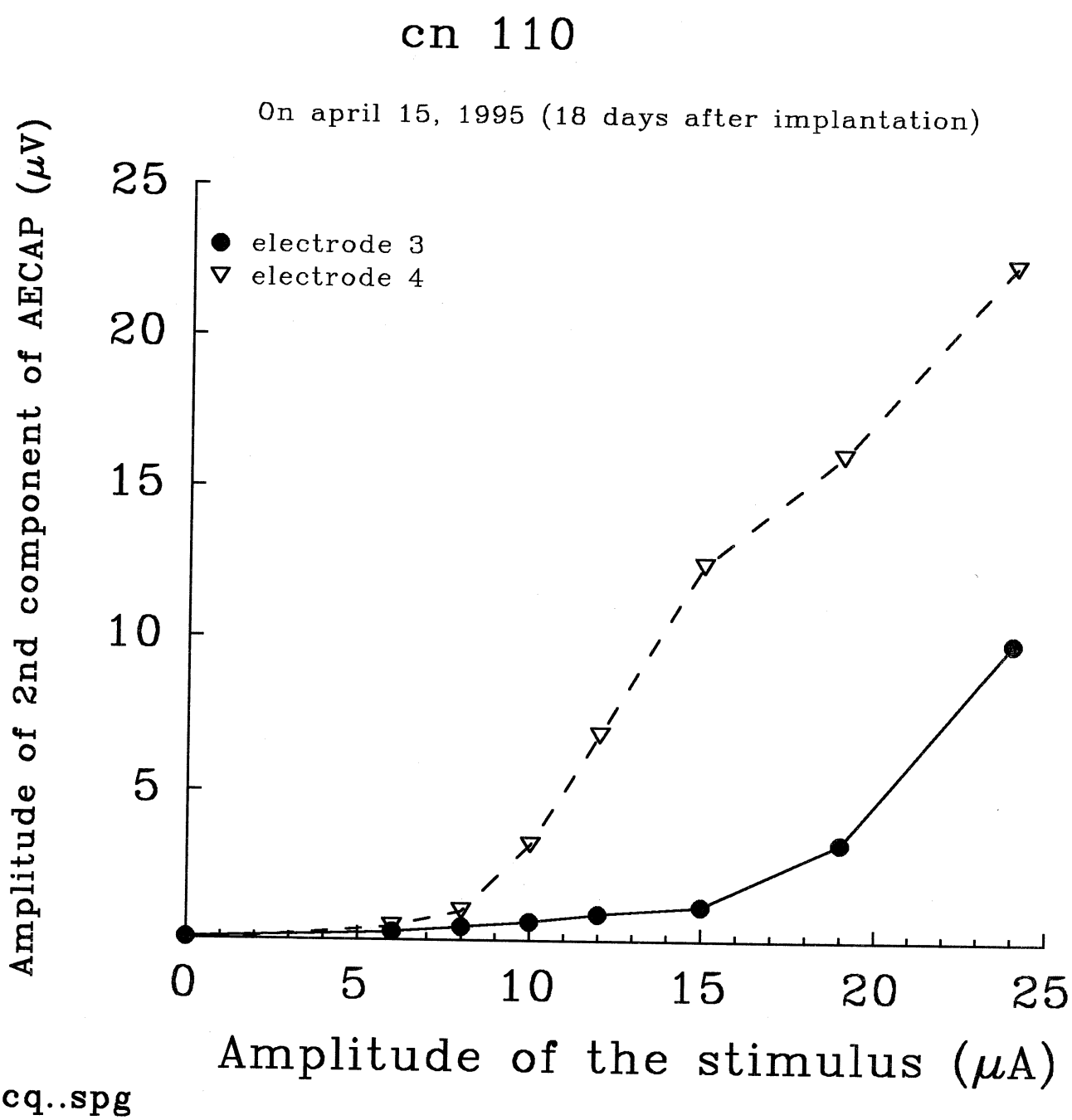
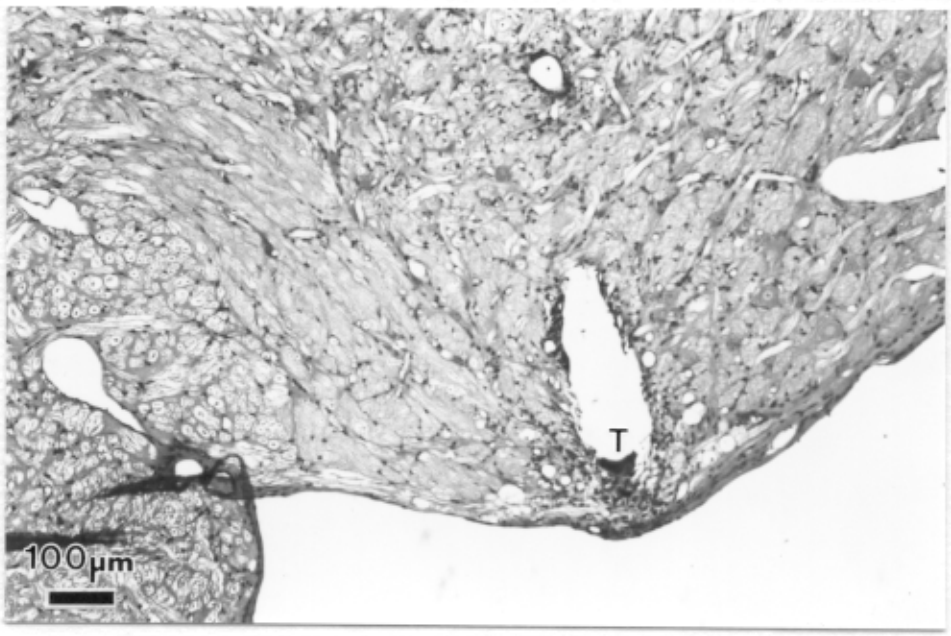
