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

Contract No. NO1-DC-5-2105

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SUMMARY AND ABSTRACT

The overall goal of this contract is to develop an auditory prosthesis based on multisite microstimulation within the cochlear nucleus. During the first quarter of the new contract cycle, we have been evaluating, in the cat model, the implantation of an array of 4 long (4 mm) closely-spaced (300 μm) microelectrodes. The length and spacing of the elements 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 results from these experiments have been somewhat disappointing, in that an unacceptable high percentage (3 of 6) of the implants failed, and the cochlear nuclei were infarcted by the 4-element arrays. There is evidence from the histologic evaluations that the injury is due to mechanical distortion and shearing of tissue and blood vessels that occurs when closely-spaced electrodes are inserted. The problem may be exacerbated when the electrode elements are slightly misaligned from the axis of insertion. We have modified our procedure for aligning the microelectrode shafts ~~are~~ and we working to define more precisely the mechanisms that are responsible for the implant failures.

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 24 to 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 0.8 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 assembly of 2 to 4 iridium stimulating electrodes was inserted by stereotaxis into the left 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 response (AER). In previous studies we have computed the recruitment (growth) curve of the evoked response from the amplitude of the earliest component of the AER. Since the latency of the early component of the AER is less than 1 msec, it represents neuronal activity evoked directly (rather than transsynaptically) by the microstimulation in the cochlear nucleus, and

projecting to the inferior colliculus. Thus, the early component is a direct index of the effect of prolonged stimulation on the excitability of neurons in the cochlear nucleus near the tip of the stimulating electrode. However, the early response is of relatively low amplitude, and thus the signal-to-noise ratio is superior when the second component is used. Consequently, we have computed the recruitment curves from the second component, rather than from the first component, of the AER. This approach was validated in QPR#11, Contract NO1-DC-2-2400. For each AER, the amplitude of the second component was measured after the AER 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 actual recruitment curve, which representing the recruitment of the excitable neural elements surrounding the microelectrode, is generated by plotting the amplitude of the early component of each of several AER's against the amplitude of the stimulus pulse used to evoke the AER.

For histologic evaluations, 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

Nine integrated microelectrode arrays were implanted into 8 cats. Seven arrays contained 4 microelectrodes, one contained 3 microelectrodes and two contained 2 microelectrodes. The results from the implantation of the 4-element arrays have been mixed. One animal (CN-94) was lost from the study when the percutaneous connector detached from the skull. Three implants (CN-95, 98, and 100) failed completely . At the time of surgery, good evoked responses with thresholds less than 8 µA were recorded in

the inferior colliculus, but within 2 weeks, the threshold of the evoked response increased to over 100 μA. Subsequent histologic evaluation of the implant sites showed severe infarction of the cochlear nucleus, probably as a result of the rupture of an arteriole or venule. Three of the 4 element arrays continued to function well at one month to 3½ months after implant (CN96, 98 and 99) and the threshold of the evoked responses remains below 8 μA for all electrodes in which a low threshold response was obtained at the time of implantation. One animal (CN-98) was sacrificed 3 months after implantation of the array, to confirm the good histologic status of the cochlear nucleus, and monitoring is continuing for the other two. The 3-element array (CN-101) continues to function well one month after implantation, and both of the 2-element arrays (CN-102) continue to function at 11 days after implantation. It has been our experience that if these implants survive the first two weeks in vivo, most will continue to function until the animals are sacrificed.

Figure 1A and 1B show histologic sections (cut in the frontal plane), through the PVCN of Cat CN98. Figure 1A shows the area of the tips of electrodes 1 and 2 (H & E stain). This animal was sacrificed 3 months after implantation of the 4-element array. There are small glial scars surrounding the sites of the electrode tips (T), but the surrounding neuropil appears to be healthy, and there are no microcavitations or evidence of healed microhematomas. Figure 1B shows the sites of the tips of electrodes 3 and 4 (Nissl stain). There are small glial scars in the vicinity of the electrode tips (T), but the surrounding neuropil, and the embedded neurons within 50 μm of the tip appear healthy.

