tested with an overcast sky. Since these differences in cloud conditions had no apparent effect, results for all subjects have been grouped together.

For five subjects the correct positioning of the head was determined by a headboard preset by the experimenter; for 11 subjects it was determined by the subject's own estimate. Since this factor had no effect on the results, all 16 subjects have been combined below.

The subjects experienced some initial difficulty in assuming the correct head positions and in fixating a point on the "surface" of the sky. For this reason, the first two trials for each subject are considered as practice, and results are reported only for the last two trials. It should be noted, however, that the results for the practice trials were very similar to the results for the final trials.

Of the 16 subjects, 14 saw the horizon afterimage as larger than the 90° afterimage; 13 saw the horizon image as larger than the 45° image. The two subjects who did not report the effect described above both experienced extreme difficulty in following the instruction to fixate a point on the "surface" of the sky. It will be remembered that all judgments in the main experiment were monocular; after the monocular trials, both of these subjects were given a binocular trial, whereupon they reported the horizon image larger than the zenith image. Omitting these two subjects, the mean size-ratio for the horizon/90° comparison was 1.625, with S.D.=.252. For the horizon/45° comparison, the mean size-ratio was 1.50, with S.D.=.266. Thus it can be seen that the perceived size of the afterimage varies in a manner predictable from Emmert's Law and the reported appearance of the sky as a flattened dome.

It is interesting to note that the magnitude of the effect reported above is quite similar to Kaufman and Rock's results for the moon illusion, the horizon moon/zenith moon ratio varying from about 1.35 to about 1.50, depending on the conditions of observation in their study.

The present study illustrates the way in which sensory inputs become significant objects as they are mapped into psychological spaces. Conversely, the object can be used as a probe for investigating the nature of these spaces.

WILLIAM L. KING
HOWARD E. GRUBER
Department of Psychology, University of Colorado, Boulder

References and Notes

1. For a discussion of this hypothesis see *Helmholtz's Physiological Optics*, J. P. C. Southall, Ed. (Optical Society of America, 1925), vol. 3, pp. 290 ff.
2. A. H. Holway and E. G. Boring, *Am. J. Psychol.* **53**, 109 (1940).
3. L. Kaufman and I. Rock, paper presented at the meeting of the Eastern Psychological Association, New York, Apr. 1960.
4. H. Gruber, W. King, S. Link, paper presented at the meeting of the Western Psychological Association, Seattle, Wash., June 1961.
5. E. G. Boring, *Sensation and Perception in the History of Experimental Psychology* (Appleton-Century, New York, 1942), p. 292.

19 October 1961

Drug Administration to Cerebral Cortex of Freely Moving Dogs

Abstract. A method is described to implant a permanent indwelling polyethylene tube venting to the surface of the cerebral cortex of the dog. Morphine, amobarbital, or imipramine was administered through the tube, and behavioral changes were observed in unanesthetized and unrestrained animals. The results are different from those occurring after intraventricular injection.

Other workers have described the effect of topical application of drugs to the cerebral cortex. In their experiments, the animal was anesthetized or immobilized, and usually a large area of the cortex was exposed (*1*). This report, however, describes a new technique for administering drugs to the cortex in conscious and unrestrained dogs, permitting the observation of behavioral changes. By this technique, the drugs were injected into the arachnoid space (*2*) overlying the cerebral cortex, through a polyethylene tube permanently implanted in the skull (intra-arachnoid injection over cerebral hemisphere).

In this study employing the intra-arachnoid injection over cerebral hemisphere, three drugs were given. The results from the intra-arachnoid injection were compared with those from intraventricular injection of the drug through a permanently implanted cannula, in order to study the site of action of drugs.

To install the tube, a midline incision of about 5 cm was made near the vertex of the head of the dog under pentobarbital anesthesia. The surface of the skull was exposed and a hole 4.5 mm in diameter was drilled through the skull directly above the lateral ventricle (*3*). In this hole either a polyethylene tube for intra-arachnoid injection or a metal cannula for intraventricular injection was implanted. The location of the hole was carefully determined in order to permit the intraventricular implantation. The determination was done without the use of stereotaxic apparatus which produces deafness. Using the external occipital protuberance as the center of a circle, I drew an arc intersecting the midline close to the vertex of the skull. The radius of the arc was half the distance between the supra-orbital process of the frontal bone and the external occipital protuberance. The hole was drilled at a point 6 mm lateral to this midline intersection. The hole was perpendicular to the Frankfort horizontal plane, as determined by the external meatus of each ear and the lower edge of the ocular orbits.