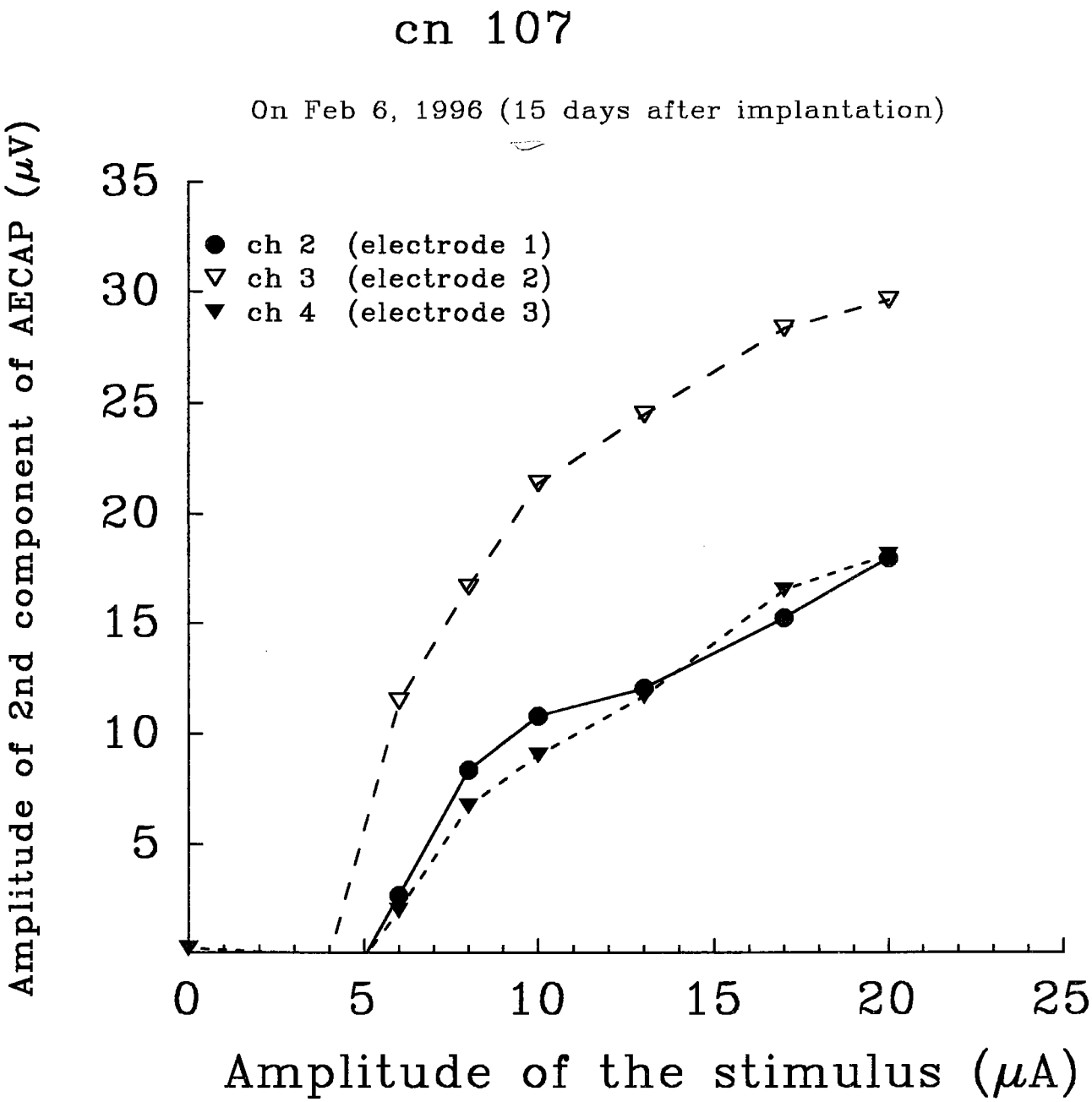

