meperidine, 0.2 mg./kg. morphine and 0.02 mg./kg. oxymorphone are about the same, meperidine causes considerably more, and morphine considerably less, respiratory depression than oxymorphone. The results of this study confirmed the previously reported (Lunn, J. N., and others: Pharmacologist 3: 66, 1961) findings on the protective and antagonistic effects of N-allyloxymorphone on narcotic-induced respiratory depression.

Halothane Uptake by Man at a Constant Alveolar Concentration. EDMOND I. EGER, II, M.D., and NERI P. GUADAGNI, M.D., *Department of Anesthesia, University of California Medical Center, San Francisco, California.* *Method:* Halothane uptake by man at a constant alveolar concentration was determined in ten healthy human beings. Uptake was obtained from the difference between inspired and expired (end-tidal) concentrations times alveolar minute volume. The technique and instruments used are essentially the same as those of Sechzer, Linde, and Dripps (ANESTHESIOLOGY 23: 161, 1962), except that in our study the inspired concentration of halothane was periodically altered to hold the end-tidal concentration constant. Figures thereby obtained were converted to milliters uptake per 70 kg. at an alveolar concentration of 0.8 per cent halothane. *Results:* Uptake during the first minute averaged 81 ml.; was 47 ml. at five minutes, 34 ml. at ten minutes, and 28 ml. at 20 minutes. Uptake decreased slowly thereafter and at 160 minutes was 12 ml./minute. Considerable variation in uptake occurred; the mean standard deviation equalled one-third of the uptake figure. *Discussion:* If alveolar anesthetic concentration equals brain concentration, a constant alveolar concentration reflects a relatively constant "depth" of anesthesia. The above figures thus provide a guide to the average amount of halothane required to maintain a stable light level. Deeper anesthesia would require somewhat greater quantities. An increase in alveolar concentration would not result in a proportional increase in uptake because of the concomitant decrease in cardiac output. [Supported in part by United States Public Health Service Grant GM-K3-17, 685, and 2G-63.]

Determination of Anesthetic Potency. ROBERT M. EPSTEIN, M.D., S. H. NGAI, M.D., DONALD C. BRODY, M.D., and DAVID M. RITTENBERG, PH.D., *Departments of Anesthesiology, Pharmacology, and Biochemistry, Columbia University, College of Physicians and Surgeons, New York, New York.* Recent proposals of a new theory of the mechanism of the anesthetic action of inert gaseous agents depend on correlation of certain physical properties of these agents with the partial pressures required to produce anesthesia These pressures, from the literature, are useful approximations based on observation of small numbers of animals, differing in species and studied by varying techniques. One way to test theories of anesthetic action would be to detect small shifts in anesthetic potency after maneuvers which may alter the affinity of these agents for lipid or watery phases in the brain. To make such testing feasible, a more precise measurement of the absolute potency of anesthetics and the range of variation encountered is necessary. *Method:* The median anesthetic dose (AD_{50}) of a number of commonly employed agents was determined in Swiss mice, using the loss of righting reflex as an end point. Approximately ten mice per dose were exposed in a plastic chamber to a high flow of anesthetic in oxygen at constant inspiratory concentrations. The period of exposure was sufficiently long to allow brain equilibration to occur. Concentrations of the anesthetics were determined by techniques appropriate to the individual agents. *Results:* The AD_{50} and 95 per cent confidence limits as gas tensions in millimeters of mercury determined by probit analysis were: chloroform 6.4 (6.0–6.8), halothane 12.9 (12.6–13.2), cyclopropane 125 (121–129), ethylene 1,033 (1,003–1,081), and nitrous oxide 1,144 (1,112–1,179). Reproducibility was tested by repetition of studies for nitrous oxide. The separately determined values were 1,135 and 1,152 mm. of mercury and were not significantly different. Nitrous oxide was, therefore, used for further studies. Pretreatment of mice with 0.9 per cent NaCl in large doses (60 ml./kg. subcutaneously 48 and again 24 hours before study) increased the N_2O AD_{50} to 1,265 (1,238–1,297, $P < .05$), with reproducibility similar to that found in the controls. Pretreatment with 0.9 per