Figure 1C shows the recruitment curves of the amplitude of the evoked response recorded in the right inferior colliculus of cat cn98, described above. The threshold of the response from microelectrodes 1, 2 and 3 was approximately 8 μA, which is consistent with the good condition of the neurons and neuropil very close to the tips. Electrode 4 never gave a good evoked response, probably because of its very lateral position in the PVCN (Figure 1B). Figure 1D shows the recruitment curves for the 3-microelectrode array (cn101) 21 days after implantation. The thresholds of the evoked responses are 6 μA or below, indicating that the excitable neural elements within 40 μm of the tip remain healthy.

Figure 1E shows the recruitment curves for the pair of 2-element arrays (cn102), 11 days after implantation. We are continuing to monitor these animals.

Figure 2A shows a frontal section through the PVCN of Cat CN100, one of the animals in which the implant failed. This animal was sacrificed 7 days after implantation of the 4-element array, when the threshold of the evoked response increased to over 100 μA. A portion of 2 of the electrode tracks can be seen embedded in the large hematoma which occupies much of the central part of the infarcted PVCN. The large infarct consists mostly of red blood cells, some of which are being scavenged by macrophages (Erythrophagatosis, indicated by the arrow in Figure 2B). Figure 2C is a horizontal section (perpendicular to the electrode shafts), through the flocculus of the cerebellum which overlies the infarcted cochlear nucleus. The electrodes were inserted through the most lateral part of the cerebellar flocculus in order to approximate the problem of implanting long electrodes into the human cochlear nucleus. This histology provides an important clue as to the processes underlying the failure of this implant. The cerebellar flocculus is isolated from the cochlear nucleus by 2 layers of pia and is supplied by different blood vessels than those which enter the cochlear nucleus. However, it, too, is severely infarcted. The 4 electrode tracks are seen at the center of the infarcted tissue, which is heavily infiltrated with red blood cells. Elongated vacuoles filled with red blood cells radiate from each track. The radial orientation of the vacuoles suggest that the tissue has been mechanically distorted and subsequently slashed by the microelectrode tips as they were inserted into the tissue and down into the cochlear nucleus. It is notable that this type of injury may occur when the electrodes are not precisely aligned along the axis of insertion. The mechanical displacement and shearing of the tissue will be greater when several closely-spaced electrodes are inserted simultaneously, since each can contribute an axis force that will displace the tissue, increasing the chance that neural elements and blood vessels within the parenchyma will be stretched until their elastic limits are exceeded (Edell et al, 1992).

We have modified our procedure for examining and documenting the alignment of the electrode shafts, using a microscope eyepiece equipped with a horizon reference line

that can be moved precisely in two dimensions. With this procedure, we can assure that the shafts are aligned within +/- 0.35 ° with respect to the axis of the introducer. Figure 2D shows the 4-element microelectrode array recovered from cat cn100, the failed implant described above. Two of the shafts are indeed slightly misaligned from the axis of insertion, by approximately 1^{o} of arc. We are now systematically examining whether this amount of misalignment is responsible for the failure of the implants. We are implanting arrays with 2, 3, and 4 microelectrode shafts, to determine the relation between the probability of implant failure and the number of closely-spaced shafts. In this context, we should note that with multisite probes, only one or two shafts would be required to give access to several points along the tonotopic gradient within the PVCN, assuming that the shaft actually penetrates the nucleus. Thus, as the number of shafts decreases, the necessity for precise placement of the array increases

REFERENCES

Edell, D.J., Van Toi, V., McNeil, V.M. and Clark, L.D. (1992) Factors influencing the biocompatibility of insertable silicon microshafts in cerebral cortex. IEEE Trans. Biomed. Engn. 39(6):635-643.