To implant the tube an incision was made in the dura mater through the hole. The polyethylene tube (Intramedic; PE 10; I.D. 0.011 inch; O.D. 0.024 inch) connected to a sawed-off hypodermic needle was inserted 2 to 3

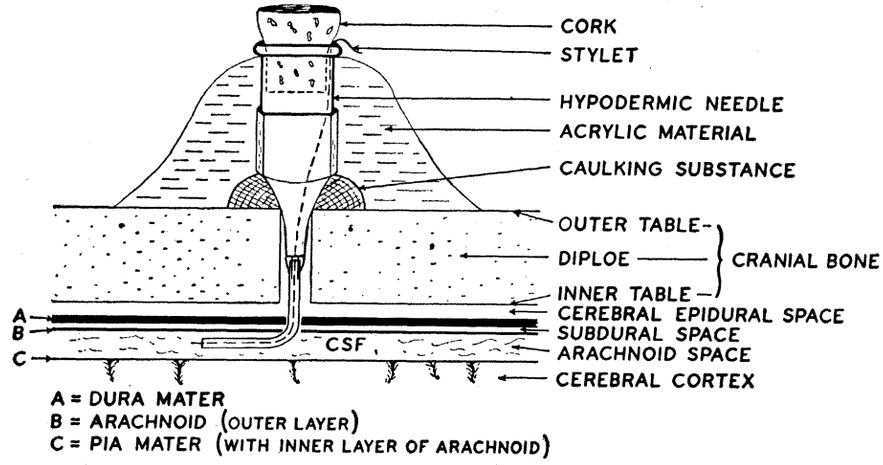

Fig. 1. Schematic representation of setup for permanent indwelling polyethylene tube into the arachnoid space.

mm into the arachnoid space. The tube and needle contained a fine silver wire stylet, and the top of the needle was closed with a cork. The needle was fixed in place with dental caulking substance and acrylic material (Fig. 1). Thus the tube was vented to the cerebrospinal fluid bathing the cerebral cortex.

For intraventricular implantation (*4*), a metal cannula specially made for this purpose (*3*) was screwed into the hole instead of the tube and needle. The cannula was likewise fixed in place with dental caulking substance and acrylic material.

A drug was not administered until 1 week after the tube or the cannula was implanted. The volume of the drug did not exceed 0.2 ml, and the *p*H was controlled. For study of the distribution of the drug, each dog was sacrificed after a single experiment and 0.2 ml of aniline blue dye was given through the tube or cannula. With intra-arachnoid injection, this dye distributed over the entire hemisphere, but was concentrated in an area about 1 cm^2 around the tip of the tube. The exact distribution depended on the direction of the tube. Intraventricular injection, however, distributed the dye throughout the ventricular system of the brain, as was reported by Kumagai *et al.* (*3*).

Results on 21 dogs (8.6 to 14 kg) were selected for this report. Morphine, amobarbital, or imipramine were administered to these dogs.

Intra-arachnoid injection of 2 mg or 4 mg of morphine HCl (three dogs) provoked no marked response except frequent scratching of the head, which suggested itching or irritation. However, 2 mg of morphine HCl injected into the lateral ventricle (three dogs) evoked, in order: licking, vomiting, defecation, signs of fear, restlessness, drooping hind quarters, profuse salivation, exophthalamus, and ceaseless pacing. Complete loss of appetite was also noticed. These symptoms started within 1 minute after the injection and continued for 6 hours. Analgesia was not found.

Intra-arachnoid injection of 50 mg of amobarbital sodium (three dogs) produced variously no change, slight motor ataxia, or a decrease of activity. An additional injection (100 mg) given 1 hour later (two dogs) caused moderate motor ataxia and muscle weakness, especially of the hind quarters. The ataxia and weakness of muscles began after 10 minutes and continued for 20 minutes. An intraventricular injection of 50 mg of the drug (three dogs) produced within 1 minute licking, vomiting, and defecation, followed by coughing, sneezing, hiccoughing, motor ataxia, and head drop (like that produced by curare). About 10 minutes after injection the animal in prone position pedaled with all legs for 2 minutes, and for the next 7 hours the dog had no appetite, wandered continuously, panted, and barked more than usual. In one experiment 10 minutes after the injection, respiration ceased for 10 minutes. The animal was readily maintained by artificial respiration and seemed conscious throughout.

