Anesthesiology
V 35, No 4, Oct 1971

Forane Uptake, Excretion, and Blood Solubility in Man

Thomas H. Cromwell, M.D., Edmond I. Eger, II, M.D.,† Wendell C. Stevens, M.D.,‡ William M. Dolan, M.D.**

With the technical assistance of Richard Shargel, Anne White, and Eunice Lim

Uptake and excretion of a new inhaled anesthetic, Forane, *in vivo* are consistent with its measured blood–gas partition coefficient of 1.4. The rate of alveolar change is similar to that of fluroxene and somewhat more rapid than that of halothane. Washin curves of volunteers exposed to a subanesthetic concentration and washout curves of volunteers exposed to an anesthetic concentration for six to seven hours (complete equilibration) are similar. Small, but significant, differences between the curves can be explained by differences in muscle blood flow and ventilation, or by the occurrence of ventilation–perfusion abnormalities. (Key words: Forane; Solubility; Induction; Recovery; Uptake; Washin; Washout.)

SOLUBILITY, uptake, distribution, and excretion are among the important characteristics of an anesthetic. These characteristics determine the rates of induction and recovery, the effects of physiologic or pathologic states such as shock and ventilation–perfusion abnormalities on depth of anesthesia, potency, and even the extent of metabolism of the anesthetic.[1-4] This report presents some solubility and uptake characteristics of a new inhaled anesthetic, Forane § (CHF_2–CHCl–O–CF_3).

Methods

SOLUBILITY IN BLOOD, OIL, AND WATER

Blood, oil, and water solubilities were determined using a modification of a technique described by Theye.[5] Three 30-ml samples of blood from the volunteers who participated in the washin studies described below were collected in calibrated, heparinized, glass syringes. These samples were injected into 100-ml calibrated glass syringes containing 50 ml of gas having a known concentration of Forane (P_1) at 37 C. Tonometry in a 37 C water bath for 45 minutes assured equilibration between gas and blood phases,[6] since we had previously determined that equilibration took half an hour. The concentration in the gas phase (P_2) was determined by gas chromatography with a hydrogen flame detector (forward determination). The gas phase was then completely expelled. Humidified nitrogen at 37 C was added to give a gas volume of slightly less than 40 ml. This mixture was tonometered for 20 minutes; then, more nitrogen was added to make the final gas volume 40 ml. The mixture was tonometered another 25 minutes and the concentration of Forane in the gas phase (P_3) was determined by chromatography (reverse determination). The "forward" and "reverse" determinations described the partition coefficients obtained by adding Forane to (forward) and removing Forane from (reverse) the same sample of blood. This double tonometry served as both a check on the completeness of equilibration and a guard against escape of Forane. Failure to obtain equilibrium or loss of Forane would cause the calculated partition coefficients to differ.

The blood–gas solubility coefficient (λ) was calculated:

$$\text{a) (forward)} = \frac{V_{gas}}{V_{blood}} \times \frac{P_1 - P_2}{P_2\,(1 - P_2)}$$

$$\text{b) (reverse)} = \frac{V_{gas}}{V_{blood}} \times \frac{P_3}{(P_2 - P_3)}$$

where V_{gas} and V_{blood} are the volumes of gas and blood used for tonometry. Changes in

* Research trainee.
† Professor of Anesthesia.
‡ Assistant Professor of Anesthesia.
Received from the Department of Anesthesia, University of California, San Francisco, San Francisco, California 94122. Accepted for publication June 25, 1971.
§ Trademark, Ohio Medical Products, Division of Air Reduction Co., Inc.

TABLE 1. Solubility Determinations

	Number of Determinations	Partition Coefficient ± SE	Forward Determination	Reverse Determination	Hematocrit (Per Cent)	Hemoglobin (gm)
Blood–gas	48	1.43 ± 0.02	1.43 ± 0.02	1.43 ± 0.04	46.4 ± 0.83	15.3 ± 0.26
Oil–gas	6	97.8	97.8			
Water–gas	16	0.61 ± 0.06	0.58 ± 0.01	0.63 ± 0.02		

gas volume due to CO_2 and O_2 were ignored. The $(1-P_2)$ factor accounts for the gas volume change due to transfer of anesthetic into the gas phase in the forward determination.

We used the same method to measure oil–gas and water–gas solubility coefficients, except that for the oil–gas solubility coefficient determination 4 ml of olive oil and 70 ml of standard humidified Forane were used with a one-hour equilibration period. Completeness of equilibration was indicated by a plateau in the concentration of Forane in the gas phase after an hour of tonometry. Reverse determinations for oil were unreliable due to error introduced from the small volume of oil used.

