A digital *p*H-meter (Orion model 801) equipped with cationic (Beckman 39137) and saturated calomel electrodes was also used to measure the extent of binding of Na^+, K^+, Rb^+, and Cs^+ with isomer IA.

The results from calorimetric and potentiometric measurements are in agreement and indicate that alkali metal ions have the following order of decreasing affinity for isomers IA and IB

$$K^+ > Rb^+ > Cs^+ \gg Na^+, Li^+ \qquad (2)$$

Thus, the permeability order for compound I has a firm thermodynamic basis, and similar thermodynamic correlations might be expected for structurally related antibiotics.

Neither Na^+ nor Li^+ has a measurable affinity for isomer IA or IB. The potassium ion, Rb^+, and Cs^+ showed stronger interaction with isomer IA than with IB; however, only in the cases listed in Table 1 was the change in heat sufficiently large to permit calculation of the attendant thermodynamic values.

Compound I represents an interesting new class of complexing agents which selectively interact with cations of the alkali metal group. The similarities in behavior of compound I and the above-mentioned antibiotics toward alkali metal cations are not unexpected if one considers the similar uncharged character and macrocyclic structures having cavities ringed with centrally oriented oxygen atoms.

REED M. IZATT
J. HOWARD RYTTING
DENNIS P. NELSON
BARRY L. HAYMORE
JAMES J. CHRISTENSEN
Departments of Chemistry and *Chemical Engineering, Brigham Young University, Provo, Utah 84601*

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Surgery in the Rat during Electrical Analgesia Induced by Focal Brain Stimulation

Abstract. *Chronic monopolar electrodes were implanted in the region of the midbrain central gray in eight rats. In three rats, continuous 60 cycle-per-second sine-wave stimulation resulted in an electrical analgesia defined by the elimination of responses to aversive stimulation while general motor responsiveness was retained. Exploratory laparotomy was carried out in these animals during continuous brain stimulation without the use of chemical anesthetics. Following surgery, brain stimulation was terminated, and responses to aversive stimuli returned. Electrodes effective in inducing electrical analgesia at the lowest currents were located at the dorsolateral perimeter of the midbrain central gray. It was concluded that focal brain stimulation in this region can induce analgesia in the absence of diffusely applied "whole brain" stimulation.*

A number of investigators have reported electrical analgesia or electrical anesthesia during diffuse application of electrical current between external scalp electrodes. The usual procedure is to apply electrodes to the opposite sides of the skull and to gradually increase the electrical current until the subject no longer responds to noxious stimulation. Comprehensive reviews of this work have appeared in the recent literature (*1*).

The purpose of the present investigation was to determine if *focal* application of electrical currents alone could induce analgesia or anesthesia without application of currents across the entire brain. Previous work in our laboratory (*2*), together with anatomical studies (*3*) and lesion experiments (*4*), suggested that stimulation of periaqueductal midbrain structures might reduce responsiveness to noxious stimulation.

Chronic monopolar stainless steel electrodes and subcutaneous grounds were stereotaxically implanted in each of eight male Wistar rats. The surgical procedure was essentially that reported by Miller (*5*). Electrodes were directed to areas in and around midbrain central gray at deGroot anterior-posterior coordinates 0.0 (*6*). To test for aversive responsiveness, a method reported by Kreele and Smith (*7*) was used. This involves the application of mechanical pressure to the paws and tail with an "analgesiometer" fashioned from a hemostat. The aversive response of the animal is scored simply as present or absent. All animals responded vigorously to hemostat-applied pressure both before and after implantation of electrodes.

Ten days after electrode implantation, each animal was tested in the following way. Continuous, constant-current, 60 cycle/sec sine-wave stimulation, starting at 5 μa root mean square (r.m.s.), was delivered through the indwelling electrode. At 15-second intervals, the current was increased in 5-μa steps until either aversive responses to hemostat-applied pressure were eliminated or 35 μa was reached. Of the eight electrodes tested, stimulation through three yielded electrical analgesia when the current reached 15, 20, and 30 μa. The three animals showing this effect were then scheduled for laparotomy.

On the day of surgery, the brain stimulation procedure was essentially the same. Since the animals were able to walk about at the levels of current used, they were secured in a supine position for surgery. Abdominal skin, muscle, and peritoneum were sectioned and retracted sufficiently to permit visualization of the abdominal cavity. This was followed by closure of the incisions with wound clips. None of the surgical procedures evoked aversive reactions. It

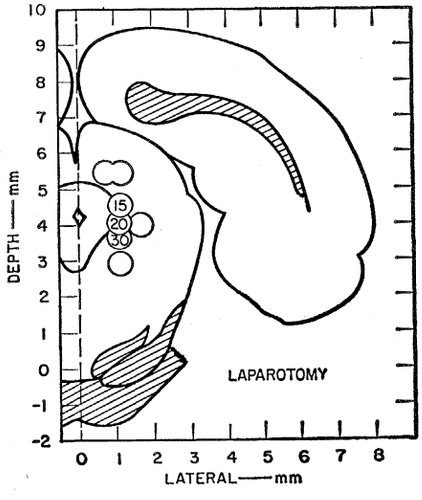

Fig. 1. Composite diagram indicating location of electrode tips through which stimulation produced analgesia.

could be demonstrated that the animals were not paralyzed, since quick movements in the animals' visual field or loud noises elicited startle and struggle (*8*).