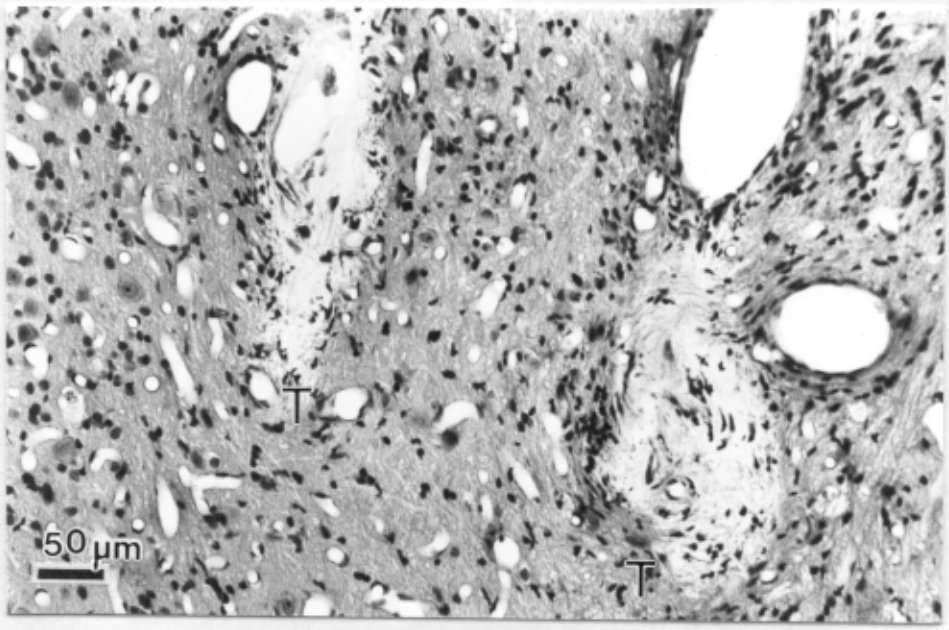
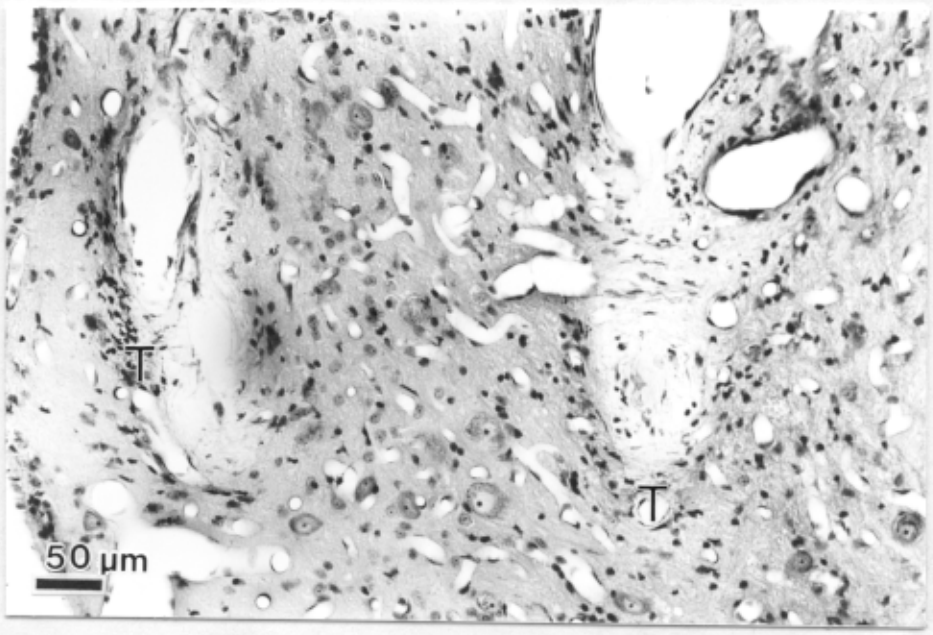