DETERMINATION OF ALVEOLAR WASHIN AND WASHOUT CURVES IN VIVO

Eight healthy male volunteers 23.6 ± 0.72 (SE) years old were studied after informed consents and routine laboratory values were obtained. The procedures, protocol and consent form had been approved by the University Committee on Human Experimentation. Studies were conducted with the subject supine. Right atrial and left brachial arterial catheters were inserted under local anesthesia. Following measurement of baseline oral temperature (thermistor probe), arterial carbon dioxide tension (electrodes), and forearm blood flow (occlusion plethysmography), the subject breathed a subanesthetic concentration of Forane (0.25 per cent, five subjects; 0.15 per cent, three subjects) through a mouthpiece and a nonrebreathing system. A nose clip prevented inspiration of room air. Background flows of 1.5 to 3 liters of oxygen and 9 liters of air gave measured inspired O_2 concentrations of 30 to 40 per cent. This flow (with Forane added) was directed into a reservoir attached to the nonrebreathing system. Excess gas was vented through a one-way valve located in the distal part of the nonrebreathing system. Forane was vaporized with a Fluotec vaporizer. End-tidal CO_2 was measured with a Beckman infrared analyzer,

TABLE 2.

	P_A/P_{INSP}								P_a/P_{INSP}		
	1 min	2 min	4 min	8 min	16 min	32 min	48 min	64 min	1 min	2 min	4 min
Subject 1	16.3	30.9	32.1	47.3	60.5	89.3			21.7	29.2	35.1
Subject 2	41.0	44.5	50.7	54.1	62.1	62.5			30.8	46.5	48.8
Subject 3	31.4	33.6	41.0	49.1	58.8	63.5			23.0	32.7	38.8
Subject 4	36.8	37.5	63.0	64.5	68.2	73.6			32.2	36.4	42.0
Subject 5	38.5	41.5	48.3	54.6	60.5	65.4	67.5	75.5	31.0	33.5	47.8
Subject 6	45.0	50.4	66.2	65.8	63.0	72.0	72.5	77.6	42.2	47.5	66.0
Subject 7	36.2	40.3	49.1	61.8	58.0	61.5	—	65.3	29.2	38.1	37.8
$\bar{X}$ ± SE	35.0 ± 3.5	39.8 ± 2.5	50.1 ± 4.5	56.7 ± 2.8	61.6 ± 1.3	69.7 ± 3.7	70.0 ± 2.5	72.8 ± 3.8	30.0 ± 2.6	37.7 ± 2.6	45.2 ± 4.0

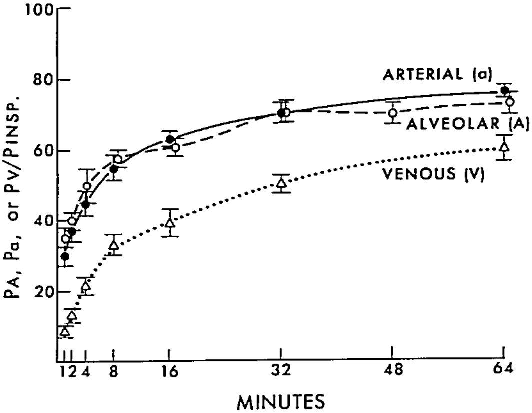

FIG. 1. Forane washin curves (arterial, solid line; alveolar, dashed line; venous, dotted line) from four subjects exposed to subanesthetic Forane concentrations for 32 minutes and three subjects for 64 minutes, ±SE. No significant alveolar–arterial difference is evident. Regression analysis of $P_A - P_a$, $P_I - P_A$ differences revealed a slope of 0.068 indicating a very small $P_A - P_a$ difference over a wide range of $P_I - P_A$ differences. Regression analyses of the washout data produced similar results, but the data were too few to be meaningful.

and the values were used to indicate the stability of ventilation and adequacy of the end-tidal samples. Blood samples (right atrial and arterial) and gas samples (inspired and end-tidal) were taken simultaneously at 1, 2, 4, 8, 16, and 32 minutes (seven subjects), and also at 64 minutes (three subjects) for Forane analysis (washin curve). Inspired and end-tidal samples were also drawn at 48 minutes without simultaneous blood samples. Forane was then discontinued, the subject breathed room air, and blood samples and end-tidal samples were again withdrawn at 1, 2, 4, 8, 16, and 32 minutes. One subject who breathed 0.25 per cent Forane was eliminated from further study after 16 minutes of washin because of sleepiness and irregular breathing. Arterial and right atrial blood samples were analyzed for Forane content by an extraction technique described previously.[1] Content was converted to partial pressure from a knowledge of the partition coefficient (see above).

