axis approximately normal to the orbital plane—appears to be about 10°K hotter than the "polar" regions. We have used quotation marks around the terms *insolation, equatorial,* and *polar* because such a mode of rotation *may* be inconsistent with the recent interpretation of radar observations (*4*). Fortunately, both kinds of observations can be repeated at various phases of Venus, perhaps with more sensitive and accurate equipment in a year or so, and other types of ground-based observations may also prove to be of significance to the question of rotation.

The other feature of interest in Fig. 1 is the anomalously warm area in the southern hemisphere of Venus, near the terminator. Observations of this region on the other three mornings, although not as detailed as those shown in Fig. 1, definitely show that the structure changes radically in temperature distribution and geographic extent over a 24-hour time interval, whereas the remainder of the disk remains unchanged. The feature may justly be described, therefore, as a storm in the atmosphere of Venus. Continued observation of such features in the future should provide a powerful means of investigating the dynamics of the atmosphere of Venus (*5*).

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Local Anesthetic Drugs: Penetration from the Spinal Extradural Space into the Neuraxis

Abstract. *Local anesthetics, injected into the spinal extradural space, can be recovered from the spinal cord and brain. Transport from the extradural space into the neuraxis is independent of an active circulation. Distribution is greatest in the periphery of the cord and is most intense near the site of injection. The drugs probably diffuse into the subperineural spaces of the mixed nerves and then pass centripetally along the spinal roots into the cerebrospinal fluid and the cord.*

Conduction anesthesia by the injection of local anesthetic drugs into the extradural (epidural) space of the spinal canal is a well-established technique in human and veterinary surgical practice, but the principal site of neural blockade is still in doubt. The possible sites of action which have been suggested are the mixed nerves in the paravertebral spaces, after passage through the intervertebral foramina (*1*), the dorsal root ganglia (*2*), or the spinal cord itself (*3*). There is some evidence both for and against each of the three possibilities, but spinal cord or neuraxial spread has not been directly investigated, although indirect clinical data suggests that it does occur (*4*).

A pilot study was carried out with colorimetric and radiometric techniques in adult dogs to determine if local anesthetic drugs do pass from the extradural space to the spinal cord and brain. Under light pentobarbital anesthesia the sacrum was exposed and a polyethylene catheter advanced through a sacral burr hole into the extradural space, until the tip was opposite the first lumbar vertebra. Extradural blockade was produced by 2 percent lidocaine (in eight dogs) or mepivicaine (in one dog), labeled with C^{14} (2 μc/ml). Adrenaline hydrochloride (1/200,000) was added to the solutions to reduce vascular absorption. These solutions were injected through the catheter by increments of 3 to 5 ml at intervals of 30 minutes, up to a total dose of 7.5 to 15 ml containing 150 to 300 mg of active drug. The animals were killed by exsanguination 45 minutes after the last injection, and the cerebrospinal fluid was drained by cisternal puncture. The epidural space and catheter were flushed with 100 ml of normal saline to remove any residual analgesic solution, and the brain was removed. The spinal cord with meninges and extradural roots was then carefully dissected out in one piece and divided between tight ligatures into four equal lengths. Each of these was dissected to provide samples of extradural roots, intradural roots, dura mater, piarachnoid, and cross sections of stripped cord.

Samples were analyzed for radioactivity by a counting method, and for unchanged lidocaine by Sung and Truant's modification of the methyl-orange technique of Way *et al.* (*5*). The former method does not distinguish between the unchanged labeled drugs and their metabolites, whereas the latter can be made highly specific for unchanged lidocaine by using an appropriate phosphate buffer at a *p*H of 6.22. Agreement between the two methods would indicate that the radioassay was measuring unchanged drug. Since the colorimetric method requires relatively large amounts of tissue for accurate results, it was not suitable for the small quantities of dura, pia, and spinal roots which were available. However, from specimens of cerebellum, medulla, cord, cerebrospinal fluid, and blood, satisfactory assay was made by both methods.

