sociation. It occurred in 12.5 per cent of the cases and comprised 50 per cent of the arrhythmias diagnosed. It was associated with hypoxia, surgical manipulation or deepening of anesthesia. Premature ventricular contractions occurred in 4 per cent of the cases and made up 40 per cent of the recognized arrhythmias. Other arrhythmias noted in the series were auricular premature contractions, auricular fibrillation, A-V block, and bundle branch block. (5) The incidence of arrhythmia was not affected by the belladonna alkaloid used in premedication, sex of the patient, or type of inhalation agent used. (6) Constant electrocardiographic monitoring of patients under anesthesia has proven to be a valuable adjunct to the administration and supervision of clinical anesthesia.

Studies of Narcotic Antagonists as Analgesics. JANE TELFORD, M.D., YOSHIO KUROSU, M.D., AND ARTHUR S. KEATS, M.D. *Division of Anesthesiology, Baylor University College of Medicine, Houston, Texas.* The previous demonstration that nalorphine was a potent analgesic in man led us to the investigation of other narcotic antagonists as analgesics in the search for a potent analgesic without undesirable side effects. Recently we have studied in man two morphinan derivatives reported to antagonize morphine in animals. These are (−) 3-hydroxy-N-(3,3, dimethylallyl)-morphinan hydrobromide (NIH 7446 and (−) 3 hydroxy-N-propargyl morphinan tartrate (NIH 6045). Initially analgesic potency of these drugs was determined. On a milligram basis NIH 7446 was equally, and NIH 6045 was twice as potent as morphine as an analgesic in relieving postoperative pain. However, when given in equivalent analgesic doses to normal subjects, NIH 7446 was only half as potent and NIH 6045 equally as potent as morphine in depressing respiration. To estimate the potency of these drugs as morphine antagonists, anesthetized patients were used. Patients under light thiopental-nitrous oxide-oxygen anesthesia were given morphine or a morphine antagonist intravenously to a total dose averaging 1 mg./kg. Controlled respiration was maintained throughout the operation with succinylcholine by infusion when necessary. After operation, alveolar ventilation and alveolar P_{CO_2} were measured simultaneously. After a suitable control period, one of the following was given intravenously: placebo, nalorphine 2.5 mg., NIH 7446 2.5 mg., or NIH 6045 2.5 mg. Measurements were repeated at 5 and 10 minutes after drug administration. Nalorphine in doses of 1 mg., 2.5 mg., and 5 mg. dramatically antagonized the respiratory depression of morphine (1 mg./kg.). In 3 patients who had received morphine 1 mg./kg., NIH 7446 produced little antagonism. In an additional 3 patients, the respiratory depression of 1 mg./kg. of NIH 7446 was similar in degree to that of morphine and was dramatically antagonized by nalorphine. NIH 6045 in doses of 2.5 mg. antagonized morphine induced respiratory depression in a manner similar to that of nalorphine. However, when NIH 6045 was given to 5 patients in doses of 1 mg./kg. intravenously, it produced only half the respiratory depression of morphine and only one quarter of that anticipated from studies of respiratory depression in normal subjects. When 2.5 mg. of nalorphine was given after NIH 6045, there was no significant change in respiration. Similarly nalorphine in doses of 10 mg./70 kg. depressed the respiration of normal subjects but in doses of 1 mg./kg. intravenously produced little respiratory depression in anesthetized patients. NIH 6045 appears to act like nalorphine, whereas NIH 7446 appears to be a morphine-like drug. The quantitative discrepancy between the respiratory depression in normal subjects following a small dose of NIH 6045 and a large dose in anesthetized patients suggests that the drug may have a dual action which depends on dosage.