Washin curves were calculated by dividing end-tidal (P_A), arterial (P_a), or right atrial

Washin Values

Pa/Pinsp					Pv/Pinsp							
8 min	16 min	32 min	48 min	64 min	1 min	2 min	4 min	8 min	16 min	32 min	48 min	64 min
40.4	61.0	84.5			4.57	4.19	12.5	18.3	30.9	44.7		
56.2	59.5	63.0			6.49	11.6	—	28.2	24.9	45.6		
44.0	64.4	71.2			11.4	15.3	20.8	36.4	—	60.7		
62.7	68.7	68.5			10.3	15.3	28.9	42.3	51.7	55.5		
59.8	—	61.8	—	73.2	7.54	14.7	20.5	31.5	39.0	41.7	—	52.2
67.5	63.6	78.1	—	79.2	10.8	16.9	23.7	39.6	45.1	51.4	—	63.7
58.2	63.2	64.7	—	74.4	8.9	16.7	—	36.4	42.1	51.1	—	62.6
55.5 ± 3.7	63.4 ± 1.3	70.3 ± 3.2	—	75.6 ± 1.8	8.6 ± 0.9	13.5 ± 1.7	21.3 ± 2.7	33.2 ± 3.1	39.0 ± 4.0	50.1 ± 2.5	—	59.5 ± 3.7

TABLE 3. Washout Values

	Pa/Pao						PA/Pao						Pv/Pao					
	1 min	2 min	4 min	8 min	16 min	32 min	1 min	2 min	4 min	8 min	16 min	32 min	1 min	2 min	4 min	8 min	16 min	32 min
32-minute group																		
Subject 2	51.2	31.9	30.7	17.1	13.2	7.8	42.5	33.9	22.2	16.1	9.9	6.8	54.3	47.2	41.2	26.0	16.1	12.0
Subject 3	67.5	56.7	37.9	20.2	13.1	9.5	54.3	42.0	35.4	19.5	10.4	7.3	70.0	61.5	43.5	30.5	20.6	17.5
Subject 4	59.4	46.5	43.0	21.0	12.3	7.3	40.6	35.2	29.8	16.0	10.2	5.4	71.7	62.8	48.5	32.4	20.4	10.0
$\bar{X} \pm SE$	59.4 ± 4.7	45.0 ± 7.2	37.2 ± 3.6	21.4 ± 2.6	12.9 ± 0.3	8.2 ± 0.7	45.8 ± 4.3	37.0 ± 2.5	29.1 ± 3.8	17.5 ± 1.0	10.2 ± 0.1	6.5 ± 0.6	65.3 ± 5.5	57.1 ± 5.0	44.4 ± 2.2	29.6 ± 1.9	19.0 ± 1.5	13.2 ± 2.2
64-minute group																		
Subject 5	50.8	30.7	30.1	28.3	21.6	14.4	33.6	27.8	22.0	22.0	13.9	9.3	61.0	50.0	48.1	34.0	26.7	22.3
Subject 6	48.5	39.0	32.3	20.0	15.5	10.6	35.4	26.0	21.9	13.6	10.1	5.7	67.6	61.4	47.5	37.1	36.0	14.6
Subject 7	54.4	37.2	35.5	27.7	21.0	14.8	42.2	31.1	25.6	18.9	12.2	10.0	72.6	65.6	50.7	38.8	29.4	22.4
$\bar{X} \pm SE$	51.2 ± 1.7	38.6 ± 0.7	34.6 ± 1.2	25.3 ± 2.7	19.4 ± 1.9	13.3 ± 1.3	37.1 ± 2.6	28.3 ± 1.5	23.2 ± 1.2	18.2 ± 2.5	12.1 ± 1.1	8.3 ± 1.3	67.1 ± 3.4	62.0 ± 1.9	48.8 ± 1.0	36.6 ± 1.4	27.4 ± 1.0	19.8 ± 2.6
Infinite equilibration																		
Subject 8	63.4	57.5	50.2	45.0	42.2	20.6	45.6	40.7	32.8	28.8	25.8	—						
Subject 9	46.0	44.0	38.5	35.8	39.0	—	51.9	48.0	47.1	47.1	38.4	27.9						
Subject 10	58.8	60.0	56.1	54.8	48.8	40.6	54.0	56.8	44.3	37.4	34.6	29.1						
Subject 11	66.8	55.0	58.2	53.5	46.0	34.4	62.5	57.4	51.1	38.7	31.2	22.5						
Subject 12	54.5	60.1	54.5	49.0	41.8	39.6	44.6	42.4	37.6	32.9	32.9	36.4						
$\bar{X} \pm SE$	57.9 ± 3.6	55.3 ± 3.0	53.5 ± 4.6	47.6 ± 3.4	43.6 ± 1.7	36.1 ± 2.5	51.7 ± 3.2	49.1 ± 3.5	42.6 ± 3.2	37.0 ± 3.1	32.6 ± 2.1	29.0 ± 2.9						

