Technical Note

Solubilities of Ethylene, Cyclopropane, Halothane and Diethyl Ether in Human and Dog Blood at Low Concentrations

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Heparinized human and dog blood were equilibrated with low concentrations (0.7 to 1.4 per cent) of anesthetics and assayed for anesthetics by gas chromatography. Partition coefficients for human blood (Hb 15 g per cent) at 37.5 C were: 0.149 for ethylene; 0.574 for cyclopropane; 2.50 for halothane; 9.96 for diethyl ether. Partition coefficients for dog blood were: 0.182 for ethylene; 0.765 for cyclopropane; 3.11 for halothane; 10.07 for diethyl ether. Ethylene and cyclopropane showed increasing solubility, whereas halothane and diethyl ether showed decreasing solubility, with increasing hematocrit or hemoglobin concentration. Comparison with previously reported values suggests that ethylene and cyclopropane have higher partition coefficients and diethyl ether a lower partition coefficient when low concentrations of anesthetic are used for the determination. Gas chromatographic head space analysis after equilibration of 3-ml blood samples in small sealed glass tubes provides an accurate method for the assay of several inhalation anesthetics in a single blood sample. The method is also convenient because it allows storage of the samples for several hours before assay. (Key words: Ethylene; Cyclopropane; Diethyl ether; Halothane; Blood:gas partition coefficient; Solubility, human blood; Solubility, dog blood; Chromatography.)

THE SOLUBILITIES of inhalation anesthetics in blood are among the most important determinants of their uptake and distribution. The range of solubilities of inhalation anesthetics currently used is almost two orders of magnitude; the range of rates of uptake by body tissue compartments is equally large. Because there is disagreement in the values for solubilities of anesthetics reported by different investigators, solubility measurements by new techniques are of interest. The solubilities of ethylene, cyclopropane, halothane, and diethyl ether reported here were determined by a new equilibration method.

Methods

Blood:gas partition coefficients were determined for each of the four inhalation anesthetics in 22 blood samples from 17 healthy young adults (eight male and nine female) and on 11 blood samples from seven healthy adult male mongrel dogs. Ten determinations were done for each anesthetic in each sample of human blood and eight in each sample of dog blood. Blood was obtained by venipuncture and prevented from clotting with heparin. All determinations were performed with blood samples which had been stored for less than 24 hours at 5 C. Blood with low hematocrit values was produced by low-speed centrifugation and removal of erythrocytes.

Blood was delivered to a 500-ml equilibration flask (fig. 1) with a calibrated 50-ml pipet. After a period of warming the blood and head space of the flask to 37.5 C, pressure was allowed to escape by opening the stopcock and puncturing the serum bottle cap with a hypodermic needle. Anesthetics were then injected into the head space of the flask in quantities sufficient to produce head space concentrations of 1.4 per cent ethylene, 0.9 per cent cyclopropane, 0.7 per cent halothane, and 0.7 per cent diethyl ether after equilibra-

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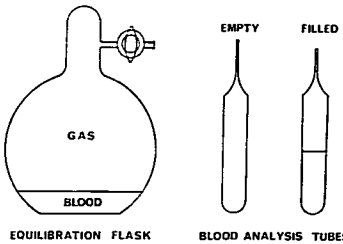

FIG. 1. Diagrams of equilibration flask (modified 500-ml boiling flask) and blood analysis tubes (modified 13 × 100-mm centrifuge tubes).

tion. The volume of liquid diethyl ether was measured precisely with a microliter syringe, whereas the other anesthetics were added in approximate quantities.

A two-hour period of slow rotation of the flask under water at 37.5 C was found to be sufficient to produce complete equilibration of anesthetic between the blood and the head space of the flask, but to insure complete equilibration the flasks were equilibrated for 8 to 16 hours. With the stopcock closed, there was no significant loss of anesthetic from the flask over 16 hours.