cn 110
On april 15, 1995 (18 days after implantation)
Amplitude of 2nd component of AECAP (μV)
electrode 3
electrode 4
25
20
15
10
5
0
5
10
15
20
25
Amplitude of the stimulus (μA)
cn110cq..spg

Figure 1

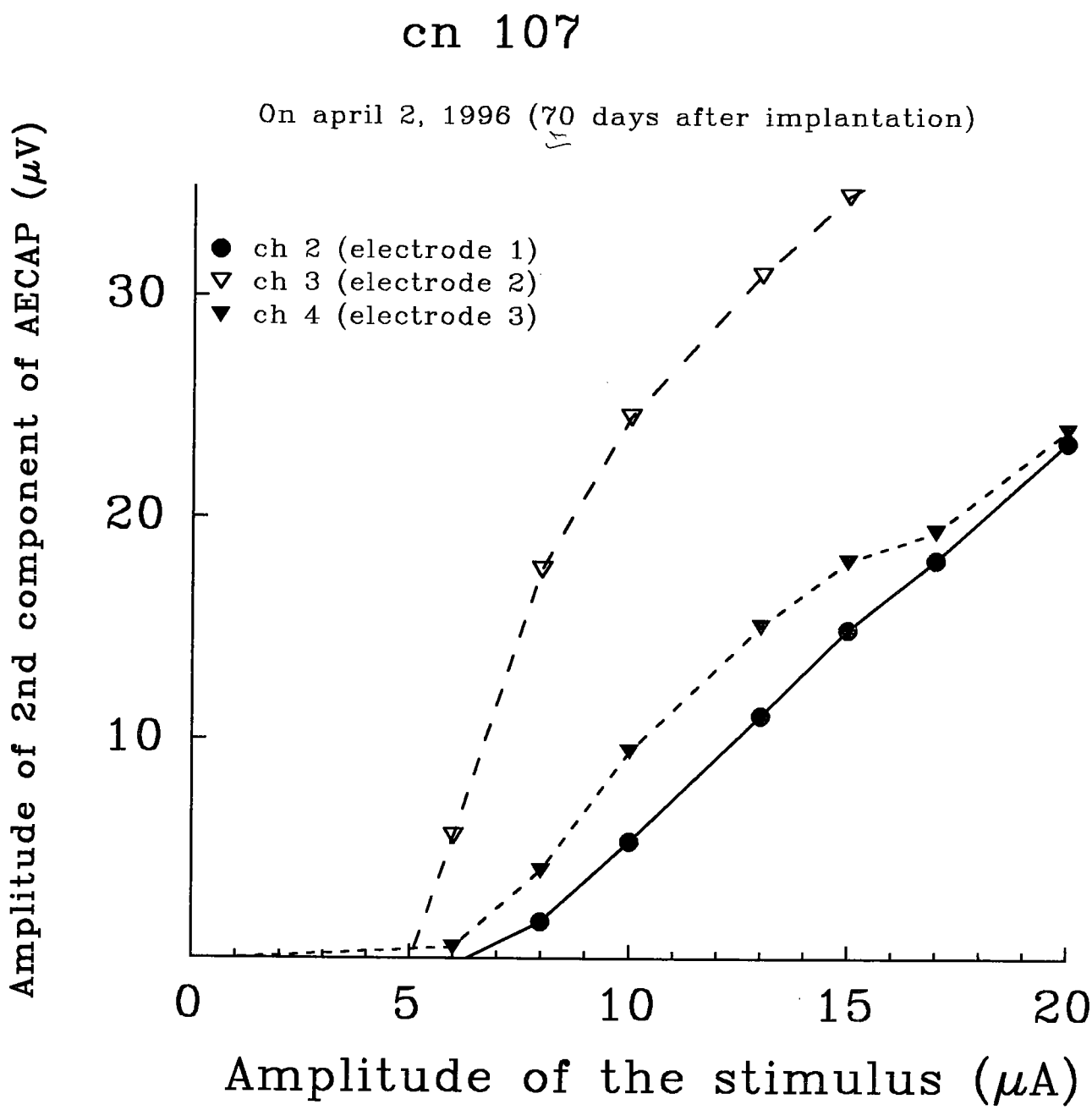


NO1-DE-5-2105 QPR 03 Fig 02



cn107cq..spg

Figure 3A



cn107eq..spg

Figure 3B

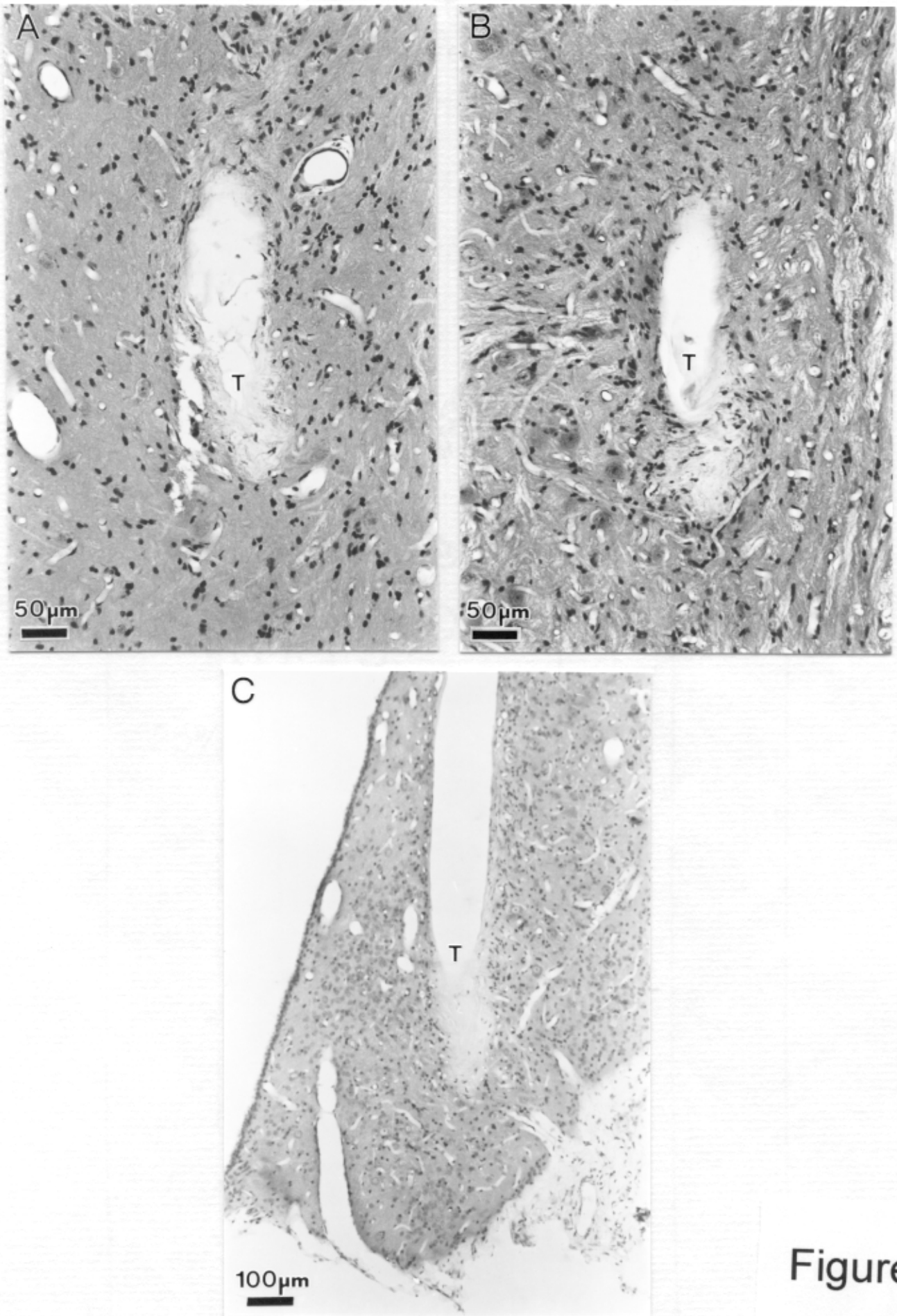
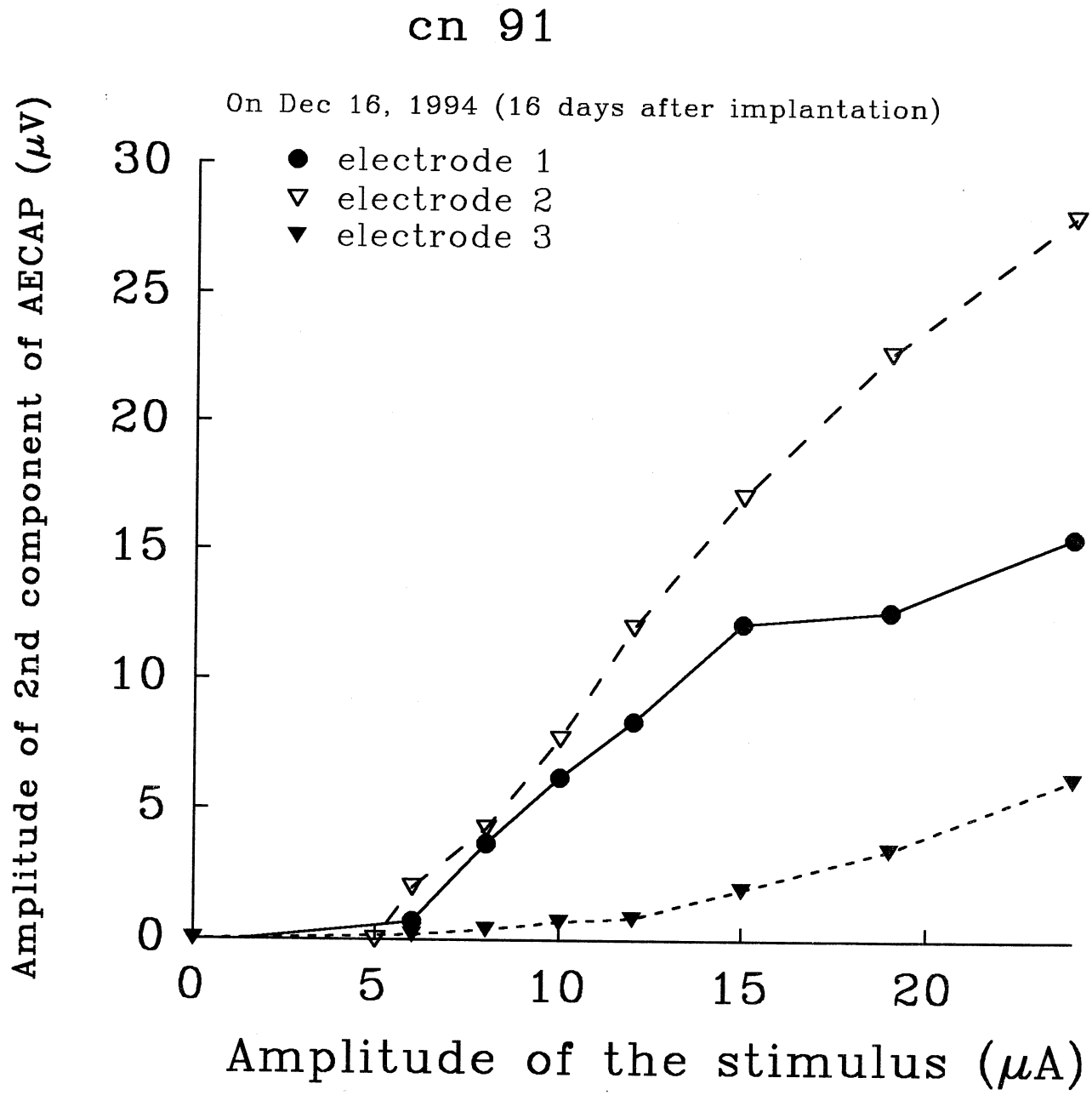