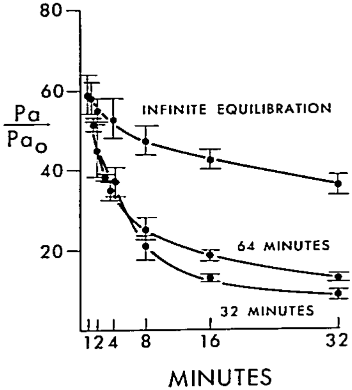

FIG. 2. Forane arterial washout curves of three groups of subjects. Infinite equilibration—five subjects anesthetized with Forane and N_2O for six to seven hours. Sixty-four minutes—four subjects exposed to a subanesthetic Forane concentration for 64 minutes. Thirty-two minutes—three subjects exposed to subanesthetic Forane concentration for 32 minutes. Increasing the time of exposure to Forane results in increasing tissue saturation and resulting decrease in rate of excretion.

(P_V) anesthetic partial pressure by the inspired (P_{INSP}) partial pressure. Washout curves for Forane were calculated by dividing end-tidal, arterial, or right atrial partial pressures by the arterial partial pressure immediately before washout began (Pa_0).

We also measured washout curves and muscle blood flow in a second group of five healthy volunteers aged 25 ± 1.0 years who had been anesthetized with Forane and nitrous oxide for 6 to 7 hours for cardiorespiratory studies during controlled respiration.[7] The prolonged anesthesia permitted more complete total-body equilibration than did the 32- and 64-minute washin experiments. The approach to complete equilibration was improved further by the following manipulation of the end-tidal Forane concentration. End-tidal Forane had been maintained at 1.3 per cent for most of the 6- to 7-hour period of cardiorespiratory study. However, a persistent inspired-to-end-tidal difference indicated continuing anesthetic

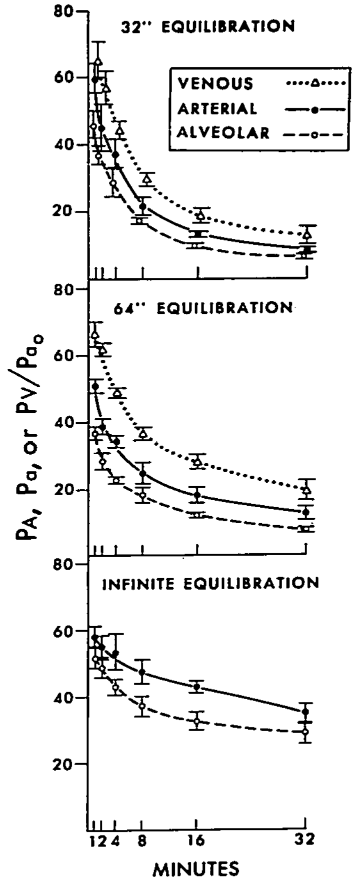

FIG. 3. Venous and alveolar washout curves added to the data in fig. 2. Alveolar–arterial and arterial–venous differences increased with prolonged exposure to Forane. This may be the result of more complete tissue saturation with time or development of ventilation-perfusion abnormalities with time or with anesthesia.