Following surgery, brain stimulation was discontinued. Some residual skin analgesia was noted for several minutes, but vigorous aversive responses to hemostat-applied pressure returned fully within 5 minutes. After 24 hours, all animals were killed and their brains were removed for histological verification of electrode placement. After a 2-week period in 10 percent formalin, the brains were frozen, sectioned at 50 μ, and stained with cresyl violet. Figure 1 is a composite diagram showing the brain region where stimulation induced analgesia to hemostat-applied pressure and to abdominal surgery. The circled numbers are the r.m.s. currents required for electrical analgesia. Circles without numbers are points at which stimulation did not induce electrical analgesia at the maximum current used (35 μa r.m.s.). As shown in this figure, effective stimulation sites are clustered at the dorsolateral perimeter of the central gray. One noneffective electrode tip was not located with certainty at histology and does not appear in the diagram.

These effects have been interpreted as analgesic since all animals could move about during brain stimulation and exhibited startle to sound and visual stimuli, but none struggled in response to hemostat-applied pressure or surgical procedures. The analgesia was attributed to electrical stimulation and not to tissue damage, which might have been caused either by electrode implantation or during the application of electrical currents, since the analgesia occurred only during and shortly after stimulation, and was entirely reversible.

This demonstration of analgesia induced by focal brain stimulation raises the possibility that electroanesthesia, typically induced by "whole-brain" stimulation, may not require undifferentiated current flow through multiple brain regions. Of all the current diffusely applied, only a small portion, passing through specific brain areas, may be required to induce analgesic effects. The remaining current may either serve no purpose or produce adverse cardiac, respiratory, and other effects encountered during the induction of electroanesthesia (*1*). Obviously, for both ethical and practical reasons, human electroanesthesia must continue to be induced from surface and not depth electrodes. However, by identifying brain systems where stimulation induces analgesia, and other regions that do not, efforts can be made to develop techniques for directing externally applied currents to "effective" brain regions. If progress is made in this direction, a safe, reliable, surgical-level electroanesthesia may eventually be developed for use in man.

DAVID V. REYNOLDS
Stanford Research Institute,
Menlo Park, California 94025

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Sex Differences in Verbal and Performance IQ's of Children Undergoing Open-Heart Surgery

Abstract. *Boys with congenital heart defects had essentially normal Verbal and Performance IQ's on preoperative and postoperative tests; but girls' Verbal IQ's were significantly lower than those of boys, and significantly lower than girls' own Performance IQ's. This sex difference among congenital heart cases reverses the usual finding that girls excel on Verbal tests.*

A project designed to evaluate the effect of heart disease and open-heart surgery on mental development finds a sex difference in the mental abilities of children with congenital heart defects. In normal, nonpathologic samples, sex differences are seldom significant. This result is due in part to the initial test construction or standardization procedure of eliminating specific test items which are "unfair to one sex or the other" (*1*, *2*). In spite of efforts to avoid "unfair" tests, investigations frequently report male superiority on arithmetic tests and tests of spatial relations, and female superiority on vocabulary and other aspects of language development (*3*). The superiority of girls in verbal ability is interpreted as due in part to the more rapid maturation of girls which is quite marked in the years of language acquisition (*4*), but this superiority continues into the adult years (*5*). Boys' higher scores on tests of spatial relations is attributed to sex-linked inherited ability, judging by the patterning of parent-child resemblance on this trait (*6*). Further evidence for a genetic basis of the patterning of test performance is found in children with chromosomal aberrations such as trisomy-21 and Turner's syndrome. Girls with this latter genetic makeup (a single X chromosome instead of the usual two) have IQ's covering the entire range of the normal curve, but there is a significant difference between their Verbal and Performance IQ's. Their Verbal scores are high relative to normal samples, and their Performance scores, especially those involving perceptual organization, are definitely low. This difference between their Verbal and Performance IQ's is significant beyond the .01 level of probability (*7*). We have found a difference in precisely the reverse direction for girls with congenital heart disease, both before and after open-heart surgery. Girls with congenital heart difficulties have low Verbal scores relative to their own Performance scores, and relative to the Verbal scores of boys.

The sample of the present study included initially 60 boys and 58 girls with congenital heart defects. These children, ranging in age from 5 to 16 years, were tested before and after surgery. More than three-fourths of the total sample had their surgery between