PHYSICAL CHEMISTRY OF HALOTHANE–ETHER MIXTURES

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EVER since the beginning of anesthesia, man has diligently sought the "ideal" anesthetic agent. With the discovery of halothane by Suckling [1] and its introduction into clinical anesthesia by Raventós,[2] many people have thought that this approached the long-sought "ideal" anesthetic agent. Halothane, at first glance, seemed to have all the advantages of ether, plus the additional advantages of non-explosiveness, pleasant induction, and diminished irritability of the gastrointestinal tract. The first of these, nonexplosiveness, has become of paramount importance because of the widespread use of electric cautery and electronic monitoring in operating rooms today.

It soon became apparent, however, that halothane had at least two major disadvantages, respiratory and cardiovascular depression.[3] The respiratory depression usually took the form of diminished tidal volume, producing rapid shallow respirations.[4] The cardiovascular depression was usually manifested by hypotension.[5] Some believed the major cause of this to be direct myocardial depression,[6] while others believed it was principally due to ganglionic blockade.[7] It occurred to Hudon and co-workers that a mixture of halothane and ether might have all the advantages of halothane plus some of the respiratory and cardiovascular stimulatory effects of ether.[8] In attempting to make such a mixture, they found that an azeotropic mixture was formed when 68 parts of halothane were added to 32 parts of ether by volume.[9]

An azeotropic mixture is a mixture of two or more liquids which will distill without decomposition in a certain ratio at a constant boiling temperature. That is to say, an azeotrope is a constant boiling mixture where the distillate has the same composition as the substance being distilled. The boiling point or vapor pressure curves of these mixtures would then show a maximum or minimum rather than a straight line curve of an ideal mixture. This is because of some chemical bonding between the components of the mixture. In the case of halothane and diethyl ether, this might be a hydrogen-hydrogen coordinate covalent bond, but this is not known yet, to the author's knowledge.

It was observed that the reaction was exothermic, that the resultant mixture occupied less volume than the volumes of the components, and that its odor was less than either of the components. In order to study some of the physical and chemical properties of halothane-ether mixtures, the following work was done. Halothane will be referred to as "Fluothane" and the azeotropic mixture as "Fluether."

METHODS AND RESULTS

The methods and results of experiments dealing with each property of Fluothane-ether mixtures will be dealt with separately. This will be followed by a separate presentation of some of the experimental errors encountered.

Specific Heat of Fluothane. In order to calculate the heat of formation of Fluothane-ether mixtures (see next section), it was necessary to know the specific heat of Fluothane. Since this had not been reported, it was determined by experiment.

The temperatures of weighed amounts of cold Fluothane [*] and hot distilled water were determined. The two liquids were then poured together into a Dewar flask fitted with a neoprene [†] stopper, stirring rod, and thermometer. While the mixture was being stirred at a con-

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[*] Fluothane (halothane), Ayerst, is 2-bromo-2-chloro-1,1,1-trifluoro ethane.

[†] Rubber stoppers were found to be unsatisfactory when used with Fluothane because impurities in the rubber were quickly dissolved by the Fluothane giving a yellow solution. Neoprene was found to be unchanged except for a slight swelling after 24 hours immersion in Fluothane.

stant rate, its temperature was measured at 15 second intervals until a constant cooling curve was obtained (usually 5 minutes) (fig. 1). The mixture was weighed immediately after mixing and again after the stirring period in order to estimate error due to evaporation. As can be seen in figure 1, the first few temperature points were unreliable due to uneven mixing during the initial stirring. The loss of heat from the entire system, however, was slow enough and constant enough to give an almost straight line. This line had a gradual slope and could be easily extrapolated back to time zero: this extrapolation gave the final temperature of the mixture. This was assumed to be the theoretical temperature of the Fluothane and water if they had been completely intermixed and had exchanged heat instantaneously. There might be some objections to this assumption, but it was believed to be accurate enough for present purposes.