Anesthesiology
V 35, No 4, Oct 1971

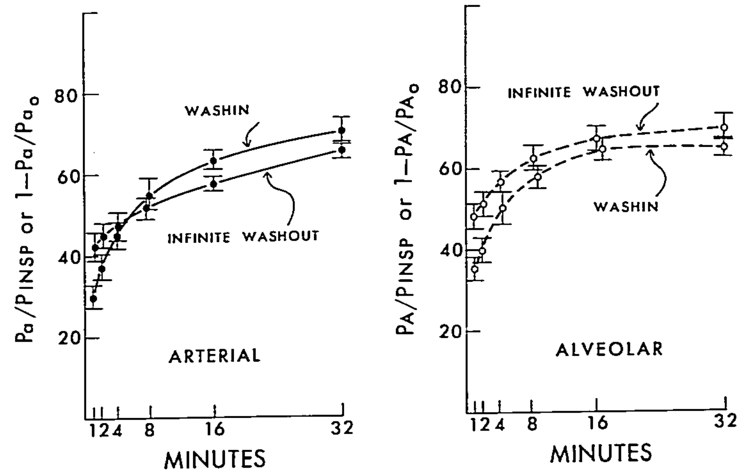

FIG. 4. Comparison of arterial and alveolar washin curves with arterial and alveolar washout curves following complete equilibration.

uptake and hence, lack of total-body equilibration. We lowered the end-tidal concentration to 0.8 to 0.9 per cent for 18.5 ± 3.3 minutes and thereby reversed the anesthetic gradient: at these end-tidal concentrations Forane was eliminated rather than taken up. Finally, the end-tidal concentration was raised to between 0.9 and 1.0 per cent and held for 13.2 ± 2.3 minutes. At this level the inspired values equaled 99.6 ± 0.23 per cent of the end-tidal values. This suggested a rough approach to total-body equilibration. Washout proceeded as in the previous study with unanesthetized volunteers except that the inspired gases contained 30 per cent oxygen in 70 per cent nitrous oxide. End-tidal and arterial samples were obtained at 1, 2, 4, 8, 16, and 32 minutes. To calculate the washout curves, Forane partial pressures in these samples were divided by the arterial Forane partial pressure immediately preceding the beginning of the washout.

For both washin and washout curves, in both anesthetized and unanesthetized volunteers, we measured arterial carbon dioxide and muscle blood flow. Pa_{CO_2} was measured at 0, 5, 15, 30, and 60 minutes, while muscle flow was measured at 10-minute intervals.

TABLE 4. Pa_{CO_2} (torr) ± SE

	Number of Subjects	0 min	5 min	15 min	30 min	60 min
Washin	7	39.3 ± 2.6	41.6 ± 2.3	42.6 ± 1.9	42.0 ± 1.9	41.3 ± 1.7
Washout, 32-minute group	4	44.0 ± 2.0	43.3 ± 3.2	42.3 ± 1.8	43.6 ± 2.8	—
Washout, 64-minute group	3	41.3 ± 1.7	39.5 ± 1.8	39.8 ± 2.9	38.7 ± 4.7	—
Washout, infinite equilibration	8	34.1 ± 1.1	32.3 ± 1.0	31.9 ± 1.0	33.0 ± 1.6	—

Results

Solubility determinations for oil–gas, blood–gas, and water–gas partition coefficients (λ) *in vitro* are listed in table 1. Pooled data for alveolar, arterial, and right atrial (venous) Forane values for washin and washout curves (32-minute, 64-minute, and infinite equilibration groups) are listed in tables 2 and 3, respectively.

Discussion

The *in-vivo* alveolar washin curve (fig. 1, table 2) is consistent with the *in-vitro* blood–gas λ determination of 1.43. The blood–gas λ for halothane is 2.3; for fluroxene, 1.37. This indicates that the rate of increase or decrease of alveolar concentration (speed of induction or recovery) of Forane should be similar to that of fluroxene and slightly faster than that of halothane. Our clinical experience with Forane corroborates this finding. Other factors also will influence time of induction: tissue–blood solubilities, which have yet to be determined. Airway irritation will limit the rate of induction. Halothane appears to be somewhat less irritating than Forane. No significant ventilation–perfusion abnormalities were present in our young healthy volunteers, as shown by the absence of alveolar–arterial Forane difference (fig. 1). The rate of increase of Forane in mixed (right atrial) venous blood is similar to alveolar and arterial washin curves, but lags behind both due to uptake by body tissues. The inspired-alveolar difference decreases with time in proportion to the decrease in arterial–venous difference. With longer exposure to Forane and resulting increase in tissue saturation, washout is delayed (fig. 2, table 3). This has also been demonstrated for N_2O, halothane, and methoxyflurane by analog computer, the effect of time being more pronounced with soluble agents.[8] Washout alveolar-to-arterial and arterial-to-venous differences increased with prolonged exposure to Forane (fig. 3, table 3). This can be explained by more complete tissue saturation or development of ventilation–perfusion abnormalities with time or with anesthesia.[2]