Figure 1A



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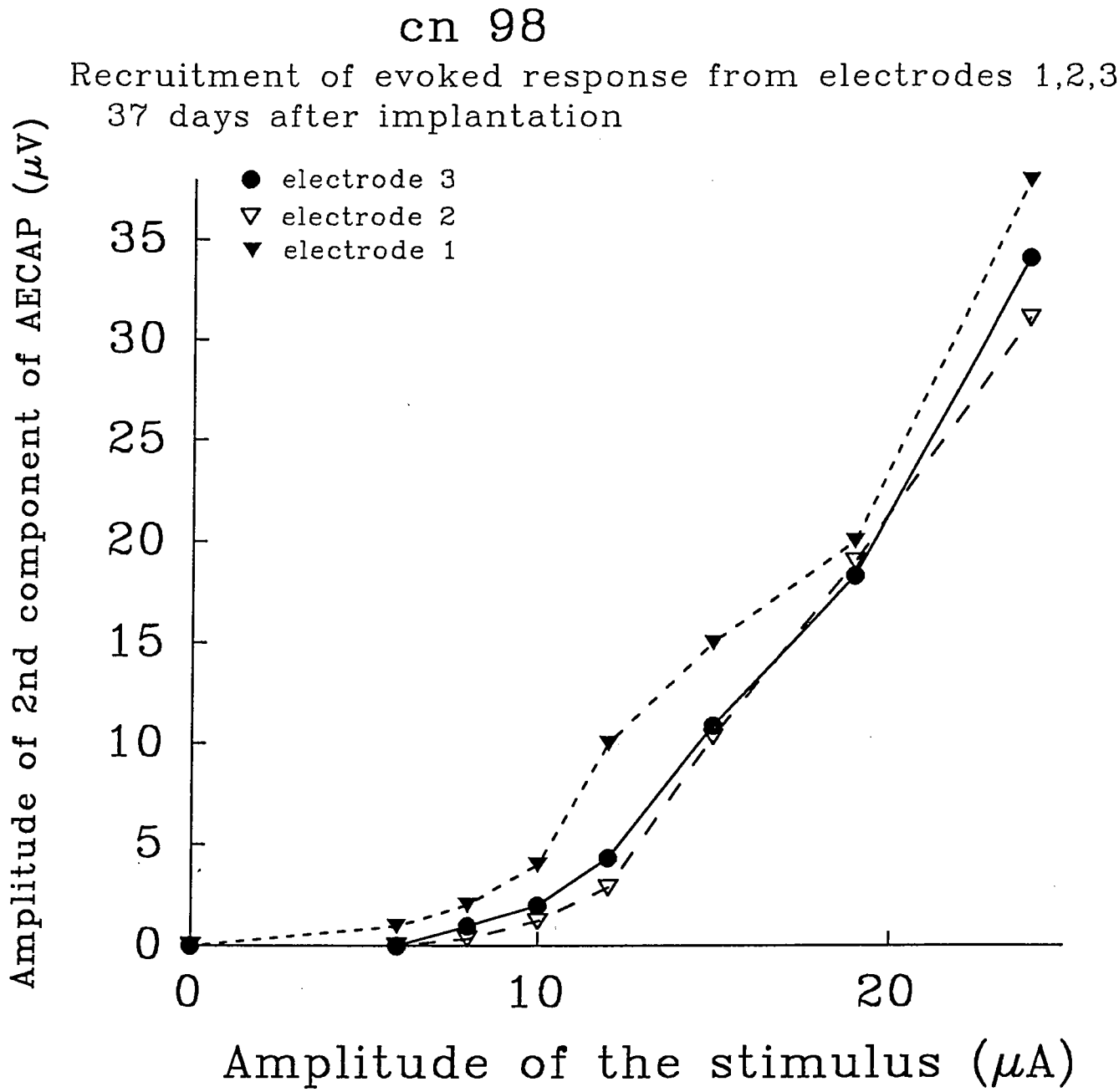

