In a fifth group of six dogs we tested the hypothesis that ether may stimulate ventilation by producing cerebrospinal fluid (CSF) acidosis. These dogs were anesthetized first with halothane to 1.5 MAC and then with ether to the same MAC. Arterial P_{CO_2} and base deficit during ether anesthesia were held at those levels found with halothane by rebreathing and addition of intravenous $NaHCO_3$. Results obtained were: during halothane: Pa_{CO_2} 43 mm. of mercury, arterial *p*H 7.33, CSF HCO_3 24.7 mEq./liter and minute volume 3.5 liters/minute. Values during ether were: Pa_{CO_2} 43 mm. of mercury, arterial *p*H 7.34, CSF *p*H 7.31, CSF HCO_3 25.8 mEq./liter and minute volume 10.0 liters/minute. In three dogs still at 1.5 MAC with ether, the inspired CO_2 was subsequently eliminated. In these dogs, Pa_{CO_2} fell to 33 mm. of mercury, arterial *p*H rose to 7.39, CSF *p*H rose to 7.36, while CSF HCO_3 and minute volume decreased to 24.1 mEq./liter and 8.5 liter/minute, respectively. *Conclusion:* We conclude that vagotomy, carotid sinus denervation and peripheral and sympathetic blockade by spinal anesthesia do not depress ventilation during ether anesthesia. Further, arterial or CSF acidosis does not explain the ventilatory stimulation associated with ether because ventilation was three times greater in the ether dogs than in the halothane dogs at nearly identical and peripheral acid base status. That Pa_{CO_2} is normal at a time that the CO_2 response is depressed suggests that ether probably produces central respiratory depression, the effect of which is antagonized by a central respiratory stimulation. The specific sites of these conflicting central effects of ether are unknown. (This work was supported in part by USPHS Grant 5 RO1 HE 07946.)

Effects of Urea Administered During Hypothermia and General Anesthesia on the Osmotic Fragility of Human Red Cells. MARK B. RAVIN, M.D., and RICHARD S. MATTEO, M.D., *Department of Anesthesiology, Columbia University, College of Physicians and Surgeons, and the Anesthesiology Services, The Presbyterian Hospital, and the Jewish Memorial Hospital, New York City.* Following a report of the occurrence of intravascular hemolysis after the intravenous administration of urea during hypothermia (Ravin, Garber, and Gibson: ANESTHESIOLOGY 25: 576, 1964), a study was undertaken in anesthetized neurosurgical patients undergoing hypothermia to determine the effects of the intravenous administration of urea on the osmotic fragility of their red cells (Matteo and Ravin: ANESTHESIOLOGY 27: 318, 1966). This study has been extended to include the effects of cyclopropane and halothane on red cell osmotic fragility. *Method:* For the urea study, a Teflon catheter was inserted percutaneously in a brachial artery prior to the induction of anesthesia. Arterial blood samples were collected in heparinized Luer-Lok syringes before the induction of anesthesia, 30 minutes after anesthesia was established, immediately before and after the intravenous infusion of urea. The usual dose of urea was 0.5 g./kg. (40 per cent solution in 5 per cent invert sugar) administered intravenously over a 15 to 20 minute period. The blood samples were immediately analyzed for serum osmolarity, *p*H, P_{CO_2}, oxygen saturation, microhematocrit and osmotic fragility. Esophageal temperature was monitored. Following induction of anesthesia with intravenous thiopental, endotracheal intubation was facilitated with succinylcholine. Anesthesia was maintained with nitrous oxide 70 per cent–oxygen 30 per cent, supplemented by intravenous d-tubocurarine and chlorpromazine. Ventilation was mechanically controlled at a minute volume 110 to 125 per cent of that estimated from the uncorrected Radford Nomogram. Similar induction technique was employed in the cyclopropane and halothane studies. However, the patients were allowed to breathe spontaneously mixtures of either cyclopropane 20 per cent–oxygen 80 per cent or halothane 0.7–1.2 per cent in oxygen. Osmotic fragility for each sample was determined by a modification of the quantitative method described by Ham (Syllabus of Laboratory Examinations, Harvard University Press, 1951, p. 162). The per cent hemolysis of the red cells at varying concentrations of hypotonic saline was determined with a Beckman Model 8 Spectrophotometer. These values were used to construct four curves of osmotic fragility for each patient. *Results:* Neither hypothermia ranging

between 29° and 34° C., nor the intravenous infusion of urea at these temperatures caused any significant change in the osmotic fragility of the red cells of the patients breathing nitrous oxide. Similarly, there was no change in the osmotic fragility of patients spontaneously breathing cyclopropane or halothane in the concentrations studied. *Comment:* Although this study suggests that the intravenous infusion of urea during hypothermia is unlikely to cause an increase in the osmotic fragility of the patients' red cells, the possibility of such an increase cannot be completely eliminated.