Mapelson has postulated that anesthetic excretion (washout) for inhaled anesthetics is

TABLE 5. Muscle Blood Flow (ml/100 ml of tissue/min ± SE)

	Number of Subjects	0 min	10 min	20 min	30 min	40 min	50 min	60 min
Washin	7	1.91 ± 0.25	2.02 ± 0.32	2.22 ± 0.44	2.78 ± 0.85	2.93 ± 0.26	2.53 ± 0.47	2.60 ± 0.43
Washout, 32-minute group	4	—	1.87 ± 0.56	1.67 ± 0.49	1.60 ± 0.58	—	—	—
Washout, 64-minute group	3	—	2.03 ± 0.59	2.83 ± 0.54	2.72 ± 0.35	—	—	—
Washout, infinite equilibration*	2	6.4	4.5	4.1	3.4			
		7.8	6.7	7.8	6.4			
		7.1	5.6	5.9	4.9			

* Only two subjects were available; therefore, values are individual values and mean.

the inverse of anesthetic uptake (washin), provided complete saturation is present (no inspired-to-end-tidal difference).[9] The inverses of the washout curves for the infinite-equilibration group (no inspired-to-end-tidal difference) have been superimposed on the washin curves (fig. 4). In support of Mapelson's theory, differences between the two groups are small, *i.e.*, less than 6 per cent for alveolar values and less than 5 per cent for arterial values. The differences, however, are significant, and the reasons for them can be explained by demonstrated differences in ventilation and muscle blood flow between the two groups. For the first 4 minutes the arterial washout curve obtained in the anesthetized subjects (infinite washout) (fig. 4*A*) is above the arterial washin curve in the unanesthetized subjects (washin), indicating a faster rate of change in the anesthetized group. This may be predicted from the greater ventilation in the anesthetized group (controlled ventilation) (table 4) and can be demonstrated by the alveolar curves (fig. 4*B*), which show a greater rate of alveolar change in the anesthetized group. However, the positions of the arterial curves are reversed after 8 minutes. This can be explained on the basis that Forane is known to cause a marked increase (300–500 per cent) in forearm muscle blood flow.[10] Muscle blood flow was considerably greater in the subjects exposed to anesthetic concentrations of Forane for six to seven hours (infinite equilibration group) than in the subjects exposed to subanesthetic concentrations (32-minute and 64-minute groups (table 5). This provides greater access to muscle stores of Forane in the anesthetized subjects, and the additional Forane input into the blood returning to the lungs decreases the rate of arterial washout. No ventilation perfusion (V/Q) abnormality existed during the washin phase in the subjects exposed to the subanesthetic concentration, as stated earlier. Ventilation–perfusion abnormalities may have been present after six to seven hours of anesthesia in the anesthetized volunteers. The occurrence of such an abnormality could also explain the differences evident in figure 4.[2]

References

1. Halsey MJ, Sawyer DC, Eger EI II, *et al.*: Hepatic metabolism of halothane, methoxyflurane, cyclopropane, Ethrane, and Forane in miniature swine. ANESTHESIOLOGY
2. Eger EI II: Respiratory and circulatory factors in uptake and distribution of volatile anesthetic agents. Brit J Anaesth 36:155–171, 1964
3. Eger EI II, Larson CP Jr: Anaesthetic solubility in blood and tissues: Values and significance. Brit J Anaesth 36:140–149, 1964
4. Eger EI II, Severinghaus JW: Effect of uneven pulmonary distribution of blood and gas on induction with inhalation anesthetics. ANESTHESIOLOGY 25:620–626, 1964
5. Theye RA: Estimation of partial pressure of halothane in blood. ANESTHESIOLOGY 29: 101–103, 1968
6. Shargel RO: A gas–liquid equilibrating rotator for simultaneous solubility or content measurements. ANESTHESIOLOGY 31:465–466, 1969
7. Dolan WM, Stevens WC, Eger EI II, *et al.*: The marriage of Forane and nitrous oxide: For better or for worse? ANESTHESIOLOGY (in preparation)
8. Stoelting RK, Eger EI II: The effects of ventilation and anesthetic solubility on recovery from anesthesia. ANESTHESIOLOGY 30:290–296, 1969
9. Mapelson WW: Inert gas exchange theory using an electric analogue. J Appl Physiol 19:1193–1199, 1962
10. Stevens WC, Cromwell TH, Halsey M, *et al.*: The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. ANESTHESIOLOGY (in press)