At the end of the equilibration period, the stopcock was opened and 3.0-ml blood samples were removed without exposure to air, using a Cornwall syringe calibrated to deliver the desired volume. The rubber serum bottle cap covering the outer opening of the stopcock prevented any exchange of gas within the flask with air during sampling. Blood samples were quickly sealed in glass equilibration tubes (fig. 1) by melting the end of the tube. The blood samples were then equilibrated with the head space of the equilibration tubes by agitation under water at 37.5 C for one to two hours. Equilibration was found to be complete in less than 15 minutes, and there was no loss of anesthetic over six hours.

Concentrations of anesthetics in the head spaces of the equilibration flask and equilibration tubes were measured by gas chromatography. Samples were taken from the flask by opening the stopcock and puncturing the serum bottle cap with the hypodermic needle on a gastight syringe. Gas samples were obtained from the head space of the equilibration tubes by snapping off the neck of the tube, covering the opening with Parafilm, and quickly taking a sample from the tube by puncturing the Parafilm with the needle of a gastight syringe.

Samples of 100 μl were injected directly into a Microtek 2500 R Gas Chromatograph. The columns consisted of 2 m × 6.35 mm copper tubing packed with 20 per cent SE-30 silicone gas rubber on Gas Chrom Q. The carrier gas was helium at 2.5 atm inlet pressure and 120 ml/min flow rate. Inlet-block temperature was 90 C, column temperature 80 C, and outlet-black temperature 90 C. A dual hydrogen-flame ionization detector was operated with hydrogen at 2 atm pressure and 60 ml/min flow rates. Scavenger gas was air at 2 atm pressure and 500 ml/min flow rate.

Under these conditions the anesthetics were well separated. Peak heights were directly proportional to the amounts of gases injected. Injections of unknown concentrations of anesthetics were compared with injections of standard gas mixtures of known concentrations. Standard gas mixtures were prepared in modified 2,000-ml flasks with standard taper fittings. These fittings were drawn out so that they could be closed by a small rubber serum bottle cap. The total volume of the flask was determined gravimetrically. Known volumes of pure ethylene and cyclopropane were injected into the standard flask by displacement by mercury from an inverted buret. Known volumes of halothane and anhydrous diethyl ether were injected using a calibrated microliter-syringe. The gas volumes of halothane and diethyl ether were calculated according to the Ideal Gas Law. Calculation of their molar volumes at low partial pressures, using van der Waals and second virial coefficients, shows that the deviation of these gases from ideality is less than 0.1 per cent. Thirty milliliters of mercury were then added to the flask. Shaking of the mercury in the flask mixed the standard gas mixture, and storage of the flask in an inverted position provided a mercury seal. Standard gas mixtures were found to lose about 1 per cent of their initial concentrations every 100 days. No standard gas mixture was used for more than a month. The measured concentrations were expressed as the volume of anesthetic as a pure gas at 0 C and

1 atm pressure (T_0, P_0) divided by its volume of distribution. The actual temperatures and pressures of the gases analyzed were taken into account in calculating their concentrations.

Losses of anesthetic from equilibration flasks and tubes or during transfer would affect the accuracy of this method. To test for possible loss, anesthetic was added to the equilibration flask in carefully measured amounts. Equilibration was carried out as described above but water was used instead of blood. The gas and water phases were analyzed by direct injection into the gas chromatograph. Samples were transferred from the flask to blood analysis tubes and sealed and, after equilibration, both phases were again analyzed by gas chromatography. No loss of anesthetic from this system was detected, and equilibration was found to be complete within the prescribed equilibration time.

The tube head-space sampling procedure was tested with a rapidly-flowing gas stream directed into the bottoms of sample tubes with a long 18-gauge needle. After sufficient time had elapsed for the tubes to be thoroughly flushed out with inflowing gas, the gas stream and gas in the tube head spaces were sampled and analyzed. Tube head-space concentrations were consistently 1 per cent less than inflowing gas concentrations for all anesthetics. Correction was made for this 1 per cent loss in calculating partition coefficients.