Studies on the Effect of Urea on Blood Pressure and Volume. JOHN TENCH, M.D., MANUCHER JAVID, M.D., AND DAVID GILBOE, PH.D. *Departments of Anesthesiology and Neurosurgery, University of Wisconsin Medical School, Madison, Wisconsin.* Analysis of over 200 anesthetic charts of patients who received urea during craniotomy revealed a consistent pattern of blood pressure increase averaging 26 mm. Hg above stabilized blood pressure. This was later followed by a decrease to an average of 20 mm. Hg below stabilized blood pressure when adequate blood replacement was not initiated. Preliminary studies under-

taken during surgery indicated that there was a definite correlation between the time of peak blood pressure and the time of lowest hematocrit, further suggesting that hypervolemia was the cause of the observed elevation of blood pressure. Studies were carried out in thirty-five 10–12 kg. mongrel dogs. All animals were anesthetized using pentothal-nitrous oxide by endotracheal technique to a depth similar to that used in the majority of neurosurgical patients. Continuous recordings of arterial and venous blood pressure, ECG and EEG were made during the experiment using a Gilson 4-channel polygraph. Animals receiving urea were administered 1.5 Gm. per kilogram body weight as a 30 per cent solution in 10 per cent invert sugar. The solution was injected at a uniform rate over a 30 minute period. Blood was removed via venapuncture at predetermined periods relating to the time of urea administration to simulate bleeding. It was found necessary to remove 30–35 per cent of the total blood volume to produce the desired level of shock. The animals were divided into 5 groups as follows: (I) urea alone, (II) bleeding alone, (III) bleeding simultaneous with urea infusion, (IV) bleeding followed by urea infusion, and (V) bleeding simultaneous with urea infusion followed by transfusion. Heart rate together with pulse pressure is generally considered to be a good index of cardiac output. In these experiments, changes in heart rate were more subtle than the changes in pulse pressure, but generally in the same direction. We have, therefore, presented our data in terms of per cent change in the stabilized pulse pressure to simplify illustration. As one would predict, group (I) animals experienced an increased pulse pressure and a decreased hematocrit as in human subjects. Animals in group (II) showed the expected decrease in pulse pressure followed by a period of partial compensation after the bleeding had been stopped. Group (III) received urea simultaneously with bleeding and showed no significant tendency to compensate while the pulse pressure was being dropped to nearly the level of group (II) after compensation. It is felt that these animals were not bled as much as the animals in group (II) since the fluid being withdrawn and measured contained urea solution, fluid from the interstitial spaces and blood. The animals in group (IV) were bled and then given urea. It is interesting to note that while there was an increase in pulse pressure when urea was given, the amount of compensation achieved was essentially the same as when no urea was administered. It is felt that this illustrates the fact that the fluid removed by hypertonic solutions of urea comes mostly from the interstitial spaces and not from the intracellular spaces. Further evidence of this is the fact that no significant shift in blood electrolytes was observed in human subjects and animals. The animals in group (V) were treated in a similar manner to those in group (III) except that a transfusion was given after a period of stabilization. In these dogs the pulse pressure returned to normal. Whereas, the elevation of blood pressure after urea is slight it should be pointed out that during craniotomy, should excessive blood loss occur, the impending fall in blood pressure may be masked temporarily during the initial period. In other words, urea may temporarily maintain the arterial blood pressure in the face of significant blood loss. Following this initial period diuresis usually occurs. The hypervolemia is succeeded by comparative hypovolemia. At this time previous blood loss may become a significant factor. Further blood loss may be much more serious in that even adequate and rapid blood replacement may not return the blood pressure to satisfactory levels. Clinically speaking, this indicates a need for awareness as to the time and amount of blood loss during those craniotomies where excessive blood loss is encountered within a short period of time. In these cases, blood replacement should be adequate and simultaneous with urea. [*Supported in part by the Wisconsin Alumni Research Foundation.*]

Prophylaxis and Treatment of Hypotension During Anesthesia and Surgery in Man. Donald P. Todd, M.D., John P. Bunker, M.D., Marie-Louise Levy, M.D., John C. Dalton, M.D., and Allen L. Friedlich, M.D. *Anesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts.* Cardio-vascular failure remains the most common serious complication during anesthesia and surgery (*Beecher, H. K., and Todd, D. P.: Ann. Surg.*