No unusual behavioral change was noticed after intra-arachnoid injection of 6 mg or 12 mg of imipramine HCl (three dogs). However, intraventricular injection of 2.5 mg (three dogs) caused vomiting and defecation within 1 minute. During the 2 hours after the injection, the following abnormal behavior was observed: slight motor ataxia, barking, twitching of the neck muscles, and behavioral depression. The depression continued for 7 hours. In another experiment in which 6 mg of the drug were injected (three dogs), depression was more marked, with slowed motor activity, drowsiness, and lack of response to previously recognized stimuli.

Thus, the behavioral effect obtained by intra-arachnoid injection differed from those obtained by intraventricular injection, the former method producing little response to the three drugs tested. However, not all drugs produced such slight response by the intra-arachnoid injection. For example, potassium chloride or acetylcholine chloride induced marked behavioral depression, and strychnine sulfate provoked generalized convulsions (*5*).

TSUKASA KOBAYASHI*
Thudichum Psychiatric Research Laboratory, Galesburg State Research Hospital, Galesburg, Illinois

References and Notes

1. J. G. Dusser de Barenne *et al., Research Publs. Assoc. Research Nervous Mental Disease* **21**, 246 (1942); J. P. Schadé, *J. Neurophysiol.* **22**, 245 (1957); R. P. Bircher *et al.*, scientific exhibit at AMA annual meeting, 26 June 1961.
2. S. Lups and A. M. F. Haan, *The Cerebrospinal Fluid* (Elsevier, New York, 1954).
3. H. Kumagai, T. Kobayashi, H. Kato, H. Sokabe, S. Yamamoto, in preparation; *Nippon Yakurigaku Zasshi* **55**, 120 (1959).
4. W. Feldberg and S. L. Sherwood, *J. Physiol. (London)* **120**, 3P (1953).
5. I am most grateful to Harold E. Himwich for his constant interest and guidance in this work.

* Fulbright research fellow on leave from the Department of Psychiatry, University of Tokyo, Tokyo, Japan.

29 January 1962

Are New Neurons Formed in the Brains of Adult Mammals?

Abstract. In an autoradiographic investigation, the production of brain lesions in rats was combined with intracranial injection of thymidine-H^3. Nuclei of numerous glia cells were found labeled in brain regions associated with the traumatized areas. In addition, some neurons and neuroblasts showed labeling, suggesting the possibility of proliferation of neurons in adult rats.

It is commonly stated that in higher vertebrates neogenesis of nerve cells is restricted to the early stages of embryonic development. This belief is based on the observation that neurons with mitotic figures are absent in the central nervous system of most higher vertebrates. However, this does not definitely rule out the neogenesis of neurons in the adult, for new neurons might arise from nondifferentiated precursors, such as ependymal cells. After multiplication, such embryonic cells could differentiate and thus add new neurons to the existing population. This hypothesis can be tested by administering to animals thymidine-H^3, a specific precursor of the chromosomal DNA, and so labeling the proliferating cells. That tritiated thymidine is, indeed, incorporated exclusively into nuclei of dividing cells was shown by several investigators by means of fine-resolution autoradiography (*1*).

In a pilot experiment, which was designed to test simultaneously the kinetics of glial proliferation after brain trauma, bilateral electrolytic lesions were produced stereotaxically in the lateral geniculate body in ten young adult Long-Evans hooded rats. The insulated hypodermic needle used to produce the lesion was employed for the unilateral injection into the lesion area of 50 μc of thymidine-H^3 (specific activity 5.21 c/mmole; total volume of aqueous solution 0.05 ml). Pairs of animals were then sacrificed 1 day, 1 week, 2 weeks, 1 month, and 2 months after the operation by cardiac perfusion with 10-percent neutral formalin. After paraffin embedding, 5-μ thick coronal sections were cut from a block extending from the mesencephalon to the rostral diencephalon. The deparaffinized sections were coated with Ilford G-5 nuclear emulsion, dried, and exposed for 2 months. The exposed slides were then developed and stained with gallocyanin chromalum. Several sections were soaked, before being coated with nuclear emulsion, in a 0.05-per-