Calculations

After equilibration of the blood in the flask, the concentration of anesthetic in the head space, C_1, was measured. The concentration of anesthetic in the equilibrated blood was λC_1. A volume of blood, V_1, was transferred to an equilibration tube. The volume of anesthetic in the blood sample, $V_1\lambda C_1$, became distributed between the blood and the head space of the equilibration tube. After equilibration of the tube, the concentration of anesthetic in its head space, C_2, was measured. The concentration of anesthetic in the equilibrated blood at this time was λC_2. The volume of anesthetic in the head space and blood was $V_2C_2 + V_1\lambda C_2$, where V_2 is the volume of the tube head space. Because this is the same volume as that initially transferred to the equilibration tube, $V_1\lambda C_1 = V_2C_2 + V_1\lambda C_2$. Rearranging this equation, we may obtain the blood:gas partition coefficient.

$$\lambda = \frac{V_2C_2}{V_1(C_1 - C_2)}$$

Although the partition coefficient probably varies with gas concentration, the variation over the concentration range considered here (0.4 to 1.4 per cent) can be presumed to be small.

Diethyl ether is so soluble in blood that the concentration change between flask and tube head space ($C_1 - C_2$) was almost zero. For this reason, the denominator of the above equation could not be accurately determined. Partition coefficients for diethyl ether were therefore calculated in the following manner: after equilibration, the total volume of anesthetic in the flask is the flask head-space volume multiplied by the head-space concentration (V_fC_f) plus the volume of the blood in the flask multiplied by the concentration of the anesthetic in the blood ($V_{bl}\lambda C_f$). According to the Ideal Gas Law the volume of diethyl ether, as a gas at T_0 and P_0, initially injected is $V_{liq}DRT_0/MWP_0$, where V_{liq} is the volume of liquid ether injected, D is its density, MW is its molecular weight, T_0 is the reference temperature (273 K), P_0 is 1 atm pressure, and R is the universal gas constant. Because no ether is lost from the system:

$$V_fC_f + V_{bl}\lambda C_f = V_{liq}DRT_o/MWP_o$$

Rearranging this equation, we obtain the blood:gas partition coefficient in measurable terms.

$$\lambda = \frac{V_{liq}DRT_o/MWP_o - V_fC_f}{V_{bl}C_f}$$

Results of any single blood sample outside of plus or minus two standard deviations from the mean were discarded (31 determinations in a total of 945). Lines were fitted by the least-squares method.

Results

Partition coefficients and the regression equations for the relations between solubility and hemoglobin and hematocrit are given in tables 1 and 2 for human blood and in tables 3 and 4 for dog blood. Figure 2 illustrates the

TABLE 1. Blood:Gas Partition Coefficient–Hemoglobin Relations for Ethylene, Cyclopropane, Halothane, and Diethyl Ether in Human Blood at 37.5 C*

	a	b	SEE	λ_{15}
Ethylene	+0.0015†	0.127	0.004	0.149
Cyclopropane	+0.0140†	0.364	0.013	0.574
Halothane	−0.0514†	3.266	0.13	2.50
Diethyl ether	−0.061†	10.87	0.20	9.96

* Hemoglobin concentrations ranged from 7.0 to 17.3 g per cent. Equations are of the form: $\lambda = a$-hemoglobin $+ b$. SEE = standard error of the estimate. λ_{15} = partition coefficient at a hemoglobin concentration of 15.0 g per cent. These relations are illustrated in fig. 2.

† Differs significantly from zero ($P < 0.05$).

relation between blood:gas partition coefficients and hemoglobin concentrations in human blood.

Discussion

ETHYLENE

The partition coefficient found for ethylene in human blood is somewhat higher than the partition coefficients obtained by Marshall and Grollman[1] and Grollman[2] (table 5), measured by equilibration of blood with 60 to 100 per cent ethylene in a tonometer, extraction in a Van Slyke apparatus, and analysis by combustion. Incomplete extraction or equilibration could have resulted in low values. If their partition coefficients were correct, the higher partition coefficient at a lower concentration of ethylene suggests that ethylene binds to a component of blood which becomes saturated at low concentrations.

