Diseases, New York, N. Y. The mechanism of increased bleeding with cyclopropane has not been determined. In order to assess the effect of cyclopropane and cyclopropane plus hypercarbia on the clotting mechanism a battery of clotting tests was performed before anesthesia, during anesthesia, after rebreathing carbon dioxide for 15 minutes (in 6 cases), and after anesthesia. These tests were the tourniquet test, bleeding time, platelet count, clotting time glass, clotting time silicone, prothrombin time, prothrombin content, factor V activity, factor VII activity, prothrombin consumption, thromboplastin generation test, thrombin clotting time, fibrinogen concentration, fibrinolytic activity, whole blood clot lysis and antiplasmin activity. Fifteen patients received cyclopropane for operations lasting one to two hours, and 6 patients undergoing two to three hour operations received cyclopropane with deliberately induced carbon dioxide levels of 56 to 62 mm. of mercury for a duration of 15 minutes. The only changes in blood clotting noticed were those in the fibrinolytic system. Fibrinolysis occurred in 10 of the 21 cases studied but 5 of these showed preoperative fibrinolysis. Thus only 4 of the patients receiving cyclopropane and one patient with hypercarbia developed intra-operative fibrinolysis. None of these patients showed increased bleeding at the operative site. This incidence of fibrinolysis is no different than

CLOTTING CHANGES WITH CYCLOPROPANE

	C_3H_6	$C_3H_6 + CO_2$
Patients	15	6
No change	9	2
Fibrinolysis	6	4
Preoperative only	1	
Preoperative and during operation	1	1
Preoperative, during and postoperatively	0	2
During operation only	4	1

that previously reported in a series of 38 cases receiving ether anesthesia (*Zucker, M. B., Siegel, M., Cliffton, E. E., Bellville, J. W., Howland, W. S., and Grossi, C. E.: J. Lab. & Clin. Med. 50: 849, 1957*). Thus it appears that the increased bleeding with cyclopropane anesthesia is not due to clotting disturbances.

A Clinical and Electroencephalographic Study of the Changes Observed in Humans During Prolonged Administration of Low, Graded Concentrations of Diethyl Ether. BENTON D. KING, M.D., STANLEY W. WEITZNER, M.D., AND HARRY A. KAPLAN, M.D. *Departments of Anesthesiology and Neurosurgery, State University of New York College of Medicine at New York City, Brooklyn, N. Y.* Investigations were undertaken to study the effects of the administration of low, graded concentrations of ether on the electroencephalogram and the behavior patterns of man. Continuous electroencephalographic recordings, simple psychological assessment, and gross sensory testing were utilized for testing. By means of an EMO vaporizer (*Anaesthesia 11: 83, 1956*), and using a nonrebreathing technique, 14 subjects were given slowly increasing, precisely graded concentrations of ether over a period of several hours. An effort was made to present subanesthetic concentrations of ether for prolonged periods in order that some semblance of body equilibration with the inspired mixture might take place. Changes in concentration were made gradually so that surgical anesthesia could not be attained rapidly. Duration and pattern of experiments varied somewhat, but in the later typical ones psychological and sensory tests were performed after the subject had been breathing concentrations of 1, 2, and 3 per cent ether, each for a period of an hour. These later experiments usually terminated when 4 per cent ether was being inhaled because of the onset of vomiting or surgical anesthesia. Several subjects vomited during the advance from 3 to 4 per cent ether; all were sufficiently coherent at the time to be able to state that they noted no prior nausea. In those instances where surgical anesthesia was produced the subjects never exhibited a true excitement stage. The general pattern of the electroencephalogram in most instances showed progressively the following changes as the ether concentration was slowly increased: (1) a dropping-out of alpha waves, (2) an increase of slow activity, (3) a lowering of the voltage, (4) an appearance of beta waves, and (5) an increase in the number of slow waves with a dropping-out of beta waves. High voltage slow waves appeared with development of surgical anes-