Duplicate samples of solid specimens were prepared for counting by the following procedure. Samples of 50 mg of wet tissue were digested for 48 hours in Hyamine hydroxide [*p*-(diisobutyl-cresoxyethoxyethyl)-dimethylbenzylammonium hydroxide], and then heated in a water bath at 70°C for 2 hours or until clear. Then 0.5 ml of 100 percent ethanol was added to each sample together with 19 ml of phosphor [0.3 percent of 2,5-diphenyloxazole and 0.01 percent of 1,4-bis-2(5-phenyloxazolyl)-benzene in toluene]. Samples of blood and cerebrospinal fluid were treated with 15 percent trichloracetic acid followed by 10*N* sodium hydroxide and extracted in ethylene dichloride for counting. Samples were assayed for C^{14} content with a Packard Tri-Carb liquid-scintillation spectrometer (model 314-X). An internal standard of C^{14} was used to correct for quenching and efficiency of counting (*6*).

In two dogs the procedure was modified for autoradiographic examination of the neuraxis. The spinal column was excised in 1-inch lengths, and the enclosed segments of cord were extruded and dropped into liquid nitrogen or a mixture of carbon dioxide and acetone. Sections were cut 25 to 30 μ thick on a cryostat at −20°C. The sections were transferred directly to microscope slides, covered with Mylar film (DuPont) 10 μ thick, and placed in contact with Ilford Ilfex "No-screen" x-ray film under gentle pressure from foam-rubber pads. The films were exposed

for periods of 20 to 80 days at a temperature of −15°C in light-proof boxes containing a dehydrating agent (Dryerite).

After 21 days' incubation, the autoradiographs showed activity concentrated in the periphery of the thoracic and lumbosacral parts of the cord, but none could be seen in the cervical cord or in the medulla. Exposure for longer periods, 45 to 80 days, showed some activity in the latter regions. In these the activity was more evenly distributed throughout the section than it was at lower sections of the spine.

There was fairly close agreement between the colorimetric and radiometric assays in those samples where both methods were used, despite the inherent difficulty of obtaining identical sampling conditions in tissues with the uneven distribution shown in Fig. 1. It therefore seemed reasonable to calculate the unchanged xylidide content of each radioactive sample from its C^{14} content. The average results from four dogs are shown in Table 1. Mean values vary widely because of the sampling difficulties already mentioned as well as because of the relatively unstandardized conditions of this pilot investigation, but certain trends are apparent. Relatively little drug was present in the dura mater itself, whereas the extradural and intradural roots on each side of it, and the piarachnoid contained larger amounts.

The comparatively low concentrations in the dura were not the result of preferential leaching by the final lavage of the epidural space with saline, for a similar relationship of dural and pial concentrations was found even if the saline irrigation were omitted, when the weights of drug in all elements of the cord were raised proportionately. For example, in one such experiment an epidural dose of 200 mg of lidocaine gave rise to a dural concentration of 1730 μg/g, whereas the piarachnoid at the same segmental level contained 2280 μg/g. Structures nearest the site of injection had the highest concentrations of drug, but significant amounts could be found in the medulla, cerebellum, and occipital cortex.

Table 1. Radiometric and colorimetric assays of brain, spinal cord, and meninges from four dogs after extradural injection of C^{14}-labeled lidocaine and mepivicaine, expressed in micrograms per gram (wet weight). Colorimetric assays for lidocaine are shown in parentheses. Abbreviations: E.D.R., extradural spinal roots; I.D.R., intradural spinal roots; C.S.F., cerebrospinal fluid; C, M, T, S, cervical, midthoracic, thoracolumbar, and sacral, respectively.

	Spinal cord and meninges					Brain			
Section	E.D.R.	Dura	I.D.R.	Pia	Stripped cord	Medulla	Cerebellum	C.S.F.	Blood
				Dog 1, 11.2 kg, 300 mg lidocaine					
C		150			200 (42)				
M	930	250	(900)	(235)	210 (210)	19 (63)	34 (72)	52 (42)	6.4 (1.6)
T	915	740			250 (310)				
S		710	930	(430)	280 (210)				
				Dog 2, 15.0 kg, 300 mg lidocaine					
C	735	120	170		50 (35)				
M	750	140	700	670	210 (200)	56 (1.0)	27 (19)	27 (32)	5.2 (3.4)
T	1380	520		580	200 (180)				
S	1080	200	745	450	135 (100)				
				Dog 3, 16.2 kg, 100 mg lidocaine					
C		440		170	125 (0)				
M	950	510			490 (105)		14 (17)	(48)	(0)
T		240		900	870 (340)				
S		240		270	190 (190)				
				Dog 4, 19.9 kg. 200 mg mepivicaine					
C	190	110	175	215	140				
M	365	335	645	630	300	9		29	2.4
T		450		780	435				
S	650	355	730	1070	265				