TABLE 2. Blood:Gas Partition Coefficient–Hematocrit Relations for Ethylene, Cyclopropane, Halothane, and Diethyl Ether in Human Blood at 37.5*

	a	b	SEE	λ_{45}
Ethylene	0.0005†	0.128	0.004	0.150
Cyclopropane	0.0046†	0.372	0.013	0.578
Halothane	−0.0165†	3.227	0.13	2.49
Diethyl ether	−0.0196†	10.82	0.20	9.94

* Hematocrit values ranged from 19 to 52 per cent. Equations are of the form: $\lambda = a$-hematocrit $+ b$. SEE = standard error of the estimate. λ_{45} = partition coefficient at a hematocrit value of 45.

† Differs significantly from zero ($p < 0.05$).

The partition coefficient for ethylene in dog blood found by Grollman[2] is higher than the partition coefficient he found for human blood. We confirm this finding.

CYCLOPROPANE

The partition coefficient in human blood at a hemoglobin concentration of 15 gm per cent, 0.574, is significantly higher than reported values, which range from 0.415[3] to 0.508.[4] This suggests that cyclopropane may bind preferentially to some component of blood which becomes saturated at low concentrations, because the partition coefficient was determined using a low concentration of cyclopropane. Lowe and Hagler[5] found a similar relation, but did not publish an equation. Laasberg and Hedley-Whyte[6] have found that variations in plasma albumin and globulin concentraton may also affect the partition coefficient.

The partition coefficient reported by Robbins[4] for dog blood is higher than those reported for human blood. We confirm this finding.

Cyclopropane was found to be more soluble in both human blood and dog blood at higher hemoglobin concentrations. The equation which we ehave found for the solubility of cyclopropane in human blood (table 1) is close to that of Possati and Faulconer[3] ($\lambda = 0.265 + 0.01$ Hb). Laasberg and Etsten[7] and Lowe and Hagler[5] confirmed this solubility–hemoglobin concentration relation, but did not publish equations.

HALOTHANE

The partition coefficients we found in human and, especially, dog blood are somewhat higher than those previously reported. In human and dog blood we found a slightly decreasing solubility with increasing hemoglobin