thesia. In those subjects in whom the ether concentration was decreased or discontinued, the electroencephalogram returned to the pre-ether pattern in the reverse of the previous order. Extensive psychological testing in some intelligent subjects indicated that changes were not marked until the 3 per cent ether level had been maintained. However, at this point there was usually euphoria, inability to learn non-meaningful material, and decline in memory for rote and meaningful material. Capacity for abstraction did not seem to be particularly impaired. Subsequent testing on another day indicated considerable amnesia for much of the ether test period. By this technique of ether administration it was impossible to produce analgesia of sufficient intensity at the 3 per cent level to have permitted a skin incision to be made. This concentration of ether is considerably higher than the mean concentration of 1.2 per cent reported during ether analgesia by Ebersole and Artusio (*Anesthesiology 19: 607, 1958*). In this study testing for analgesia was performed before surgical anesthesia was ever attained whereas Artusio (*J. Pharmacol. & Exper. Therap. 111: 343, 1954*) first produced surgical anesthesia before subsequently utilizing analgesia.

Clinical Investigation of R01-5733, a New Curare Antagonist. LUDWIG R. KOUKAL, M.D., FRANCIS F. FOLDES, M.D., JOHN F. ZEEDICK, M.D., AND DERYCK DUNCALF, M.D. *Department of Anesthesiology, Mercy Hospital and Section on Anesthesiology, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pa.* Investigation of the structure-action relationship of neostigmine analogs (*Foldes et al., J. Pharm. & Exper. Ther. 122: 457, 1958*) prompted the synthesis of a new cholinesterase inhibitor, R01-5733 (2-hydroxybenzyl trimethylammonium bromide dimethyl carbamate). In *in vitro* laboratory studies, it was found to be twice as potent an inhibitor of human plasma and red cell cholinesterase as neostigmine. According to L. O. Randall (*personal communication*) it was slightly less toxic in mice on oral administration, and on intravenous administration slightly more toxic than neostigmine; in cats its effect on neuromuscular transmission was greater than that of neostigmine. In the present study R01-5733 was administered to two groups of human subjects. Ten subjects of the first group were lightly anesthetized with a previously described technique (*Rendell-Baker et al., Brit. J. Anaesth. 29: 304, 1957*). After stabilization of the level of anesthesia at 0 time, 1.0 mg./kg. gallamine, and 5 minutes later 0.01 mg./kg. R01-5733 was injected intravenously. Respiratory rate, tidal and minute volumes, pulse rate and blood pressure were determined before and at 3, 8, 12, 16 and 20 minutes after the injection of gallamine. There was no significant change in respiratory rate throughout the observation period. The average respiratory tidal and minute volumes decreased to less than 50 per cent of the control values 3 minutes after the administration of gallamine but returned to and stayed above control value within 3 minutes following the injection of R01-5733. As noted previously (*Foldes et al., Anesth. & Analg. 33: 122, 1954*), pulse rate and to a lesser extent systolic blood pressure increased after gallamine, but gradually returned to control values within 15 minutes after the administration of R01-5733. In a second group of 50 patients, in whom muscular relaxation for intra-abdominal surgery was produced by gallamine or *d*-tubocurarine, respiratory tidal volume, pulse rate and blood pressure were determined at the end of surgery before and after the intravenous administration of 0.01 mg./kg. R01-5733. The average tidal volume of this group increased from 118 ml. to 371 ml. within 3 minutes after the administration of R01-5733. No change in pulse rate or blood pressure was observed. Recurarization was not observed in any of the patients studied. Although no additional parasympatolytic agent was used with R01-5733, the only indication of any muscarinic effect was increased salivation in about one half of the cases. Because R01-5733 can be safely administered in doses necessary for the correction of residual neuromuscular block at the termination of surgery without additional atropine, it is the agent of choice of the presently available curare antagonists. R01-5733 was also administered both intravenously and by mouth to a group of myasthenic patients. In these patients, however, R01-5733 did not seem to offer any advantages over other anticholinesterases in clinical use.