The specific heat of Fluothane was then calculated from the final temperature (described above), the initial temperatures and weights of Fluothane and water, and the specific heat of water (taken from a chemistry handbook [10]). This left the specific heat of Fluothane as the only unknown. Two assump-

TABLE 1

SPECIFIC HEATS OF FLUOTHANE AT VARIOUS TEMPERATURES

Specific Heat	Temperature
0.30	17.0
0.31	17.6
0.31	18.3
0.32	18.4
0.32	18.6
0.32	19.0
0.33	19.7
0.34	19.7
0.37	21.6
0.53	31.2
0.53	32.4
0.53	33.8

Specific heats in calories/gram/degree centigrade. Temperatures in degrees centigrade.

tions were involved: (1) that the Fluothane and water completely intermixed and exchanged heat, and (2) that the mixture of Fluothane and water was euthermic. The constancy of the cooling curves after two minutes suggested, at least, that the first assumption was valid within the limits of the experimental error. The second assumption was confirmed by a further experiment: the admixture of Fluothane and water at the same temperature gave a solution showing no gain nor loss of heat, except for the usual heat loss of the system to the ambient air.

Twelve determinations were made and it was discovered that the specific heat of Fluothane varied greatly with temperature (from 0.30 at 17 C. to 0.53 at 33.8 C.). At room temperature (25.0 C.) the specific heat of Fluothane was found to be 0.42 calories/gram/ degree centigrade (table 1).

Heat of Formation of Flu-ether. The heat of formation of Fluothane-ether mixtures was determined using the same technique described above for the specific heats of Fluothane. Here, however, Fluothane and ether ‡ at approximately the same (room) temperature were poured together into the Dewar flask.

The heat of formation of Fluothane-ether mixtures was calculated from the final temperature (described above), the initial temperatures, the weights, and the specific heats of Fluothane and ether. The specific heats of

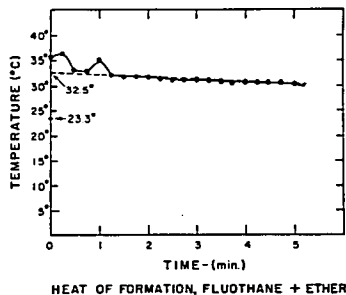HEAT OF FORMATION, FLUOTHANE + ETHER

Fig. 1. Typical cooling curve. Temperatures in degrees centigrade; time in minutes. Time zero was when the Fluothane and ether were mixed, 23.3 C. being the initial temperature of both. The dotted line indicates extrapolation back to time zero, giving a final temperature of 32.5 C. (Heat gain in this case would be 32.5–23.3 or 9.2 degrees C.) Sample curve shown is for *Heat of Formation* experiments, but same technique was used in *Specific Heat* experiment. Note: curve almost a straight line after 1½ minutes.

‡ Ether, Squibb, is diethyl ether with 0.5 per cent water and 1.5 per cent ethanol.
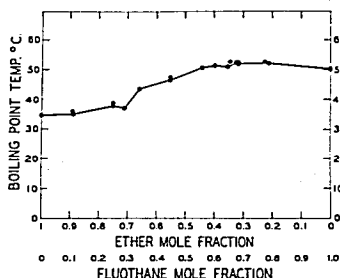
FIG. 2. Boiling points of different Fluothane-ether mixtures in degrees centigrade (corrected to 760 mm. of Hg.). Composition of mixtures expressed in mole fractions (table 2). Note: maximum or plateau at 52.7 C. and 0.65 mole fraction Fluothane which indicates an azeotope.

Fluothane were determined as described above, and those of ether were taken from a graph made from points given in a handbook of chemistry.[11] The specific heats of both Fluothane and ether varied with temperature.

