Control experiments were carried out without radioactivity and after the radioactivity had decayed, and also with $^{211}At^{-}$. No α-particles were seen in the control experiments without radioactivity. Some chemical artefact was observed.

Results. Examples of α-particle track autoradiographs of sections of the murine rectal adenocarcinoma at 30 min after i.p. injection of 6-^{211}At-astato-MNDP are shown in figure 2,a and b.

The distribution of the origins of α-particle tracks in cells of the tumors and certain normal tissues are shown in the table for unambiguous photomicrographs. At least about two-thirds of the tumor cells show localization of the compound in the nucleus, including the nuclear membrane and in a few cases unmistakeably in the nucleolus. There is early accumulation of the compound in the plasma membrane and nuclear membrane, greater at 30 min than 60 min. Activity observed just outside the plasma membrane in the fixed preparations could be due to shrinkage of the cytoplasm on fixation but may be due to outward diffusion of labeled metabolites formed in the plasma membrane.

It was found that 4.2% of the 1567 tumor cells were labeled at 30 min after i.p. injection of approximately 5 µCi 6-^{211}At-astato-MNDP and 2.2% of 3554 tumor cells were labeled at 60 min after i.p. injection of 2.4 µCi of the compound. The labeled tumor cells are proliferating cells in the growing areas of tumor with rather dense DNA staining and relatively little cytoplasm which contains RNA and are not inconsistent with the characteristics assumed for stem cells.

The many fewer tracks observed in the lungs appear to arise in alveolar cells (type II pneumocytes). Parallel biodistribution studies showed significantly lower uptake ($p < 0.001$) of 6-^{211}At-astato-MNDP into both lung and spleen in comparison with that for ^{211}At-astatide anion[20].

For practical purposes, no tracks were observed in the normal colon. No tracks were seen in the rather limited bone marrow material examined.

iscussion. α-Particle track autoradiography provides a unique opportunity for identifying the intra-cellular localization of the compound.

Further studies of the distribution of the compound are necessary. However, its possible human therapeutic application is as yet uncertain because the radiations from the electron-capture decay of ^{207}Bi of half-life 38 y in 42% of the disintegrations of ^{211}At may be associated with a significant late carcinogenic hazard if the ^{207}Bi cannot be removed from the body. Moreover, the dose of radiation to the lungs must be accurately evaluated. These aspects of the problem require further biological and microdosimetric evidence.

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Multi-electrode recording system for the study of spatio-temporal activity patterns of neurons in the central nervous system[1]

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Summary. A new type of recording microelectrode with mechanical and electrical properties suitable for use in microelectrode assemblies for neurophysiological studies in the central nervous system was developed by adaptation of principles from optical fiber technology. A microdrive for independent positioning of up to 7 electrodes for the recording of electrical activity from individual neurons was constructed. It operates by the combined action of a stepping motor and a system of independently controllable piezoelectric clutches and brakes for each electrode.

Beginning in the early 1960's, innovative techniques for the quantitative analysis of patterns of electrical impulses of individual neurons, recorded with a single microelectrode, have been developed. The results raised the expectations that suitable technical and conceptual refinements would lead to a more comprehensive clarification of the percep-

tual, cognitive, and behavioral decision and control processes in terms of neuronal activity patterns.

The single electrode technique, however, imposes serious limitations on our understanding even of basic, neural mechanisms, since the information processing properties of neural populations are not simply the additive property of the function of single cells[2]. Theoretical considerations proposed by v. Foerster[3] were also based on the concept of population activity. In such models of ensemble activity, elementary functional units composed of suitably interconnected neurons, perhaps functioning as recursive computing elements[4], and embedded in a tesselation of analogous elements, could be envisioned as forming dynamically shifting patterns of activity in the spatio-temporal domain[5]. The observations of Verzeano and Negishi[6], and Noda and Adey[7] began to provide suggestive, though tenuous evidence for functional interactions of neurons capable of dynamical shifts with different behavioral states. Moreover, evidence was obtained in support of the notion that correlated discharge pattern in 2 or more neurons are stimulus-selective, thus giving support to the idea of stimulus encoding by clusters of correlated neuron discharges[8].