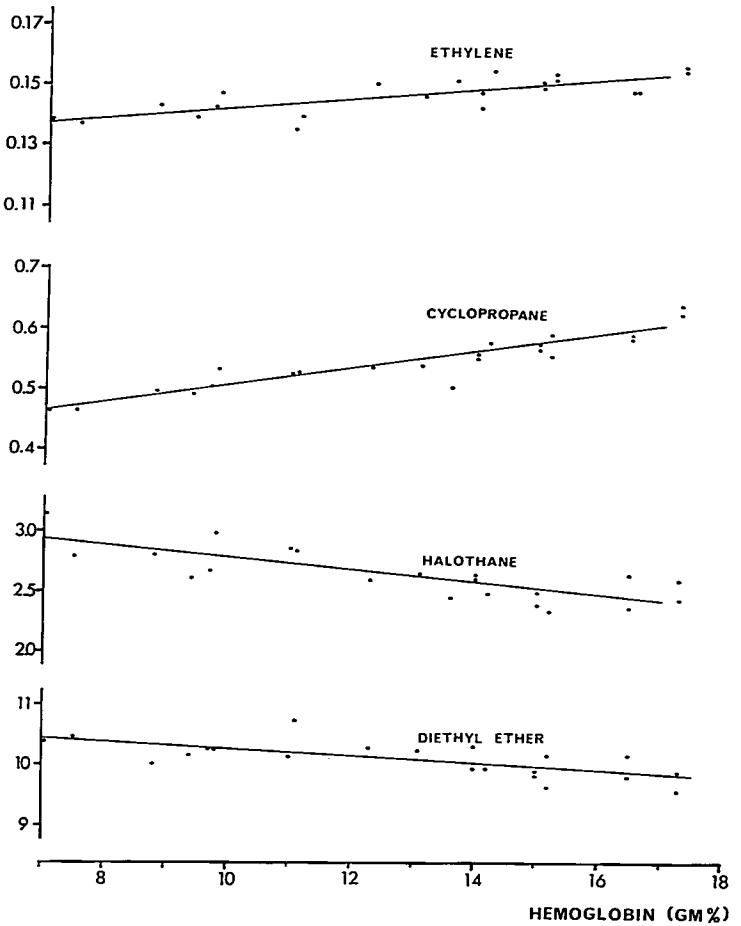

FIG. 2. Relations between blood:gas partition coefficients and hemoglobin concentrations of ethylene, cyclopropane, halothane, and diethyl ether in human blood at 37.5 C. Each point represents ten determinations on a single blood sample. Equations for the least-squares lines are given in table 1. Graphs of the relations given in tables 2 to 4 are similar.

TABLE 3. Blood:Gas Partition Coefficient–Hemoglobin Relations for Ethylene, Cyclopropane, Halothane, and Diethyl Ether in Dog Blood at 37.5 C*

	a	b	SEE	λ_{15}
Ethylene	0.0054†	0.101	0.007	0.182
Cyclopropane	0.0337†	0.260	0.028	0.765
Halothane	−0.0035	3.158	0.21	3.11
Diethyl ether	−0.0068	10.17	0.40	10.07

* Hemoglobin concentrations ranged from 11.7 to 17.8 g per cent. Equations are of the form: $\lambda = a \cdot$hemoglobin $+ b$. SEE = standard error of the estimate. λ_{15} = partition coefficient at a hemoglobin concentration of 15.0 g per cent.
† Differs significantly from zero ($P < 0.05$).

concentration. The relation which we have found in human blood is close to that reported by Han and Helrich [8]:

$$\lambda = 3.2 - 0.06 \text{ (Hb) at 38 C}$$

Lowe and Hagler [5] found a similar relation, but did not publish an equation. Laasberg and Hedley-Whyte [6] have found that variations in plasma albumin and globulin concentration may also affect the partition coefficient.

DIETHYL ETHER

Partition coefficients reported for diethyl ether range from 9.96 to 15.6.[9] There is no constant relation between the reported partition coefficients and the concentrations of diethyl ether used in determining them. Lowe and Hagler [5] found a lower partition coefficient (10.8) using a gas concentration of 4 per cent than using 50 per cent (15.0), but did not state the species, hemoglobin, or temperature of their measurements. The results of other partition coefficient measurements reported do not demonstrate any clear relation to the gas concentrations at which they were measured. Giller and Noehren [10] found no difference between the partition coefficients for human and canine blood; we have found very little difference. The decrease in the partition coefficients with increasing hemoglobin concentrations is very small. Lowe and Hagler [5] found a similar relation but did not publish an equation.

TABLE 4. Blood:Gas Partition Coefficient–Hematocrit Relations for Ethylene, Cyclopropane, Halothane and Diethyl Ether in Dog Blood at 37.5 C*

	a	b	SEE	λ_{15}
Ethylene	0.0018†	0.105	0.007	0.185
Cyclopropane	0.0111†	0.284	0.030	0.782
Halothane	−0.0020	3.192	0.21	3.10
Diethyl ether	−0.0048	10.28	0.40	10.06

* Hematocrit values ranged from 34 to 51 per cent. Equations are of the form: $\lambda = a \cdot$hematocrit $+ b$. SEE = standard error of the estimate. λ_{15} = partition coefficient at a hematocrit value of 45.
† Differs significantly from zero ($p < 0.05$).

Comment

The partition coefficients found for ethylene, cyclopropane, and halothane are generally higher than those previously reported; those for diethyl ether are lower. Comparison with other reported values shows that these differences might be explained by the fact that the partition coefficients were determined using very low concentrations of anesthetics in the gas phase at equilibrium. They cannot be explained by assuming a systematic loss of anesthetic from the flask or equilibration tube. The equations for the partition coefficients show that losses of anesthetic from the system would have resulted in lower partition coefficient values for ethylene, cyclopropane and halothane, and higher partition coefficient values for diethyl ether. The results were, in fact, in the opposite direction. Although the flask and tubes were equilibrated for about four times the time necessary for equilibration, a disequilibrium would have resulted in a lowering of all partition coefficient values. We are unable to find any systematic errors in these partition-coefficient determinations which might explain the differences.

