flow rate of 25 ml./minute and escaped freely from a needle in the cisterna magna. Radiological controls showed that unilateral filling of the subarachnoid space above one hemisphere could be accomplished if the burrhole was placed laterally from the midline. The heart was then fibrillated by electroshock applied through the closed chest wall. Comparisons between fronto-occipital EEG tracings from the right and the left hemisphere served as a basis for the evaluation of the protective effect of the oxygen depot. *Results:* In 12 dogs, electrical activity on the oxygen-supplied hemisphere survived an average of 5 minutes 46 seconds longer than on the control hemisphere. Two dogs were successfully defibrillated after seven minutes of circulatory arrest and exhibited clinical signs of unilateral brain damage with a focus on the unprotected hemisphere. Thus, it appears that introduction of gaseous oxygen into the subarachnoid space can prolong cortical survival time during circulatory arrest. [Supported by USPHS Grant B–2915 (C1).]

Infiltration of Epinephrine During General Anesthesia with Halogenated Hydrocarbons. R. S. MATTEO, M.D., R. L. KATZ, M.D., and E. M. PAPPER, M.D., *Department of Anesthesiology, Columbia University College of Physicians and Surgeons, and the Anesthesiology Service, The Presbyterian Hospital, New York, New York.* The belief that epinephrine should not be given during trichlorethylene anesthesia because severe ventricular arrhythmias may result is based mainly on experiments performed on dogs and cats in which epinephrine was injected intravenously. In this study the incidence of ventricular arrhythmias in man following subcutaneous epinephrine injection during trichlorethylene anesthesia was determined. *Method:* All patients received nitrous oxide (50–70 per cent), oxygen, and trichlorethylene through a nonrebreathing circuit. Calibrated vaporizers were used to deliver known concentrations of trichlorethylene, a maximum of 1 per cent for induction and an average of 0.3 per cent for maintenance. The electrocardiogram was observed continuosuly and direct tracings were made of any arrhythmias. Tidal volume and minute ventilation were measured with a Wright meter. Two hundred and eight patients were studied, most of them undergoing plastic surgery. One hundred and eight served as a control group. One hundred received epinephrine 1:60,000 subcutaneously in the head and neck area—dose of 6 cc. at 5-minute intervals to a total dose of 30 cc. (500 μg). *Results:* In the control series, 6 ventricular arrhythmias occurred (5.5 per cent). Bigeminy of 45 and 50 seconds' duration was noted on two occasions. Occasional premature ventricular contractions lasting up to two minutes were seen in 4 patients. These arrhythmias followed breath-holding, coughing on the endotracheal tube and inadequate ventilation. Correction of the underlying anesthetic problem in each case resulted in a return to normal rhythm. No ventricular arrhythmias were seen in the 100 patients receiving epinephrine except for one patient in whom premature ventricular contractions lasting one and one-half minutes occurred two hours after the last injection of epinephrine. The arrhythmia occurred during hypoventilation and disappeared with improved ventilation. *Comment:* This study suggests that epinephrine in the doses stated above may be injected safely during nitrous oxide, oxygen, and trichlorethylene anesthesia provided the percentage of trichlorethylene is low (up to 0.6 per cent) and ventilation is adequate. A similar series with halothane and cyclopropane is now in progress.

Effect of Halothane on the Heart. JOHN E. MAZUZAN, JR., M.D., CALVIN HANNA, PH.D., and JOHN ABAJIAN, JR., M.D., *College of Medicine, University of Vermont, Burlington, Vermont.* Conflicting reports regarding the impact of halothane on the human heart deter or limits its use by many. Since our clinical success with halothane, based on over 15,000 cases, is difficult to reconcile with much of the published data, we examined a representative segment of our surgical population. *Method:* Our routine, relatively rigid system of administration includes alphaprodine HCl, levallorphan tartrate-scopolamine premedication followed by accurately vaporized halothane-oxygen in concentrations of 2 per cent or less. Cardiac output, which is really total tissue blood flow, was serially measured in

