Anesthesiology and Psychiatry, Yale-New Haven Medical Center, Yale University School of Medicine, New Haven, Connecticut. It is well known that local anesthetics block the transmission of impulses along peripheral nerves, but their effects on the central nervous system are still obscure. The purpose of this investigation was to evaluate the effects of local anesthetics on the central nervous system by development of a method for transitory blocking of precise cerebral areas by means of a long-term microinjection of local anesthetics. The hippocampal region was selected as a target because of its easily recognizable pattern of spontaneous high voltage electrical activity and the facility with which typical after-discharges may be evoked. *Methods:* Experiments were performed on adult monkeys. Under pentobarbital anesthesia, assemblies of "chemitrodes" formed by one microcannula (no. 29 stainless steel tubing) and several electrodes, were permanently implanted into the brain with the aid of stereotaxic instrumentation. After animals recovered from anesthesia and surgery, controls were established and then dibucaine in concentrations from 2.5 per cent to 10 per cent was injected through the chemitrode tubing by means of a Harvard pump. Characteristic features of these experiments were that: (1) studies were carried out on fully conscious animals; (2) drugs were injected directly into the brain substance and not into the ventricles, vessels or over the cortex; (3) injection rates were very slow (8–12 μl./hour); (4) injections were prolonged continuously for 1–4 days; and (5) effects were monitored for weeks. *Results: The local spontaneous electrical activity* was depressed for 1–4 weeks in the injected region with minor or no modifications in other cerebral areas. During the recovery period, spikes, bursts, and seizure activity appeared in the injected area and lasted for several days. *Local excitability* (thresholds for after-discharge) in the injected structure rose from control value of 0.5–1.0 ma. to above 6 ma. and then slowly returned to control value in 2–4 weeks, without modifying the after-discharge threshold of any other recorded area. *Pattern and spread of electrically evoked after-discharges* were modified by dibucaine injection. The frequency was slower and less regular after injection of dibucaine and in some cases the duration of after-discharges increased. The injected area was much less receptive than normal to the spread of after-discharges originating in other areas of the brain, and its spontaneous spikes, burst, and seizure activity did not spread to other cerebral structures. These facts showed a great functional independence of the injected area with respect to the rest of the brain. *Behavioral observation* revealed a transitory decrease in aggressiveness of the animals without modifying alertness or appetite, and without producing other behavioral manifestations. *Controls* showed that intracerebral injections of saline with *p*H 5.1–7.0, and of 0.5 per cent dibucaine did not produce detectable effects. *Histological study* showed that the chemitrode tracts were formed by a well limited capsule beyond which neuronal morphology was normal, proving that dibucaine had not produced detectable chemical lesions. *Conclusion:* It is concluded that very slow, long term intracereberal injections in unanesthetized monkeys are technically feasible and that it is possible to produce localized blocking of cerebral functions which last greatly in excess of duration of action of the local anesthetic. (This research sponsored by the Josiah Macy Jr., Foundation, U. S. Public Health Service and Office of Naval Research.)

Comparative Evaluation of the Ventilatory Effects of Diethyl Ether and Methoxyflurane in Man. C. PHILIP LARSON, JR., M.D., EDMOND I. EGER, II, M.D., MUSA MUALLEM, M.D., D. ROBERT BUECHEL, M.D., EDWIN S. MUNSON, M.D., and JOHN EISELE, M.D., *Department of Anesthesiology, University of California Medical Center, San Francisco.* During light to moderate surgical anesthesia in unpremedicated subjects, diethyl ether is a ventilatory stimulant as evidenced by a Pa_{CO_2} at or below normal (Severinghaus, J. W., and Larson, C. P., Jr.: Handbook of Physiology, Sec. 3, Vol. II, 1962: p. 1225). Ventilatory response to inhaled CO_2 is reported to be displaced to the left of control, again indicating respiratory stimulation (Cobb, S.: ANESTHESIOLOGY *19:* 359, 1958). However, a decrease in slope of the CO_2 response, indicating respiratory depression, is also reported (Gabbard,