Figure 4



cn91aq.spg

Figure 5A

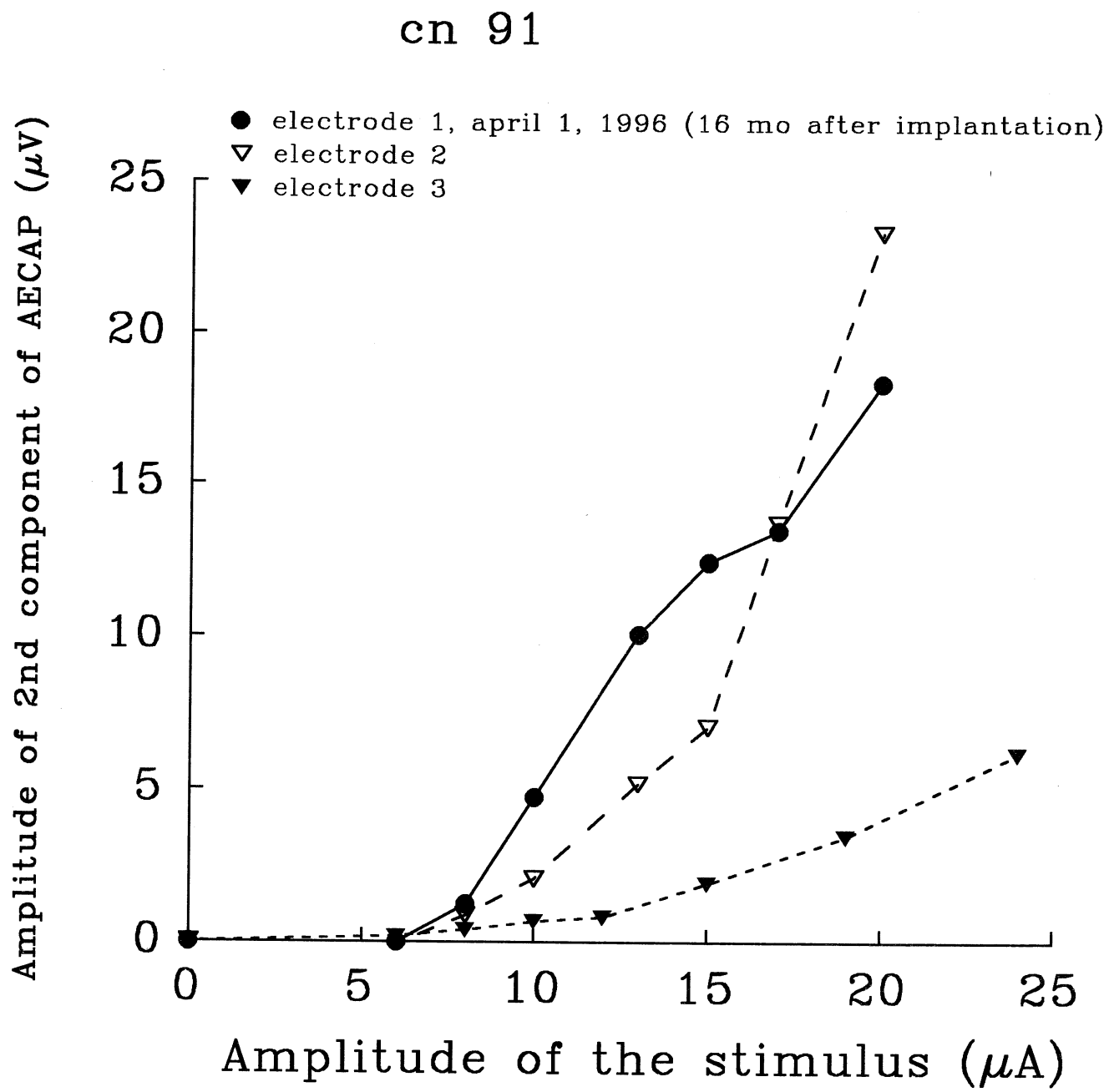


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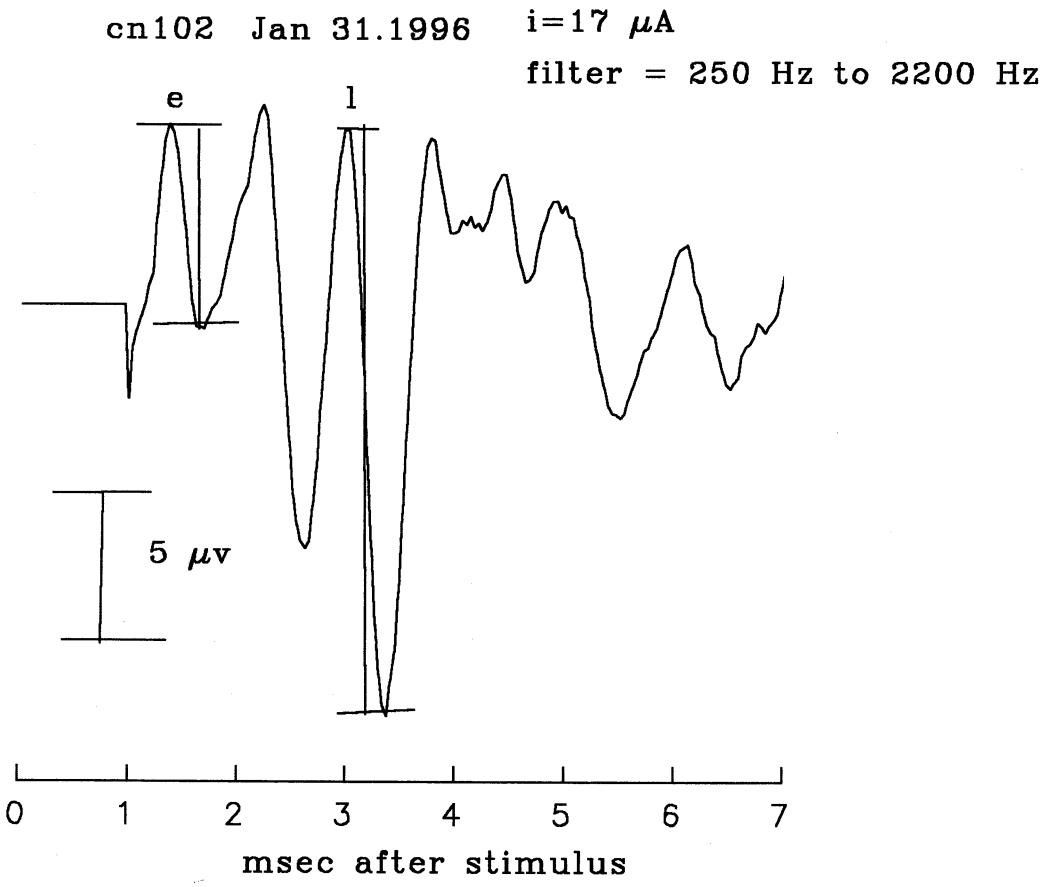
Figure 5B