Twenty separate determinations were done on various compositions of Fluothane and ether. There was no significant difference between the heat of formation in samples with an excess of either Fluothane or ether, and the azeotrope. It was assumed, therefore, that the heat of formation resulted from the stoichiometric combination of about 0.65 moles of Fluothane and 0.35 moles of ether (see below, and figure 2). Therefore, the heat of formation was reported as calories per mole of Flu-ether and was found to be + 1,200 ± 200. §

Boiling Points and Distillation of Flu-ether Mixtures. An aliquot of each of the twenty samples prepared during the heat of formation experiments was placed in a flask with a neoprene stopper, thermometer, and reflux condenser (water cooled). A spark proof hot plate was used and as an added precaution, the entire apparatus was placed in a chemical hood fitted with shatterproof glass. The tip of the thermometer was so placed that it was surrounded by vapor passing to the condenser, and was bathed in a steady stream of the reflux condensate. Stem and barometric correc-

§ Standard deviation. The + before the 1200 denotes an exothermic reaction.

tions were made. The aliquot was weighed before and after refluxing to determine loss by evaporation, which ranged from 1 to 3 per cent by weight. After 3 to 5 minutes of vigorous boiling and refluxing, a steady temperature was usually observed. The boiling points so obtained were plotted against their mole fractions ≠ (fig. 2). As can be seen, mole fraction Fluothane about 0.65 shows a maximum of 52.7 C.

Distillations of Fluothane-ether mixtures were done utilizing a conventional still and condenser, but fitted with a small internal condenser that would reflux the mixture on the thermometer tip near the flask outlet (fig. 3). This gave a fairly accurate measurement of the distilling temperature without using a fractional column and the temperatures correlated well with the boiling points done separately (as described above) on various fractions of the distillate. In a typical distillation of an azeotropic mixture, 98 per cent of the mixture
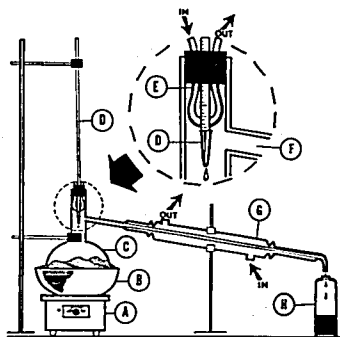

FIG. 3. Schematic of still used to distill Fluether. *A.* Sparkproof hotplate. *B.* Sandbath. *C.* Round bottom flask. *D.* Thermometer. *E.* Internal reflux condenser. *F.* Outflow of vapor to external condenser. *G.* External condenser (both condensers water cooled). *H.* Bottle to collect aliquot of distillate.

≠ Mole Fraction Fluothane =
$$\frac{\text{moles Fluothane}}{\text{moles Fluothane} + \text{moles ether.}}$$
[Moles Fluothane =
$$\frac{\text{grams Fluothane}}{\text{gram molecular weight of Fluothane,}}$$
e.g. 197.39 grams of Fluothane = 1 mole of Fluothane.]

TABLE 2

Boiling Points of Fluothane-Ether Mixtures
of Different Proportions

Boiling Points vs. Mole Fractions

Boiling Point 760 mm. of Hg)	Mole Fraction Fluothane	Mole Fraction Ether
34.20	0.000	1.000
35.90	0.108	0.892
34.90	0.110	0.890
37.78	0.246	0.754
37.78	0.246	0.754
37.92	0.249	0.751
38.76	0.249	0.751
37.03	0.287	0.713
43.73	0.339	0.661
46.67	0.447	0.553
47.45	0.449	0.551
50.76	0.558	0.442
51.53	0.602	0.398
52.10	0.647	0.353
52.70	0.654	0.346
52.55	0.674	0.326
52.49	0.682	0.318
52.45	0.682	0.318
52.19	0.682	0.318
52.51	0.776	0.224
52.39	0.788	0.212
50.62	1.000	0.000

Temperature in degrees centigrade corrected to 760 mm. of mercury. Proportions in mole fraction. Note: Mole fraction ether, 1.000 = pure ether. Mole fraction Fluothane, 1.000 = pure Fluothane. (See figure 2.)

distilled over with a change in the specific gravity of only 0.02 units. A slight rise during the last half of the distillation may have been due to some decomposition from the prolonged heating in the presence of light. This may

TABLE 3

Specific Gravities of Various Proportions
of Fluothane and Ether

Specific Gravity	Mole Fraction of Fluothane	% Fluothane by Volume	% Fluothane by Weight
0.715	0.000	0.00	0.00
0.851	0.108	11.09	24.41
1.018	0.250	25.38	46.42
1.266	0.449	45.17	68.42
1.487	0.654	66.33	83.42
1.510	0.674	68.45	84.63
1.618	0.777	77.47	90.24
1.861	1.000	100.00	100.00

Specific gravities (Column 1) are densities related to distilled water at 25 C.

also account for a slightly higher specific gravity (1.51) seen with the distillations than (1.49) with the boiling point experiments for the azeotrope (table 3 and next section). For precise work, perhaps vacuum distillation would be preferable to avoid possible decomposition.