over 90 patients to determine whether tissue needs are adequately met. A reliable ear-piece densitometer technique, capable of accurately detecting alerations in arterial concentration of an indicator dye without repeated arterial blood drawings, made this large scale evaluation possible. Coomasie blue, a new dye with essentially no toxicity and a clearance time intermediate between Cardio-green and Evans blue, has the additional advantage of sufficient stability to permit accurate prepackaging in disposable carpules. The accuracy of this ear-piece densitometer was found to be comparable to Fick measurements and other dye-dilution systems (Taylor, S. H., and Shillingford, J. P.: Brit. Heart J. *21:* 497, 1959). Recent thinking on cardiovascular regulatory adjustments establishes the general premise that cardiac output tries to adjust to tissue needs. Warren, in describing his and Stead's work on the changes seen with sudden, acute increase in tissue-demand, says "heart rate, stroke volume and cardiac output increased precipitously while right arterial pressure remains unchanged or falls slightly" (Stead, E. A., Jr., and Warren, J. V.: Arch. Int. Med. *80:* 237, 1947). This significant finding seriously questions the validity of explaining cardiac output adjustments in the intact man solely by hypotheses derived from the length-tension relationship originally observed in the heart-lung preparation by Starling. Furthermore, material on exercise-response in trained unpremedicated subjects shows the compensatory regulation to increased oxygen demand of exercise is predominately produced by increased heart rate and increased oxygen extraction with a minor contribution coming from increased stroke volume. (Rushmer, R. F., and Smith, O. A., Jr.: Physiol. Rev. *39:* 41, 1959.) The problem is to determine if there are analogous adjustments in the opposite direction in the premedicated surgical patient during halothane 2 per cent—oxygen 98 per cent anesthesia. *Results:* Our measurements indicate an 18 per cent reduction in oxygen consumption with halothane, and 98 per cent oxygen breathing produces an increase A-V oxygen difference (increased extraction/unit volume of blood). The variable that made a significant difference in the cardiac output was the carrier gas oxygen. Using air breathing via an anesthesia machine as the control state, 25 surgical patients had a fall in heart rate of 5 per cent and in cardiac output of 30 per cent (S.D. ± 14) after 15 minutes of oxygen breathing. This finding is in line with the Fick principle, since A-V oxygen difference is easily increased 1.5 to 2 volumes per cent on 100 per cent oxygen inhalation. With this increased extraction per unit volume of blood, a smaller volume of blood adequately supplies tissue demands; cardiac output fall is paralleling tissue needs. In 32 patients, again using air breathing as a control, halothane-oxygen for 15 minutes produced a 22 per cent fall in rate and a 49 per cent reduction in cardiac output. To test whether this output reduction represented decreased ability to pump or whether it represented compensatory change, rate was increased with atropine. Cardiac output returned to a level 29 per cent below air control while rate went above control. The heart is capable of a positive response, reaching the same level as observed with 100 per cent oxygen breathing. In 15 patients 100 per cent oxygen breathing was used as the control. With the addition of 2 per cent halothane there was a 15 per cent fall in rate and a 23 per cent fall in output—a reduction that closely follows the measured 18 per cent in oxygen consumption. An almost parallel fall in rate and output is noted here. By increasing rate with atropine output returned to control with rate going above control. The proposal is that reductions in rate and output are neural-mediated adjustments to (1) lessened tissue demand for oxygen and (2) increased extraction. The concept of neural-mediated change was tested with observations on three patients with complete heart-block—who, of course, have rates independent of CNS control. A 6 year old boy showed no change in heart rate or blood pressure with 20 minutes of halothane. An 83 year old woman showed no change in heart rate, blood pressure or cardiac output. A 75 year old man presented a widely varying blood pressure and pulse according to the manipulations of his supportive isoproterenol infusion both before and during anesthesia for implantation of an artificial pacemaker. The moment the pacemaker was switched on, the blood pressure and heart

rate became fixed with the blood pressure at a normotensive level. Six days later, with the pacemaker functioning, 2 per cent halothane anesthesia failed to budge his blood pressure or rate. *Comment:* This preliminary work prompts the conclusion that changes accompanying clinical halothane anesthesia are essentially benign compensatory regulations. Capability to return pumping function to or toward control level by rate change alone strongly challenges the concept that clinical concentrations of halothane expose the myocardium to undue degrees of direct depression.