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Figure 1C

cn 101

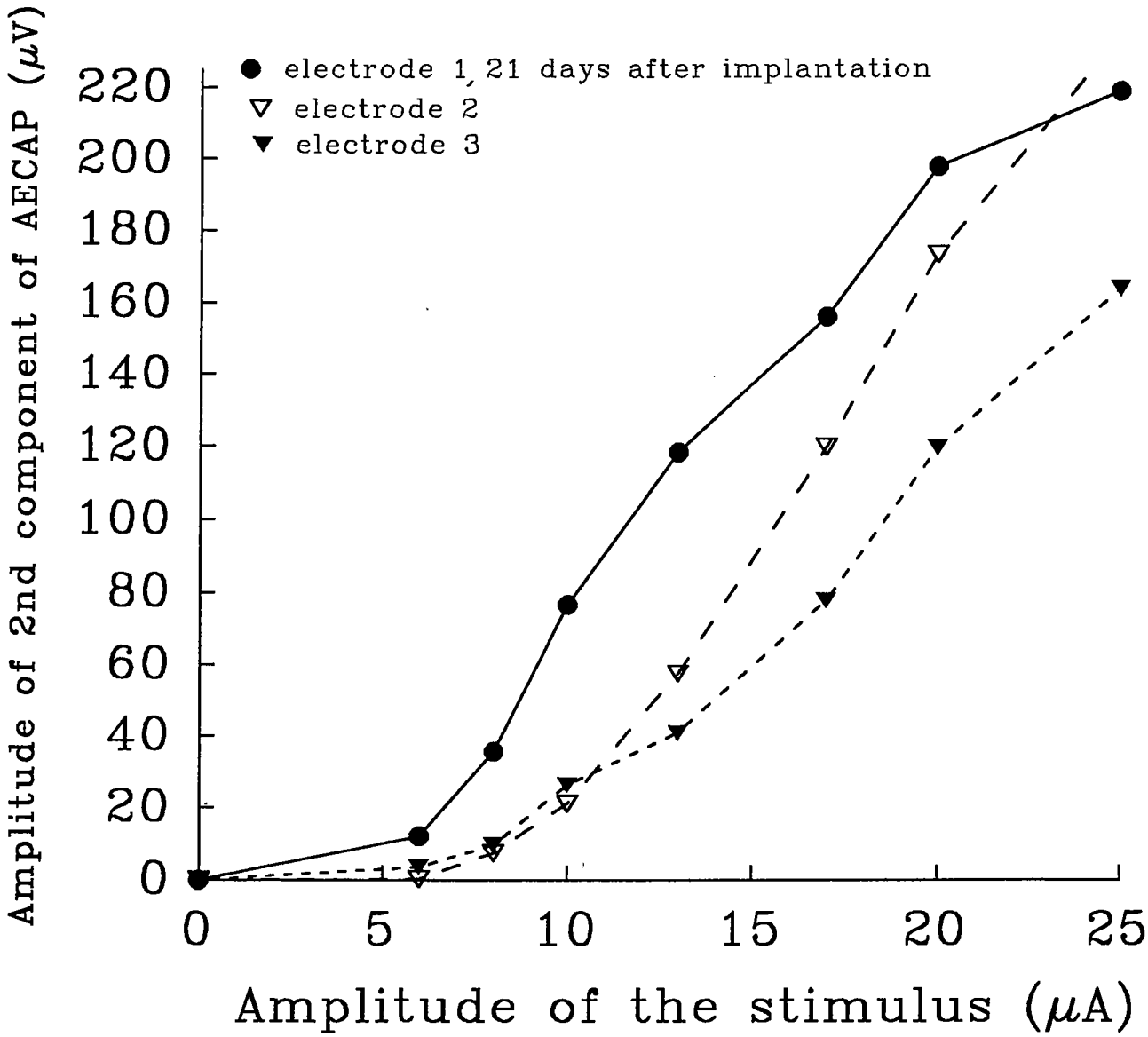