Venous-blood concentrations were consistently low, and transport into the neuraxis appeared to be at least partly independent of the blood stream. This was confirmed by making extradural injections of 200 mg of lidocaine at the level of the first lumbar vertebra in three dogs after death by exsanguination. Colorimetric assays of the unstripped cords (cord and piarachnoid) from these experiments showed an average lidocaine concentration of 588 μg/g (wet weight) in the lower thoracic region, 129 for the cervical, 384 for the midthoracic, and 429 for the lumbosacral. Similar assay of cisternal cerebrospinal fluid, cerebellum, and medulla resulted in values of 27, 92, and 88 μg/g.

These results demonstrate that the dura is not a functional barrier to the passage of local anesthetics from the spinal extradural space into the neuraxis, and they confirm a previous suggestion that intracranial structures can be affected by excessive doses of local anesthetics given into the extradural space (*4, 7*). The route by which these drugs enter the neuraxis is still a matter of conjecture. One pathway may be by diffusion through the perineurium of the mixed spinal nerves into the subperineural space, and then centripetally along the nerve roots to the spinal cord and subarachnoid space (*8*). The high concentrations in both the extradural and the intradural portions of the spinal roots suggests that this is a likely possibility. Alternatively, diffusion may take place directly across the dura into the cerebrospinal fluid. Partitioning between cerebrospinal fluid and neuraxis would then be determined by the high oil-water solubility ratio of these lipophilic drugs (*9; 10*).

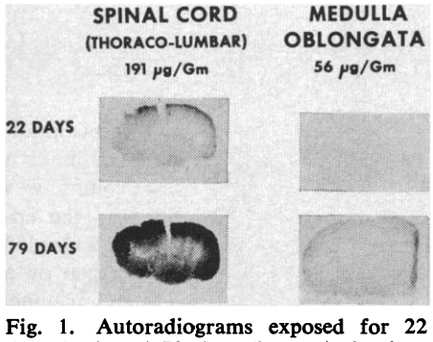

Fig. 1. Autoradiograms exposed for 22 days (top) and 79 days (bottom). Sections of spinal cord (thoracolumbar) and medulla oblongata of dog killed 45 minutes after epidural injection of 200 mg of C^{14}-labeled lidocaine. Sections contain 191 μg/g and 56 μg/g of lidocaine, respectively. Dense line on right of medullary section is an artifact from folding of tissue.

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Intracranial Self-Stimulation in Man

Abstract. *Intracranial self-stimulation techniques, modified for use with neuropsychiatric patients, provide data suggestive of positive and negative reinforcing properties of brief electrical stimulation to various subcortical structures of the human brain.*

Olds and Milner (*1*) first demonstrated in 1954 that rats will press a lever in order to obtain brief electrical stimulation to various subcortical regions via permanently implanted electrodes. Subsequently, this finding has been replicated many times in rats, and the species generality of the phenomenon has been extended in controlled studies to include the goldfish, guinea pig, bottlenose dolphin, cat, dog, goat, and monkey. These and other data relating to the reinforcing properties of electrical stimulation to certain brain areas have been comprehensively reviewed in a recent article by Olds (*2*).

Since Heath's initial observations (*3*), several reports have appeared describing subjective experiences of an apparently pleasurable nature accompanying electrical stimulation of deep structures in the human brain (*4–6*). Only two previous attempts have been made, however, to employ intracranial self-stimulation (ICSS) techniques with human subjects. Sem-Jacobsen and Torkildsen (*5*) report that patients have stimulated their own brains by means of a button switch wired into the stimulation circuit, and Heath (*7*), prior to this research, equipped a patient with a small portable self-stimulator with three buttons which permitted delivery of electrical stimuli of fixed parameters to any of three subcortical sites.