Most of the least-square lines (see tables 1–4) showed an increase or decrease of solubility with increasing or decreasing hematocrit or hemoglobin. For those anesthetics with a positive relation, the anesthetic is more soluble in erythrocytes than in plasma. For those with a negative relation, the opposite is true. These relations have also been found by other authors, as mentioned above.

TABLE 5. Partition Coefficients for Ethylene, Cyclopropane, Halothane, and Diethyl Ether in Blood at 37 C to 38 C Reported since 1900

Species and Anticoagulant	Partition Coefficient	Temperature (C)	Concentration (Per Cent)	Method*	Reference
Ethylene					
Human oxalated, Hct 47	0.140	37.5	60–70	TE CHM	1
†	0.140	37.5	100	TE CHM	2
Canine	0.160	37.5	100	TE CHM	2
Human, heparinized	0.149	37.5	1.4	FE GC	‡
Canine, heparinized	0.182	37.5	1.4	FE GC	‡
Cyclopropane					
Human, oxalated	0.470–0.508	38.0	100	TE CHM	4
Human, oxalated	0.457	37.5	100	TE VSN	11
Human, heparinized, Hb 15 g per cent	0.415	37.0	100	FE MS	3
Human, heparinized	0.420	37.0	†	SE GC	9
Human, in ACD solution, Hb 15 g per cent	0.429	37.0	100	FE GC	7
Canine, oxalated	0.513	38.0	100	TE CHM	4
Human, heparinized	0.574	37.5	0.9	FE GC	‡
Canine, heparinized	0.765	37.5	0.9	FE GC	‡
Halothane					
Human, pooled	2.3	37.0	†	FE IR	12
Human, heparinized	2.42	37.0	†	SE GC	9
Human, heparinized, Hb 15 g per cent	2.3	38.0	3.4	FE GC	8
Human, heparinized	2.3	37.0	1	TE HEX GC	13
Human, heparinized, Hb 14.2 g per cent	2.42	37.0	3.4	SE GC	6
Canine, heparinized, Hb 9–15 g per cent	2.3	37.0	0.3–3.8	SE GC PP	14
Human, heparinized	2.50	37.5	0.7	FE GC	‡
Canine, heparinized	3.11	37.5	0.7	FE GC	‡
Diethyl ether					
Human, defibrinated	14.9	37.0	2.4	CHM	15
†	12.2–12.5	37.0	†	SE MS	16
†	11.2	37.0	†	SE MS	17
Human	12.13	37.0	8.9	FE IR	18
Human, heparinized	15.6	37.0	†	SE GC	9
Human, heparinized	12.	37.0	0.272	TE DST GC	19
Canine, defibrinated	15.20	37.0	1.2	FE CHM	20
Human and canine, pooled, oxalated	14.0	37.5	†	TE GC	10
Human, heparinized	9.96	37.5	0.7	FE GC	‡
Canine, heparinized	10.07	37.5	0.7	FE GC	‡

* Abbreviations: TE, tonometer equilibration; CHM, chemical assay; FE, flask equilibration; GC, gas chromatography; VSN, Van Slyke-Neill assay; MS, mass spectrometry; SE, syringe equilibration; ACD, acid-citrate-dextrose; IR, infrared assay; HEX, hexane extraction; PP, partial pressure determination; DST, quantitative distillation.

† No information.

‡ This study.