n102g.spg

Figure 6

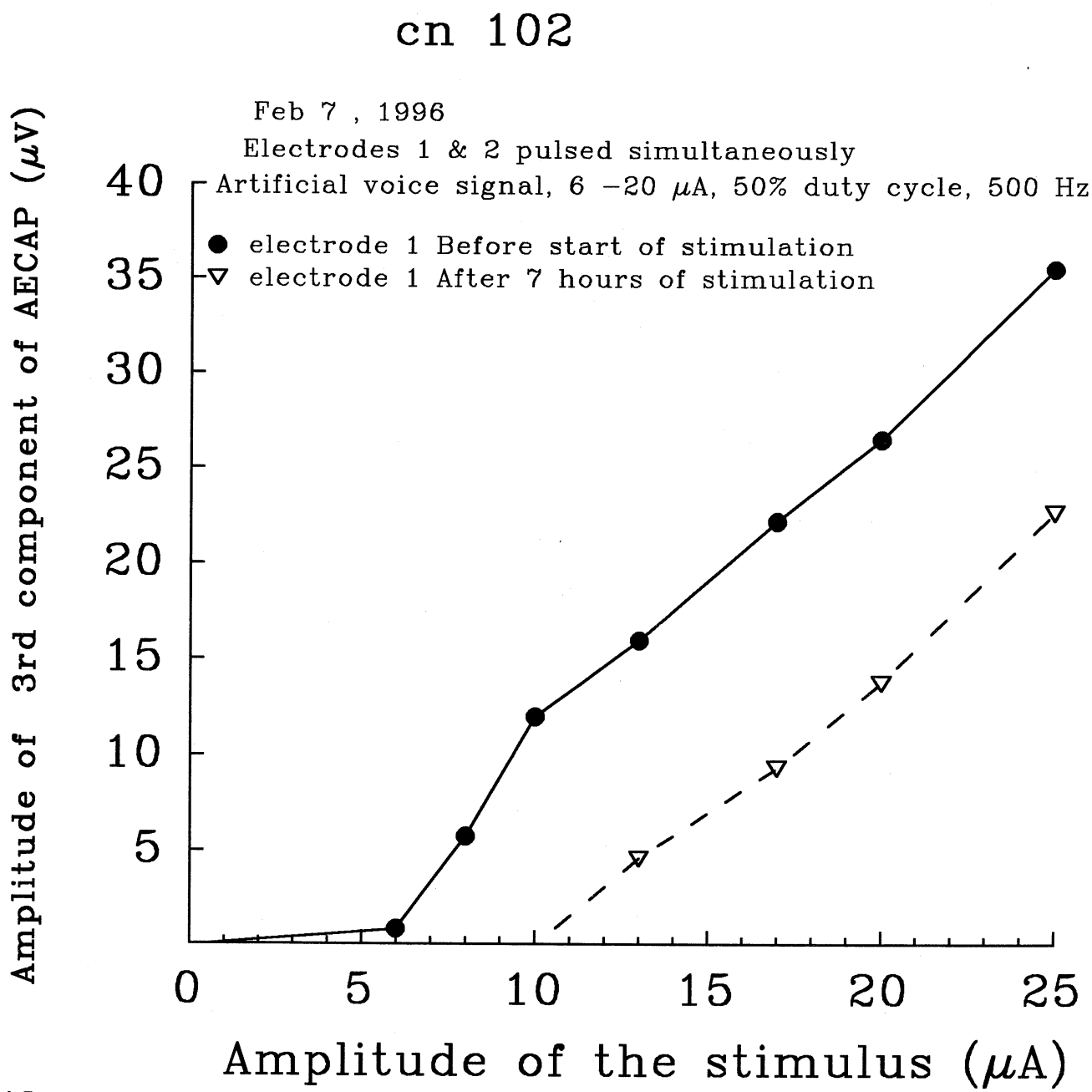

cn 102
Feb 7 , 1996
Electrodes 1 & 2 pulsed simultaneously
Artificial voice signal, 6 −20 μA, 50% duty cycle, 500 Hz
electrode 1 Before start of stimulation
electrode 1 After 7 hours of stimulation
Amplitude of 3rd component of AECAP (μV)
40
35
30
25
20
15
10
5
0
5
10
15
20
25
Amplitude of the stimulus (μA)
cn102i2q..spg

Figure 7A

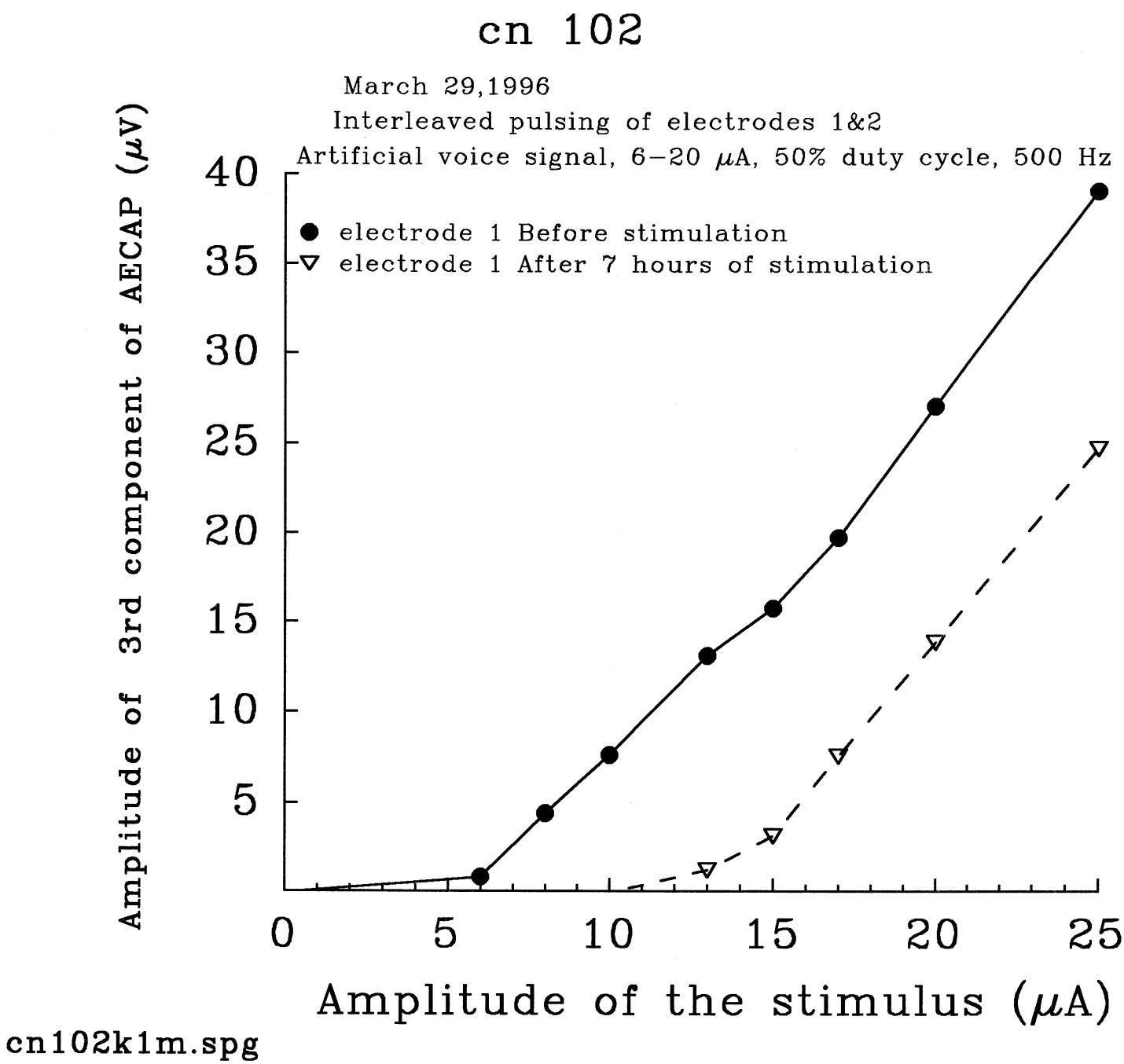

cn 102
March 29,1996
Interleaved pulsing of electrodes 1&2
Artificial voice signal, 6–20 μA, 50% duty cycle, 500 Hz
electrode 1 Before stimulation
electrode 1 After 7 hours of stimulation
Amplitude of 3rd component of AECAP (μV)
40
35
30
25
20
15
10
5
0
5
10
15
20
25
Amplitude of the stimulus (μA)
cn102k1m.spg