Our own efforts since 1972 were directed towards developing a technique for the simultaneous recording of activity in clusters of individual neurons with the principle objective of enabling the quantitative analysis of spatial and temporal patterns of activity of neurons distributed in neuronal structures subserving perceptual activity of different levels of complexity. To this end, we set out to meet 3 principal design specifications: a) in contrast to arrays of fixed electrodes that have been developed recently[9], we wanted independent position control of the different electrodes to obtain optimal signal to background separation at each electrode under the experimenter's control; b) sampling of neural activity at different horizontal and vertical dimensions of the neural tissue at the experimenter's discretion; c) reduction of size of the individual electrodes to minimize tissue damage and mutual mechanical interference by closely spaced electrodes.

Furthermore, we attempted to draw to whatever extent possible on commercially available procedures and products. We based our development on the idea that these objectives could be attained by adaptation of methods developed in optical fiber technology rather then by the integrated circuit techniques used by other investigators[10].

Fiber microelectrodes. To meet the requirements listed under (c), we sought to reduce the gross dimensions of the microelectrodes close to the limits set by the required mechanical stability. In the present design, fibers of 100 µm OD are used. The strength of these fibers is sufficient to penetrate the dura in chronic preparations. If the dura is removed, fibers of considerably smaller dimensions are feasible.

Starting material for the electrodes are 100 µm OD Nonex-glass fibers with a 12-µm tungsten core[11]. A conical tip is then ground by manually rotating the fibers against a spinning diamond grinding wheel. Rotating the fibers inside a thin hypodermic needle improves guidance and increases the grinding force. We found it more effective to replace the manual grinding process by an automatic device which could be programmed to produce tip configurations of various geometries in order to achieve an optimal ratio of effective electrode surface to the volume distribution of the neuron's electrical field (fig. 1). The grinding process is favorable in this respect since it produces microgrooves on the electrode tip, which substantially increase the recording surface and, therefore, the tip capacitance. The characteristic tip capacitance of these electrodes is 2–2.5 pF/µm^2, which is considerably higher than the tip capacitance of etched electrodes. Depending on the tip geometry and grinding conditions, electrodes with tip impedances between 60 and 500 kΩ (at 10 kHz) can be fabricated. Since the electrodes are guided inside stainless steel capillaries, crosstalk is well below the noise level.

The simplest way of connecting the electrodes to the amplifier input is by carefully breaking the glass mantle on the other end, and attaching the core conductor to a terminal contact with conducting silver paint.

At an axial force of 10 p (1 pond = 0.035 oz) the free buckling length of these fibers is 8.5 mm. In tissue the fibers can penetrate several times that deep without significant axial deviation[12]. Detailed information on the fabrication of fiber electrodes and on their electrical characteristics is given in Reitböck[13].

The tungsten-glass fiber electrodes are best suited for the recording of extracellular action potentials from large cortical neurons. For recordings from small cortical neurons and fibers, and for the recording of slow potentials, silver-silverchloride plated platinum-rhodium-quartz fiber electrodes as described[13] are preferable.

The multi-electrode drive (fig. 2). The fiber electrodes are guided by insertion into stainless steel capillary tubes of 120 µm ID and 220 µm OD. 7 such tubes, in a concentric arrangement, are combined within a larger stainless steel tube (A) of 700 µm ID and 1 mm OD. This tube, sealed by an O-ring, can be inserted into a recording chamber which may be implanted on the skull of the experimental animal[14]. In order to prevent fluids from entering the capillary tubes, the fiber electrodes penetrate a thin latex membrane that seals the tip of the 1-mm tube. The guide capillaries (B) are interrupted at the capillary trap (C) in order to stop a possible flow of ascending chamber fluid. Electrode movement is accomplished in the following way: The guide tubes terminate on a rigid platform (G) opposite to 7 piezoelectric coupling elements (brakes) (E) which, if activated, securely hold the fibers in their position. Exactly aligned with these tubes is another set of tubes (F) and piezoelectric coupling elements (clutches) (J) attached to a movable platform which is driven in 1-µm steps by a stepping motor (O). If an electrode is to be moved, the brake is electrically disengaged via connectors (L) and the clutch is activated via (M). Thereby, the fiber electrode becomes mechanically connected to the moving platform for forward or backward movement in multiples of 1-µm steps. If a recording position with good isolation of single unit potentials is reached, the clutch is electrically disen-