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Figure 1D

cn 102

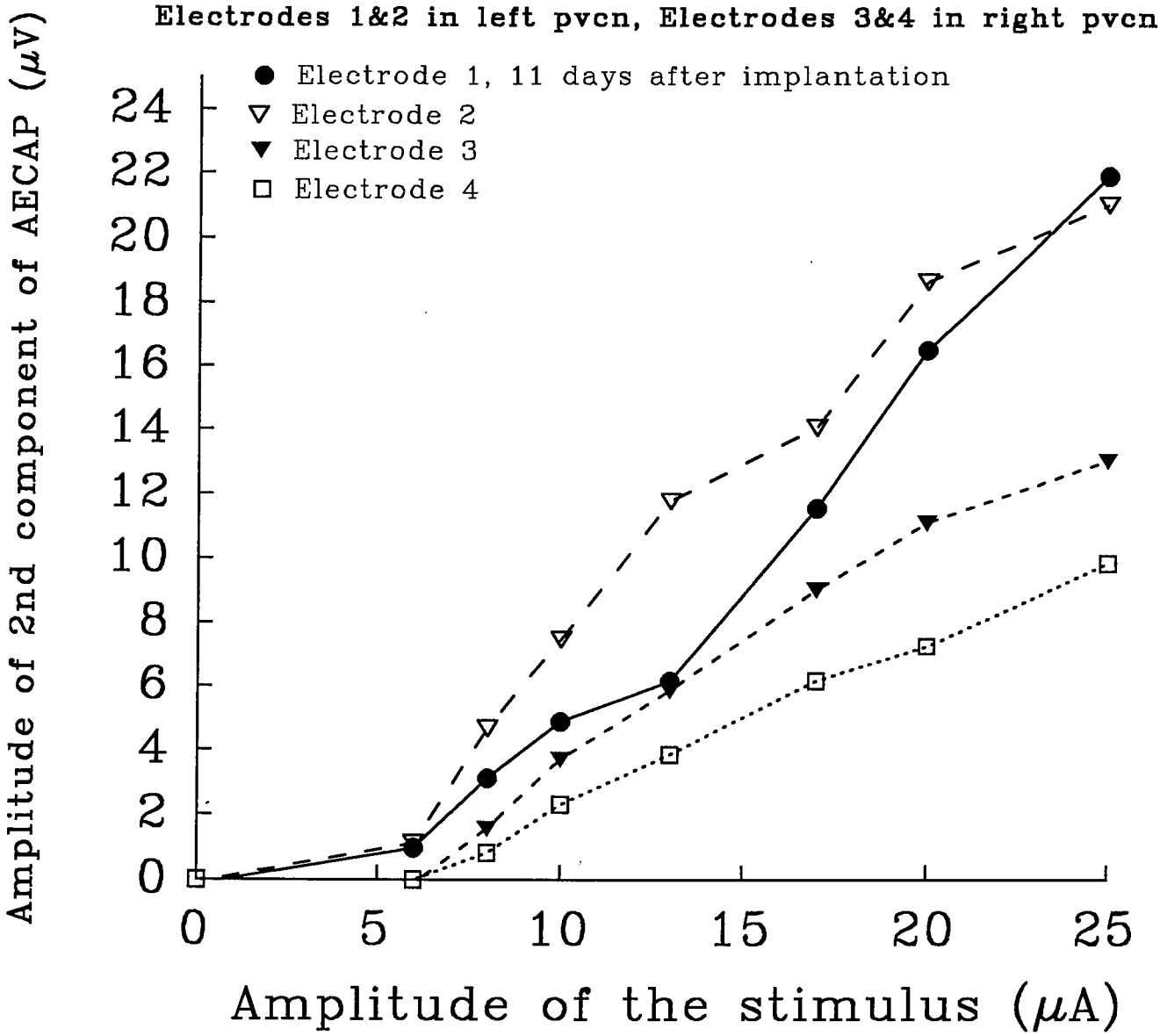