Figure 7B

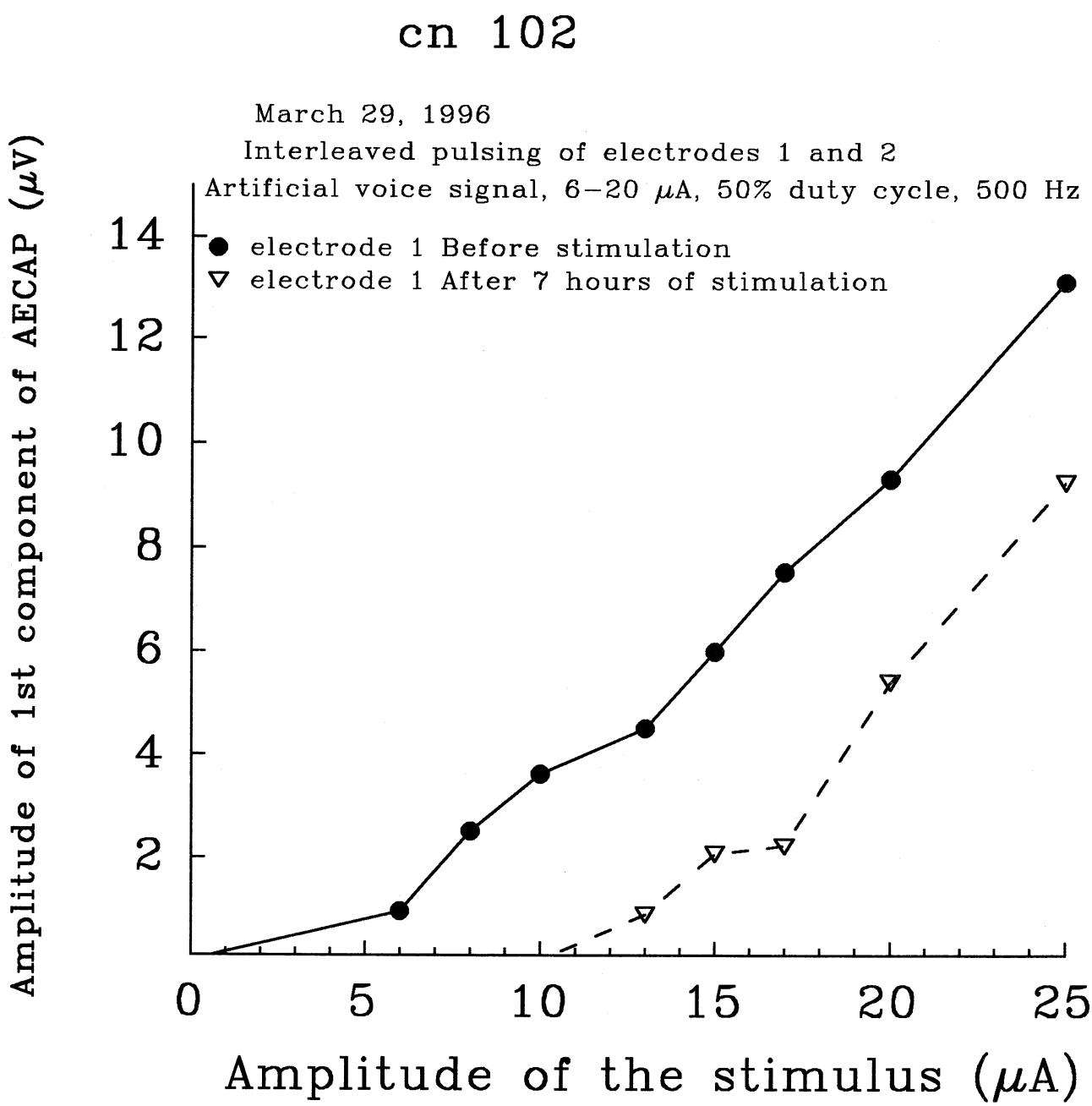

cn 102
March 29, 1996
Interleaved pulsing of electrodes 1 and 2
Artificial voice signal, 6−20 μA, 50% duty cycle, 500 Hz
electrode 1 Before stimulation
electrode 1 After 7 hours of stimulation
Amplitude of 1st component of AECAP (μV)
14
12
10
8
6
4
2
0
5
10
15
20
25
Amplitude of the stimulus (μA)
cn102k1e.spg