Effect of Anesthesia and Blood Replacement on Glycolysis and the Citric Acid Cycle. OLGA SCHWEIZER, M.D., and WILLIAM S. HOWLAND, M.D., *Memorial Sloan-Kettering Cancer Center, New York City.* Knowledge of the effect of anesthetic agents on glycolysis and Kreb's cycle in normotensive patients is essential to the investigation of carbohydrate metabolism in shock. *Method:* For this purpose hematocrit, oxygen saturation, *p*H, P_{CO_2}, base excess, standard bicarbonate, total carbon dioxide, glucose, pyruvate, lactate, citrate, α-Ketoglutarate and malate levels were obtained in 50 patients anesthetized with ether and 50 with halothane, nitrous-oxide and oxygen. Acetyl coenzyme-A and ATP determinations were performed in 25 patients of each group. The Astrup technique was used to determine acid base values and enzymatic methods for pyruvate were used to determine lactate, ATP and components of Kreb's cycle. Huckabee's formula was employed for excess lactate determinations. Arterial blood samples were obtained prior to operation, at two hour intervals and at the end. No deviations from standard anesthetic or fluid replacement methods were employed except for substitution of saline for glucose solutions. The blood was warmed after 3 units had been given and 44.6 mEq. of sodium bicarbonate administered intravenously after every fifth unit. *Results:* Age, sex, clinical status, operative procedures, duration of anesthesia and blood replacement were comparable with both agents. Blood pressure, pulse, hematocrit, *p*H, oxygen saturation and carbon dioxide tension were not significantly altered with either agent. Halothane produced less metabolic acidosis than ether although the administration of sodium bicarbonate to transfused patients made accurate interpretation difficult. For a more definitive analysis of the components of carbohydrate metabolism the ether and halothane groups were separated into 4 subgroups: (1) no blood and no excess lactate, (2) no blood and excess lactate, (3) blood and no excess lactate, and (4) blood and excess lactate. With one exception, acids of the Kreb's cycle (α-Ketogluturate, citrate and malate) showed no significant changes with ether or halothane in any category. The administration of comparable volumes of blood produced equal and statistically significant ($P = 0.001$–0.005) citrate elevation with both anesthetic agents. The close correlation between volume transfused and citrate values showed exogenous citrate to be the main source of this acid. The presence or absence of excess lactate produced no marked variations in the Kreb's cycle with either agent. Major differences appeared in the products of glycolysis. Although glucose, pyruvate and lactate levels rose in all categories with both agents, ether produced lactate levels two (group 1), three (group 2) and four times (group 3 and 4) higher than halothane. The following figures show the total production of pyruvic, lactic and citric acids during operation: Group 1 (ether: 0.60 mEq., halothane, 0.23 mEq.); Group 2 (ether: 2.00 mEq., halothane, 0.60 mEq.); Group 3 (ether: 1.54 mEq., halothane, 0.72 mEq.); Group 4 (ether: 3.07 mEq., halothane, 1.08 mEq.). Lactate and pyruvate contributed the major part of the acid. Although 27 patients developed excess lactate with each agent, the amount of excess lactate was approximately 2.5 times greater with ether. The number of adenosine triphosphate determinations performed is too small to draw definitive conclusions. However, ATP seems to show a more significant increase with halothane than ether. Several investigators (Brewster, W. R., Jr., *et al.:* Amer. J. Physiol. *171:* 37, 1952; Greene, N. M.: ANESTHESIOLOGY *22:* 404, 1961) and others attributed the effect of ether on lactate values and excess lactate production to the sympathomimetic action of the agent, with resultant diminution in tissue perfusion and anaerobic metabolism. Other workers (Price,