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Figure 1E

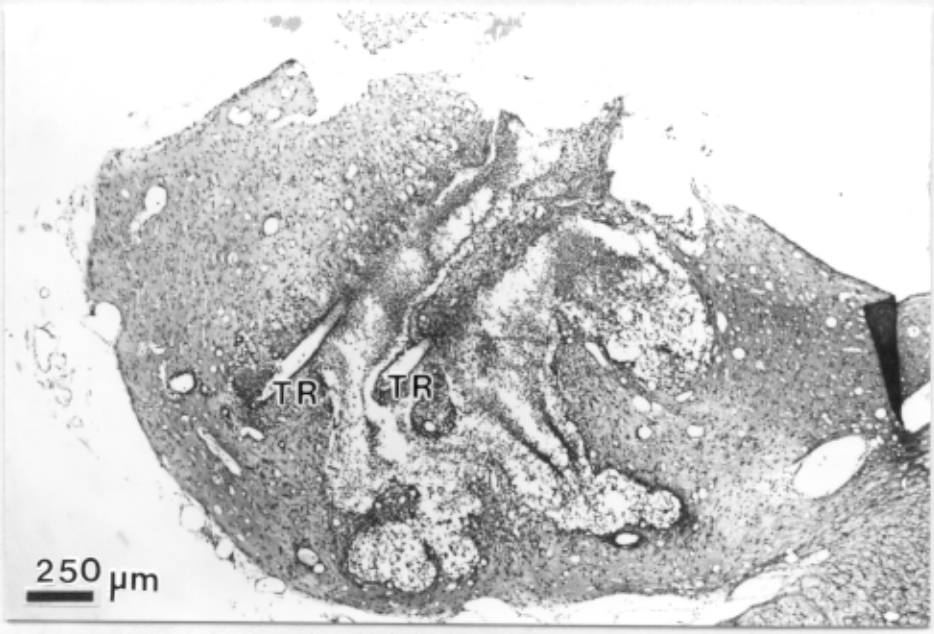
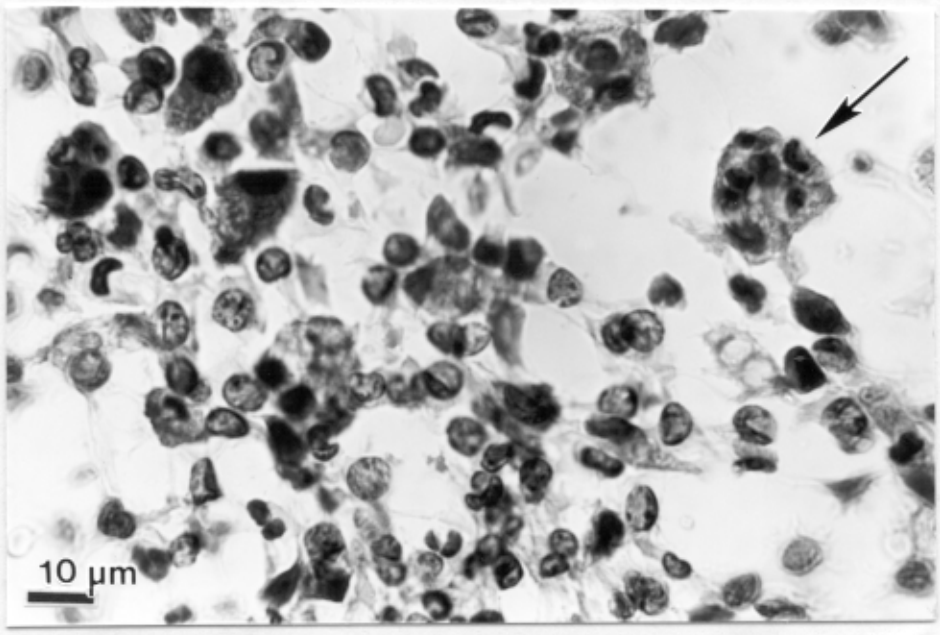