Assay of Anesthetics

The equilibration of blood with the head space of a small sealed tube provides a method of assay for one or several anesthetics in blood. The concentration of anesthetic in the blood before equilibratoin is C_0 and the volume of anesthetic is C_0V_{bl}, where V_{bl} is the volume of the blood sample. After equilibration, the volume of anesthetic in the blood is distributed between the blood and the head space of the tube. The concentration of anesthetic in the head space after equilibration, C_h, is measured by gas chromatography. The con-

centration in the blood after equilibration is λC_h, where λ is the known solubility of the anesthetic in blood. The volume of anesthetic in the head space and in the blood is $V_hC_h + V_{bl}\lambda C_h$. Since no anesthetic is lost from the tube during equilibration,

$$C_oV_{bl} = V_hC_h + V_{bl}\lambda C_h$$

Therefore, the original concentration of anesthetic in the blood is:

$$C_o = \frac{C_h(V_h + \lambda V_{bl})}{V_{bl}}$$

Because the pressure in the tube increases during the equilibration of blood due to the loss of anesthetic from the blood and the warming and humidification of the air in the head space of the tube, this increase in pressure should be estimated from the vapor pressure of water and the anesthetic concentration and taken into account in determining the concentrations of anesthetics in the head space.

The 220 samples of human blood analyzed in the process of determining partition coefficients were treated as examples of blood analyzed in this manner. The coefficient of variation of these analyses was 4.7 per cent for ethylene, 3.0 per cent for cyclopropane, 2.7 per cent for halothane, and 2.5 per cent for diethyl ether. Because the partition coefficients for ethylene, cyclopropane, and halothane were derived from the same analyses of blood, it was not possible to detect a systematic error in the assay of these anesthetcis. Because the partition coefficient for diethyl ether was determined by a different technique, the analysis of blood containing known concentrations of diethyl ether, using this partition coefficient, can, however, detect a systematic error. Values for diethyl ether by this method were found to be systematically 1.7 per cent below known concentrations. Because this may be the result of loss of anesthetic from the blood sample or equilibration tube head-space sample during handling, it is likely that other anesthetics may also systematically be in error by minus 1 or 2 per cent.

The equilibration of a blood sample with the head-space of a small tube provides a convenient, rapid and simple method by which single blood samples may be assayed for multiple anesthetics by gas chromatography. Samples can be taken in rapid sequence during experiments or in clinical situations and stored for at least six hours before assay. In our laboratory, this method has been used for the assay of as many as 100 blood samples in a single afternoon. Because of the possibility of combustion, it is not expected that this method of assay would be useful for anesthetics in their explosive concentration ranges.

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Drugs

NEUROLEPTANESTHESIA A comparison of neuroleptanesthesia with anesthesia with nitrous oxide, opiate, relaxant, or halothane was made in 400 patients undergoing open-heart surgery. Repeated administration of a fixed mixture of droperidol and fentanyl resulted in overdoses of both agents. Separate administration of droperidol and fentanyl was not accompanied by the adverse effects (chest-wall rigidity) seen when the combination was used. Neuroleptanesthesia provided greater cardiovascular stability and ease of management than did anesthesia with the other agents studied. Postoperative ventilatory support was considerably easier in the patients given neuroleptanesthesia than in those given the other agents. Neuroleptanesthesia is preferred for most patients requiring cardiac surgery. (*Jacobson, E., and others: Neuroleptanesthesia for Open Heart Surgery: A Comparative Study of 400 Patients, Der Anaesthesist 19: 16 (Jan.) 1970.*)

AEROSALS, ASTHMA AND DEATH The pressurized aerosols widely used in the treatment of asthma and chronic bronchitis contain bronchodilators (*e.g.*, isoproterenol) and a mixture of fluorocarbons as propellants. This study was undertaken following reports of sudden deaths among young people "sniffing" these fluorocarbons and after a notable increase in the death rate from asthma during the 1960's. The arterial and venous blood levels of fluorocarbons were measured in four volunteers and two patients after various "doses" from a commercially-available inhaler. Low but detectable concentrations of the propellants were found in both venous and arterial blood at different intervals following exposure. Although the significance of these low blood levels of fluorocarbons is not known, it is suggested that further work is necessary to elucidate the possible relationship to the catecholamines inhaled and potentially fatal cardiac arrhythmias. (*Dollery, C. T., et al.: Blood Concentrations in Man of Fluorinated Hydrocarbons after Inhalation of Pressurized Aerosols, Lancet 2: 1164–1166, 1970.*)