J. G.: Ann. Surg. *136:* 680, 1952). In contrast to the above findings with ether, Walker (ANESTHESIOLOGY *23:* 639, 1962) found that moderately deep methoxyflurane anesthesia produced alveolar hypoventilation. No comparative studies have been reported with either of these agents. We determined Pa_{CO_2} and CO_2 responsiveness in 8 patients anesthetized with diethyl ether and 6 patients anesthetized with methoxyflurane. In addition, we compared these results with those obtained for halothane, fluroxene, and cyclopropane previously reported by Munson (ANESTHESIOLOGY *27:* 222, 1966). Anesthetic effects on ventilation were compared at equipotent anesthetic doses. The standard of equipotency used was the minimum alveolar concentration (MAC) required to eliminate movement in response to surgical incision. *Method:* Following determination of an awake CO_2 response slope, anesthesia was induced with cyclopropane and maintained with either diethyl ether or methoxyflurane. Orotracheal intubation was performed in all subjects, but no surgery was performed during the study. Constant alveolar anesthetic concentrations were maintained at multiples of MAC ranging from 1.1 to 3.4 for ether, and from 0.89 to 2.42 for methoxyflurane. MAC is 1.9 per cent for diethyl ether and 0.16 per cent for methoxyflurane. Alveolar ether, methoxyflurane, and CO_2 concentrations were determined with infrared analyzers. Ventilation was measured with a recording ventimeter, and blood/gas values with appropriate electrodes. After maintaining alveolar anesthetic and CO_2 partial pressure constant for an interval calculated to allow for cerebral equilibration, tidal volume, respiratory rate, and arterial P_{CO_2} were measured at MAC and at multiples of MAC. Similarly, ventilatory responsiveness to CO_2 increase was determined at MAC and its multiples. *Results:* Mean Pa_{CO_2} values (in mm. Hg) for the ether study were: 35.6 ± 2.5 awake; 37.5 ± 3.7 at 1.23 MAC; 36.2 ± 4.5 at 1.78 MAC; 38.3 ± 6.5 at 2.39 MAC; 36.9 ± 8.2 at 2.9 MAC; and 55.3 ± 14.9 at 3.26 MAC. Values for methoxyflurane were: 36.5 ± 1.8 awake; 45.8 ± 3.4 at 1.06 MAC; 51.7 ± 3.7 at 1.44 MAC; and 62.7 ± 6.9 at 2.18 MAC. Mean ventilatory response slopes (liters/minute/mm. Pa_{CO_2}) expressed as a fraction of the awake slope were for ether: 0.7 at 1.23 MAC; 0.56 at 1.78 MAC; and 0.33 at 2.39 MAC. Mean slopes for methoxyflurane were: 0.53 at 1.06 MAC and 0.49 at 1.44 MAC. *Conclusions:* Ether and methoxyflurane, like halothane, fluroxene and cyclopropane depress ventilatory responsiveness to CO_2, the magnitude of the depression increasing with anesthetic depth. Ether maintains resting Pa_{CO_2} at or below the awake level up to 2.9 MAC. In contrast, Pa_{CO_2} progressively rises with increasing alveolar methoxyflurane and halothane concentrations, no difference between these anesthetics appearing at any equivalent anesthetic level. The effects of fluroxene and cyclopropane on resting Pa_{CO_2} lie between those of halothane or methoxyflurane, and ether. (Supported in part by USPHS Grant 5 RO1 HE-07946-03.)

Uptake and Distribution of Anesthetic Agents in Mice and Rats. HARRY J. LOWE, M.D., JOHN L. EVERS, M.D., and KARL HAGLER, M.D., *Millard Fillmore Research Institute, Buffalo, New York.* The existence of any type of vasoconstrictive effect due to oxygen on blood vessels could significantly reduce the transport of oxygen and anesthetics administered at elevated pressures. Sensitive, rapid analytical methods for determining anesthetic concentrations in tissues permit the use of these agents in measurements of organ blood flow. *Methods:* The amounts of anesthetic agent in weighed blood and tissue specimens were determined by injecting the samples directly into the port of a hydrogen flame detector calibrated with water standards (Lowe, H. J.: ANESTHESIOLOGY *25:* 808, 1964). Inbred rats and mice of uniform age and weight were exposed to a known concentration of anesthetic agent in a glass chamber (1,500 ml.) provided with an efficient magnetic stirrer, CO_2 absorber, and O_2 spirometer. The rate of disappearance of the anesthetic gas from the gas phase of known volume was used to calculate the rate of anesthetic uptake ($\dot{V}_{an}$ = ml. vapor/minute/kg.). Following a period of exposure, the anesthetic vapor was periodically replaced with oxygen and the rate of elimination of anesthetic vapor measured without allowing the gas concentration to exceed ½ of the initial exposure concentration. Following exposure to a given anesthetic for a given period, animals were sacrificed by