ventilated the lung compartment with the slowest turnover rate. Increasing the tidal volume decreased this proportion slightly. No difficulty was encountered in the emphysematous patients in reducing the alveolar and arterial P_{CO_2} to low values. No increase in the A–a gradient for CO_2 was observed. The CO_2 output increased to more than 250 per cent of that produced. The excess CO_2 output was directly proportional to the increase in the alveolar ventilation. Hypotension was observed in some patients but not in others from the increased airway pressures at large tidal volumes. *Conclusion:* This study shows that increasing tidal volume increases the rate of turnover in lung gas in emphysematous patients as effectively as it does in the lungs of the normal patient. The rate of turnover is directly proportional to the alveolar ventilation and inversely proportional to the functional residual capacity of the lung.

Interrelation of Cough Suppression and Respiratory Depression. J. R. CALVERT, M.D., J. E. STEINHAUS, M.D., PH.D., G. A. MARTIN, B.S., and J. C. MCFARLAND, B.S., *Emory University School of Medicine, Atlanta, Georgia.* Recent studies with intravenous lidocaine have suggested that the cough reflex can be depressed without marked respiratory depression in contrast to the traditional depressants. This investigation studied a series of compounds to determine if the depression of the cough reflex paralleled the depression of respiration. *Method and Results:* The first part of the study was carried out in rabbits intubated blindly after the induction of light thiopental anesthesia. The test drug was administered intravenously in doses of 2.5 mg./kg. at intervals of two minutes until spontaneous cough disappeared. At this time the minute volume was measured by a spirometer. The endotracheal tube was moved a distance of 1 cm. three times to elicit cough. If cough occurred, the administration of the test drug was continued in the same dose at two minute intervals until cough could no longer be elicited. The minute volume was again obtained. Drugs tested included morphine and meperidine from the narcotic group; thiopental, chlorpromazine, and promethazine from the phenothiazine group; tripelennamine, methapyrilene, diphenhydramine, and antazoline from the antihistamine group, and lidocaine, a local anesthetic. In addition to the minute volume, observations were made to determine the general level of central nervous system depression at the point of cough suppression. As in previous studies, thiopental and the opiates produced severe respiratory depression without satisfactory suppression of cough. The phenothiazines depressed cough with a moderate increase in minute volume, but the animals appeared quite depressed at the end of the procedure. The antihistamines depressed the cough, with an associated increase in minute volume. It was noted that many of these animals could stand upright with the endotracheal tube in place at the end of the test. Minute volume following lidocaine was not significantly changed from the normal, and central nervous system depression was intermediate between that seen with the antihistamines and the phenothiazines. The second part of the study compared the effect of morphine and lidocaine on the cough reflex and respiration of healthy patients scheduled for gynecological surgery. Induction was accomplished with thiopental (6.6 mg./kg.), and intubation, with the aid of succinylcholine (40–60 mg.). Nitrous oxide and oxygen were administered by a nonrebreathing system. Lidocaine 75 to 100 mg. or morphine 5 mg. was given intravenously every minute for four doses, then every two minutes until either the cessation of breathing or the cessation of cough and its related movements. EEG, ECG, blood pressure, minute volume and intraesophageal pressure were monitored. In six patients receiving morphine the end point was reached with doses ranging from 20 to 60 mg., and in all cases they became apneic before cough or its related movements were suppressed. At the end point of the lidocaine series all seven patients had complete suppression of cough, and their minute volumes ranged from 2.25 to 7.0 liters/minute with lidocaine dosages of 300–800 mg.