Figure 7C

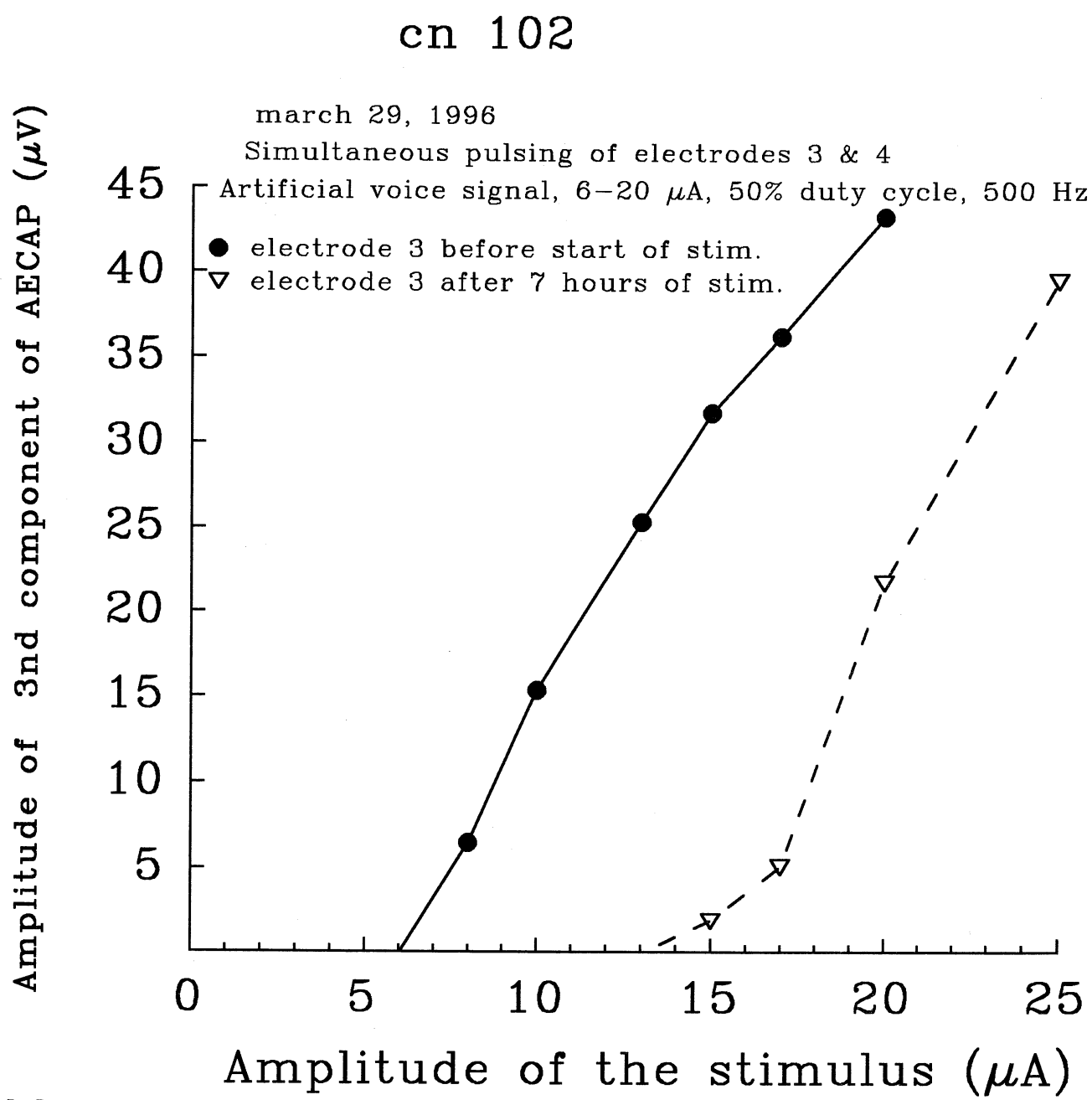


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Figure 8A

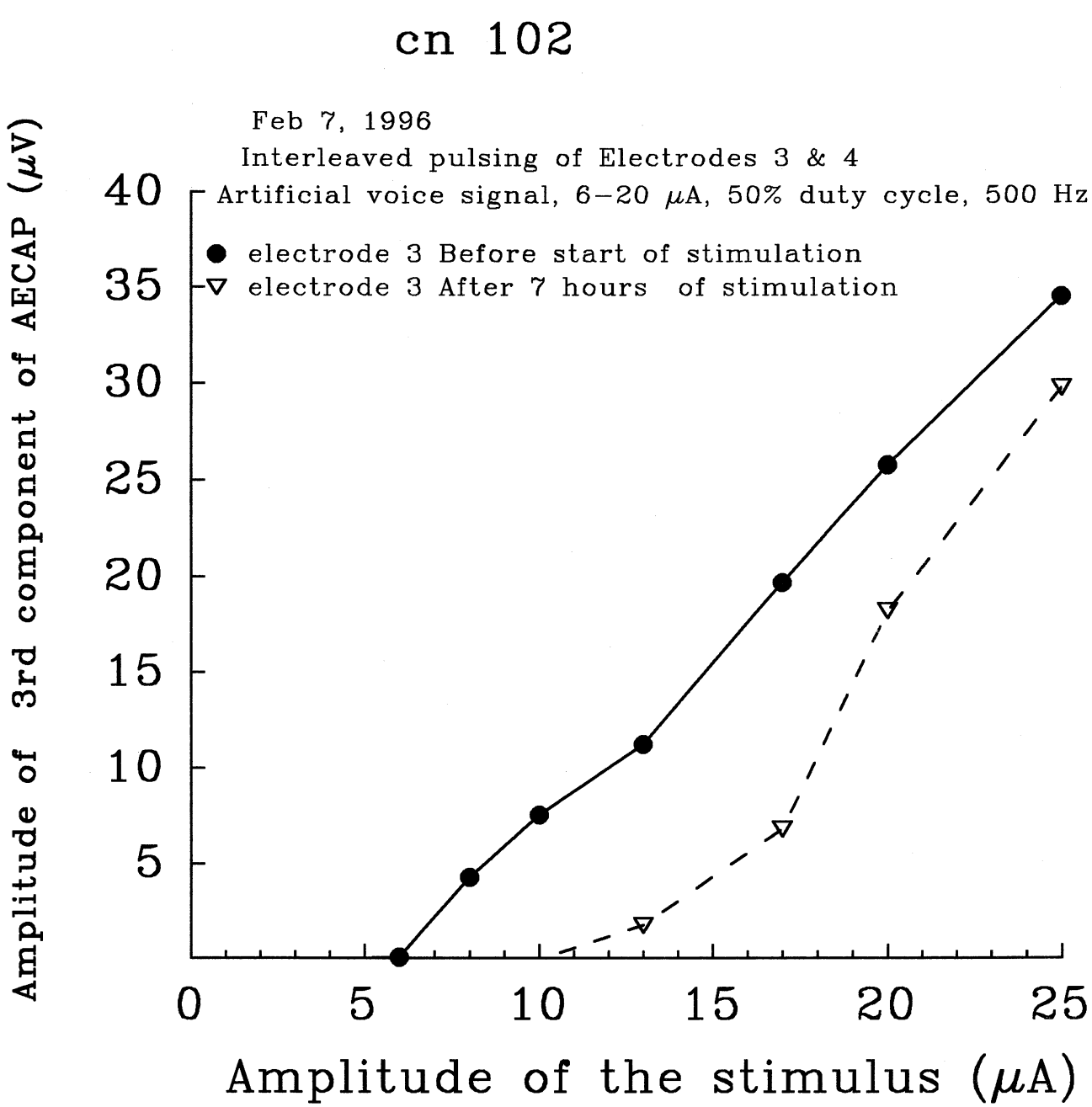
cn 102
Feb 7, 1996
Interleaved pulsing of Electrodes 3 & 4
Artificial voice signal, 6–20 μA, 50% duty cycle, 500 Hz
electrode 3 Before start of stimulation
electrode 3 After 7 hours of stimulation
Amplitude of 3rd component of AECAP (μV)
40
35
30
25
20
15
10
5
0
5
10
15
20
25
Amplitude of the stimulus (μA)
cn102i3q..spg

Figure 8B