The present study represents an exploratory attempt to investigate human ICSS behavior under strict laboratory conditions such as have been characteristically employed in animal studies. A full report of results to date is in preparation. The present report summarizes some of the major findings.

In the series of depth electrode studies at Tulane (*3, 8, 9*), the primary motivation has always been therapeutic. Only patients who have failed to respond satisfactorily to existing therapies have been studied and treated with these techniques. Electroencephalographic recordings from depth electrodes permit more exact localization of disordered function. More information thus becomes available concerning the nature of the disease processes under study, and more precision is possible when intervention, surgical or other, is indicated, as, for example, in epilepsy and other neurological disorders. With schizophrenic patients, focal electrical stimulation to selected subcortical sites has been shown to produce at least temporary therapeutic benefit (*3, 5, 8*) and, in the Tulane studies, stimulation of activating and "pleasure-inducing" regions has particularly benefited retarded, anhedonic, chronic schizophrenic patients. A vast number of animal ICSS data attest to the powerful reinforcing properties of intracranial stimulation and its consequent efficacy in the modification of behavior (*2*). Moreover, some of these data (see, for example, *10*) implicate abnormal functioning of brain "reward systems" as a primary factor in certain mental disorders, demonstrate the unique value of ICSS techniques in elucidating central effects of psychoactive drugs, and promise eventual pharmacological control of reward-system function in man. The potential usefulness of ICSS procedures in the study and treatment of disordered human behavior is readily apparent. The present research was designed to explore ICSS techniques and to provide preliminary data on effective stimulus parameters and brain "reward" areas in man.

Findings presented here were obtained from a chronic catatonic schizophrenic patient (No. B-12) with multiple depth electrodes in place for 4 months prior to this study. Implanted electrodes were of two types: the "regular" single silver ball (*8*), and a stainless steel array providing multiple contact points (*11*). A roentgenographic, stereotaxic technique was employed for accurate implantation and subsequent maintenance of the electrodes (*12*). Patient B-12 is a 35-year-old male with a history of schizophrenia since childhood who has been continuously hospitalized without improvement for the past 9 years. Among other symptoms, he displays a marked tendency toward perseverative behavior which limited ICSS techniques suitable for use with him.

During experimental sessions the subject was seated alone in a soundproof room with a large lever and a hand button available to him. All stimulation, recording, and control apparatus was housed in an adjoining room from which the subject could be observed through a one-way–vision window. Communication with the subject was by means of an intercom system. For all work reported here, the stimulating wave form was a monophasic rectangular pulse of 0.2 msec duration, delivered at 100 pulses per second for a fixed stimulus train of 0.5 second. Stimulation was provided by a Grass S-4 stimulator through a stimulus isolation unit and stimulus monitoring device to the subject. Unless otherwise specified, stimulation was bipolar between electrodes 4 mm apart. The lever and hand button allowed the subject to stimulate his own brain. Functioning of these switches, however, could be controlled by the experimenters to provide current with one device and not the other, or currents of different intensity with the two devices. No visual or auditory cues which might signify such changes were available to the subject.

In our earliest work with a single lever it was noted that while the subject would lever-press at a steady rate for stimulation to various brain sites, the current could be turned off entirely and he would continue lever-pressing at the same rate (for as many as 2000 responses) until told to stop. Such data obviously justified no conclusions as to reinforcing or "rewarding" properties of the stimulation, but did underscore the need for stringent controls in brain stimulation work with human subjects. Three additional techniques have produced reliable evidence of reinforcing effects of ICSS in man. We have called these the *three current levels, free choice,* and *forced choice* procedures.

The *three current levels* method utilized a single lever. Subject was instructed to respond to a tone signal by pressing the lever (self-stimulating). If he felt nothing or if the stimulus felt neither "good" nor "bad," he was to press three times; if it felt "bad," he was to press less than three times; if it felt "good," he was to press repeatedly as long as he wished or until told to stop (arbitrarily after ten responses). After extensive exploration of a given electrode site for preliminary determination of rewarding and aversive