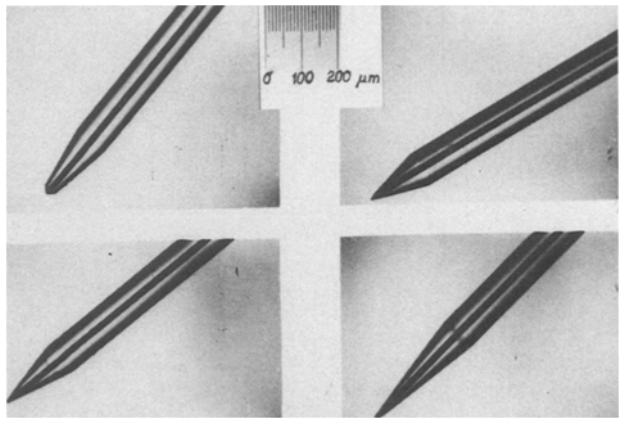

Figure 1. Tungsten-Nonex glassfiber microelectrodes with various tip configurations. For high electrode impedances, a double conus can be ground (upper left quadrant); a small grinding angle results in low electrode impedance (lower right quadrant).

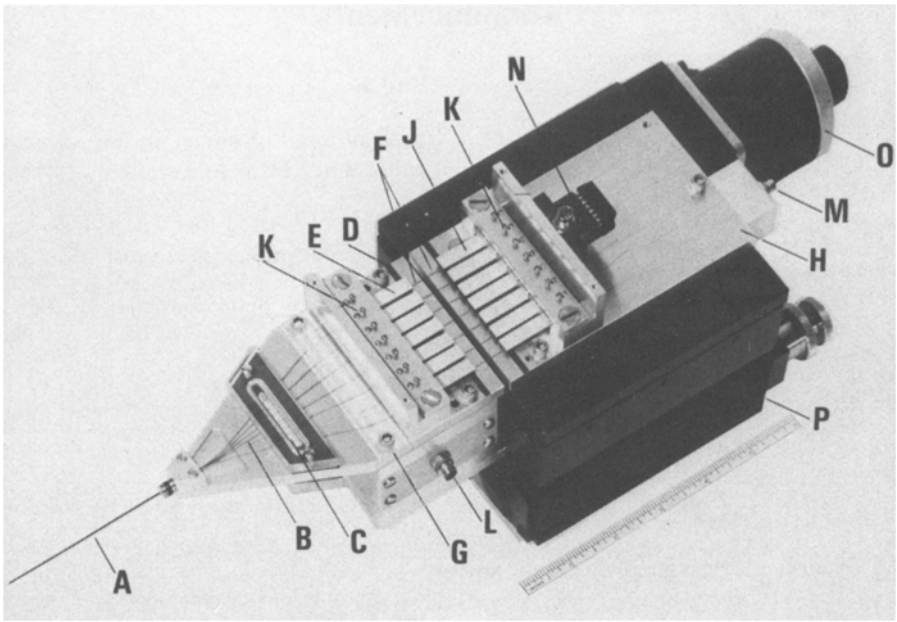

Figure 2. Microdrive for independent position control of seven microelectrodes. The outer guide tube (A) contains the 7 steel capillaries (B) in which the fiber electrodes travel. The capillaries terminate in the capillary trap C. In exact alignment, a 2nd section of the capillary tubes guides the fibers to an elastic layer (D) for engagement with the brake (E). 2 short sections of capillary tubes (F) align the fibers over the gap between the rigid (G) and the movable (H) platform of the microdrive. A system of 7 clutches (J) selectively engages the electrodes with the movable platform (H). 2 sets of screws (K) are provided for the positional adjustment of the clutches and brakes. The control of the clutch and brake movements occurs via 2 seven-pin (and ground) connectors (L) and (M). The fiber electrodes terminate at the connector assembly (N). The movable platform (H) is driven by the stepping motor (O), and the entire assembly is mounted on a manual microdrive (P).

gaged and the brake is engaged, thereby keeping the electrode in position. Each of the remaining electrodes is similarly brought into the recording position. Associated with each fiber is a digital counter, that indicates the total electrode movement.

The piezoelectric clutches and brakes (made of bimorphs with an elastic liner), as well as the speed and direction of the stepping motor, can be controlled via a keyboard or by a computer. Mechanical adjustment of the brake and clutch bimorphs is via 2 pairs of screws (K).

This configuration of electrodes and drive was arrived at as the result of several developmental steps and modifications dictated by experiences gained with experimental trials. The multi-electrode drive is particularly suited for recordings from cortical areas. The 100-µm fiber electrodes used in this design are sturdy enough to penetrate the dura mater. Recordings from structures up to 10 or even 15 mm below the cortical surface are possible if slight radial deviations are acceptable. Experimental results obtained with a 19-channel recording system[15] based on the design principles described in the foregoing have been reported[16,17].

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