***d*-Tubocurarine and the Blood-Cerebrospinal Fluid Barrier.** ELLIS N. COHEN, M.D., *Department of Anesthesia, Stanford University Medical School, Palo Alto, California.* The existence of a blood-brain barrier to *d*-tubo-

curarine is of both theoretical and practical importance. Experimental studies previously undertaken have failed to resolve this question satisfactorily. Under normal circumstances, there is little likelihood that intravenously administered *d*-tubocurarine should penetrate the central nervous system. It has been suggested, however, that stress situations of asphyxia, electrolyte imbalance, hemorrhage, etc., may weaken this selectiveness of entry. The availability of a sensitive fluorescent method for the quantitative analysis of *d*-tubocurarine in plasma and cerebrospinal fluid has permitted the evaluation of this problem. *Method:* Fifteen mongrel dogs were given *d*-tubocurarine by intravenous or intra-arterial route and studied under stress conditions. The study groups included a control, those receiving massive intravenous doses of *d*-tubocurarine, those made acidotic, those subjected to hypoxia, those made hypokalemic, and a group given *d*-tubocurarine into the carotid artery. Anesthesia was induced with sodium pentobarbital, and mean arterial pressure, electrocardiogram, and electroencephalogram were monitored via a multichannel recorder. Cisternal puncture was performed with a 20 gage spinal needle and adapted for sampling of spinal fluid. Determinations of *p*H, P_{O_2}, P_{CO_2} and serum potassium were made at appropriate intervals. Following a paralyzing dose of *d*-tubocurarine (0.3 mg./kg.), plasma and cerebrospinal fluid samples were drawn at five, fifteen, thirty, and sixty-minute intervals and analyzed in duplicate for *d*-tubocurarine content. *Results:* Despite plasma levels in the control group of 0.6–2.6 γ/ml., no *d*-tubocurarine could be found in the cerebrospinal fluid. Likewise, in the group given massive doses of *d*-tubocurarine (1.5–3.0 mg./kg.), resulting in plasma levels of 4.7–11.8 γ/ml., no drug was found in the cerebrospinal fluid. The group rendered acidotic (*p*H 6.91–7.02), and the hypoxic group (P_{O_2} 26–36 mm. of mercury) also failed to show presence of any muscle relaxant in the central nervous system. The hypokalemic animals (K^+ — 3.4 mEq./l.) evidenced a reduced tolerance to both the anesthesia and to the intravenous *d*-tubocurarine, yet none of the latter was measurable in the cerebrospinal fluid. Finally, the injection of large amounts of *d*-tubocurarine (1.5 mg./kg.) directly into the carotid arteries did not produce chemical evidence of transfer into the brain. *Discussion:* The most satisfactory explanation for this blood-cerebrospinal fluid barrier, suggested by Brodie (J. Pharmacol. Exp. Ther. *130:* 24, 1960), is that factors of dissociation constant and lipid solubility control the passage of drugs by simple diffusion from the blood into the cerebrospinal fluid. Since *d*-tubocurarine must be considered to be dissociated throughout all *p*H ranges, and our studies of its lipid solubility yielded very low values (Heptane—.023, Olive Oil—.059), both these factors operate towards reducing passage of the drug into the brain.

Experimental Studies of Coronary Arterial Flow Using the Square-Wave Electromagnetic Flowmeter. D. LeRoy Crandell, M.D., Edgar Lee Marston, M.D., and Jesse H. Meredith, M.D., *Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina.* This study deals with the application of the square-wave electromagnetic flowmeter to quantitate the volumetric rate of blood flow through an unopened coronary artery. An experimental method for the study of coronary arterial flow alterations resulting from surgical manipulation and drugs used in anesthetic practice is of clinical importance. Previous studies have used cannulating techniques with heparinization to measure coronary arterial flow. With the square-wave electromagnetic flowmeter (Denison, A. B., Jr., Spencer, M. P., and Green, H. D.: Circulat. Res. *3:* 39, 1955), the pulsatile and mean flow through the intact coronary artery can be recorded. Young adult mongrel dogs, ranging in weight from 16 to 40 kg., were studied. They were lightly anesthetized with intravenous pentobarbital sodium, their tracheas intubated, and their lungs ventilated with a piston-type respirator. Through a left thoracotomy, the proximal portion of the anterior descending branch of the left coronary artery was isolated to allow the placement of a small magnetic probe measuring 0.8 × 1.0 × 3.0 cm. Adjusting gain and damping of probe currents permitted phasic and mean flow measurements. Zero flow references were secured by momentary occlusion of the vessel.