Effect of Methoxyflurane on Electromyogram, Neuromuscular Transmission, and Spinal Reflex. S. H. NGAI, M.D., and EDGAR C. HANKS, M.D., *Departments of Anesthesiology and Pharmacology, College of Physicians and Surgeons, Columbia University, and the Anesthesiology Service, The Presbyterian Hospital, New York, New York.* Methoxyflurane (Penthrane) in anesthetic concentration produces profound muscular relaxation with minimal changes in electroencephalographic pattern. The basis for the muscular relaxation during methoxyflurane anesthesia was studied in man and in decerebrate and spinal cats. *Methods and Results:* MAN: Methoxyflurane was administered with a closed circle carbon dioxide absorption system using an Ohio no. 8 vaporizer. With increasing concentrations the electrical activity of abdominal muscles decreased and finally disappeared, coinicidental with loss of muscle tone. The twitch response of hypothenar muscles to electrical stimulation of ulnar nerve remained unchanged. CATS: Comparable results were obtained in decerebrate and spinal cats. Methoxyflurane was vaporized with a Vernitrol (3.7 per cent at 25.5° C.) and after appropriate dilution with oxygen, administered through a nonrebreathing system. Inhalation of methoxyflurane in an inspired concentration of 2 per cent for 30 minutes or longer did not significantly reduce the tibialis twitch response to peroneal nerve stimulation. However, with an inspired concentration of approximately 0.2–0.3 per cent, methoxyflurane abolished the reflex response of the quadriceps to stimulation of the central end of the divided ipsilateral or contralateral sciatic nerve. In spinal animals there was usually no appreciable change in the electroencephalographic pattern. The corneal and masseter reflexes remained active. Parallel studies were carried out with nitrous oxide, cyclopropane, halothane and diethyl ether in spinal cats. Nitrous oxide (80 per cent) caused a slight increase in tibialis twitch response. The spinal reflex was depressed but not abolished. Cyclopropane (10 per cent) also increased the tibialis twitch response. The spinal reflex was abolished when the inspired concentration reached a range of 7.5–15 per cent at which time high voltage slow rhythm appeared in the electroencephalographic tracing and the corneal and masseter reflexes disappeared. Halothane (1 per cent) had no significant effect on the tibialis twitch response. It abolished the spinal reflex when the inspired concentration reached 0.4–0.6 per cent at which time the corneal reflex became sluggish or absent. The electroencephalogram retained the low voltage fast rhythm. Diethyl ether (7.5–20 per cent) reduced the tibialis twitch response to approximately 50 per cent of control level. Five to 6 per cent of diethyl ether in the inspired mixture was required to abolish the spinal reflex. With this concentration the electroencephalogram showed a sleep pattern and the corneal and masseter reflexes also disappeared. *Comment:* The results indicate that the inspired concentrations of cylopropane, halothane and diethyl ether required to abolish the spinal reflex in the cat approximate those for surgical anesthesia. On the other hand, methoxyflurane abolished the spinal reflex at an inspired concentration less than that required for surgical anesthesia. It may be concluded, therefore, that methoxyflurane produces muscular relaxation principally through its depressant action of the spinal cord. It has no appreciable effect on neuromuscular transmission as tested in nerve-muscle preparation *in situ.* [Supported by the USPHS, grant No. B31 and the Abbott Laboratories.]

Effects of THAM Used with Normal Acid-Base Balance and with Respiratory Acidosis and Alkalosis During Anesthesia. F. E. NOE, M.D., E. SEKINO, M.D., and F. E.