Figure 2A



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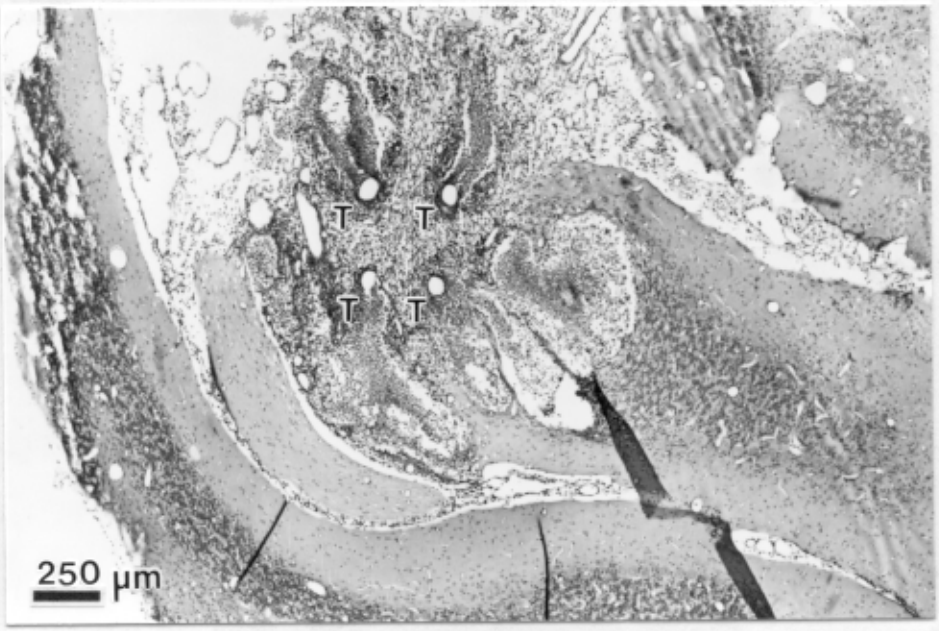

Figure 2C

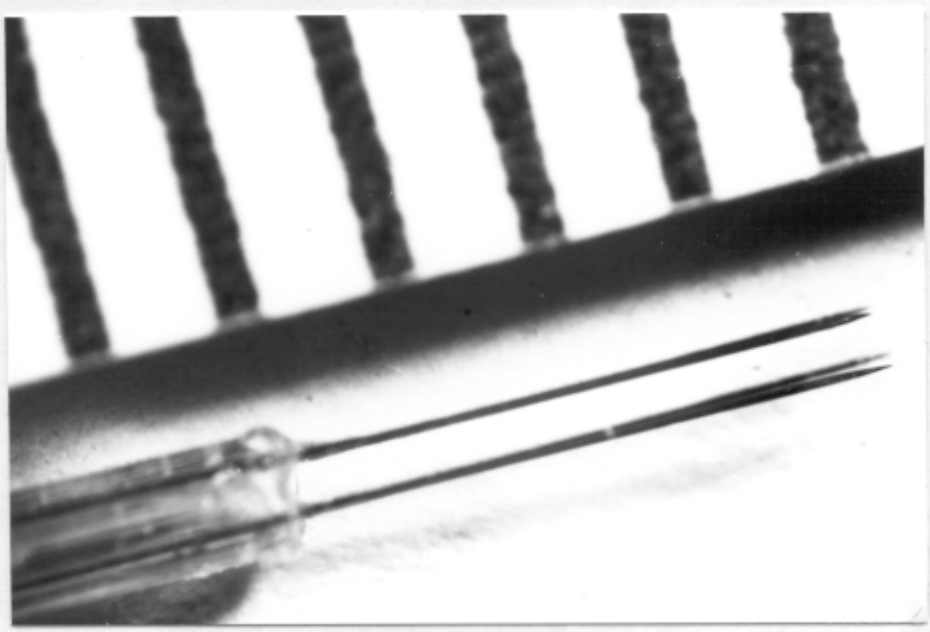

Figure 2D