cent NaCl in 99 per cent D_2O by the same schedule resulted in a mean liver water deuterium concentration of 14 per cent and increased the AD_{50} to 1,338 (1,288–1,396). This reduction in potency relative to saline controls was statistically significant (relative potency 1.06, 95 per cent limits 1.01 to 1.11). The AD_{50} of these animals fell progressively toward normal over the next month on normal water intake. Repetition of the study after a four-month interval was performed using oral deuterium oxide feeding. The control AD_{50} for nitrous oxide at this time was 1,230 mm. of mercury (1,160–1,302) and for animals maintained on 5 per cent dextrose in water, unchanged at 1,236 mm. of mercury (1,154–1,297). Feeding of 5 per cent dextrose in 60 per cent D_2O for 96 hours altered the AD_{50} to 1,296, with a mean liver water deuterium concentration of 23 per cent. This increase was not statistically significant. Unlike animals injected with D_2O, these animals developed marked hyperirritability, anorexia, and oligodipsia. [Supported by USPHS Grants RG9069 and B31C.]

A Ventilation-Blood Acid-Base Diagram. B. RAYMOND FINK, M.B., *Department of Anesthesiology, Columbia University, College of Physicians and Surgeons, New York, New York.* The ventilation ratio stimulated by H^+ and CO_2, expressed in the Gray equation: $V = 0.22\ H + 0.262\ CO_2 - 18$, can be represented on the same graph as the acid-base balance of blood, if the latter is expressed in terms of (H^+) rather than pH, in the Henderson buffer equation for bicarbonate. On the H^+–P_{CO_2} diagram so derived, a series of parallel ventilation isopleths is obtained for $V = 0, 1, 2, 3 \ldots$, on each of which all combinations of (H^+) and P_{CO_2} theoretically stimulate the same ventilation. The slope of the isopleths, $-0.262/0.22$, shows the relative effectiveness of H^+ and CO_2 as stimuli of ventilation. This ratio appears to be about the same in pentobarbital-anesthetized dogs and cats as in unanesthetized man. The spacing of the isopleths, $1/0.22$ units on the H^+ axis and $1/0.262$ units on the CO_2 axis, expresses the sensitivity of the ventilatory mechanism to acid-base stimulation. Wider spacing (smaller coefficients) would show reduced sensitivity, as observed for example in general anesthesia. The constant term, -18, defines the intercepts. The H intercept of an isoventilation isopleth is found by putting $CO_2 = 0$, when $0.22 = V + 18$ and $H = (V + 18)/0.22$. The H^+–P_{CO_2} diagram contributes some new insights to the evaluation of respiratory and metabolic acidosis. Respiratory acidosis, or retention of carbonic acid, is ordinarily considered to exist when the arterial CO_2 tension exceeds 40 mm. of mercury. This definition is too rigid, since 40 mm. of mercury is the appropriate reference P_{CO_2} only when metabolic acid-base disturbance is absent. In metabolic acidosis, acid-induced hyperventilation tends to lower (H^+) toward 39. 8 nE/l (pH 7.40). The consequent fall in P_{CO_2} is self-limited, because it decreases the stimulus to hyperventilation, equilibrium being reached when $F_{A_{CO_2}} \cdot V = k \cdot M_{CO_2}$, or $V = k \cdot M_{CO_2}/F_{A_{CO_2}}$. Here k is a proportionality constant such that $V = 1$ when $F_{A_{CO_2}}$ corresponds to 40 mm. of mercury. The calculated values of V are greater than unity and form a "CO_2 isoelimination curve" along which the volume of CO_2 eliminated in the waking steady state would be constant. This curve shows the physiological limit of ventilatory compensation for metabolic acidosis. The CO_2 tensions on this line are below 40 mm. of mercury, the divergence increasing with the base deficit. Thus, in metabolic acidosis a P_{CO_2} of 40 mm. of mercury would constitute CO_2 retention and represent a partial failure of the physiological compensatory process. The extent of the disturbance can be gauged from the difference between the H^+–P_{CO_2} diagram-predicted ventilation ratio and the ventilation ratio actually observed. In a typical case of 1 per cent halothane anesthesia, the observed V was 0.7, whereas the H–P_{CO_2} diagram-predicted V was 4.0. The acid-base ventilation response was, therefore, $0.7/4.0 = 0.18$ of normal. With 2 per cent halothane, the response fell to $0.5/5.5 = 0.09$ of normal. With ether anesthesia, the acid-base balance on the H–P_{CO_2} diagram often predicts a V below zero, although the observed V may actually be greater than unity. Presumably, a potent respiratory drive other than the acid-base drive is also present. In metabolic acidosis in the waking state, excess ventilation is usually observed. This can be