Various distillations were done which reconfirmed the fact that most of the distillate comes over as Flu-ether.

Specific Gravities. Because of the great volatility of ether and Fluothane, neoprene stoppered 25 ml. volumetric flasks were used instead of the usual pycnometers. It was thought that perhaps the errors of drainage and reading menisci would invalidate the use of flasks instead of pycnometers, but it was discovered that these errors were less than ± 0.001 specific gravity unit, which was much less than other sources of error in this experiment. Numbered flasks were weighed dry, with water, and with the mixture to be tested. Each flask was oven dried and reweighed before each determination, although the dry weight never varied more than ± 0.0015 grams (mixture weights 18–46 grams). Weighings were performed with a chain-o-matic, magnetically damped balance. The temperature was recorded with each weighing. The temperature of all the specific gravity experiments fell between 24 and 26 C.

Eight compositions of different proportions of Fluothane and ether were prepared by weight and the specific gravity of each determined. The results are shown in table 3. The specific gravities versus mole fractions show essentially a straight line. The specific gravity of Flu-ether is 1.49 at 25 C.

Vaporization. The Fluotec and F.N.S. vaporizers were calibrated with Fluothane, Flu-ether, and ether. Either pure oxygen or room air was used as the carrier gas and was run through the vaporizers after being monitored with Fisher Porter rotameters guaranteed ± 1%. The liquid Fluothane, Flu-ether, or ether was placed in the vaporizer. The weight loss of the liquid for each run was determined with a balance good to ± 1 gram. Time was measured with a stopwatch, and temperatures and barometric pressures by the usual methods. From this data could be calculated the actual percentage of the vapor passing from the
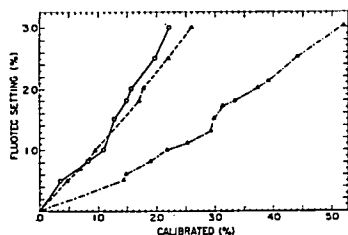
FIG. 4. Calibration of Fluotec vaporizer. Fluotec setting on ordinate. Calibrated (determined by experiment) per cent on abscissa. All percentages by volume. Legend: 1.00 mole fraction Fluothane △ ---- △ ---- △; 0.69 mole fraction Fluothane O——O——O; 0.000 mole fraction Fluothane ▲— · — — —▲.

vaporizers and this compared with the "setting" on the vaporizers.

The Fluotec calibration is shown in figure 4.

The Fluotec, as expected, showed little variation with flow rate, temperature, type of carrier gas (oxygen and room air), or time. This data is not shown. The F.N.S. vaporizer was less accurate but produced qualitatively the same results, which are not shown here.

Flammability. The flammability and explosiveness of Fluothane-ether mixtures was determined using a single high voltage spark. A 15 cm. × 1 cm. brass tube was fitted with a neoprene stopper containing two platinum wires about 8 mm. apart and a 2 mm. nylon tube. The other end of the brass tube was left open. The platinum wires were attached to an automobile induction coil, 6 volt dry cell, and a simple key switch. The "break" was used because of the higher voltage obtained and the voltage was thus limited by the distance between the platinum wires (about 8,000 volts with average humidity). The gas mixture to be tested was flowed into the brass tube via the nylon tubing. The other end of the brass tube was closed temporarily and the entire apparatus removed out-of-doors away from the vaporization source (Fluotec and F.N.S.). The end of the tube distal to the electrodes was opened and the mixture quickly fired. This technique was considered safe since: (1) Small quantities of explosive mixtures were used. (2) The system was open

at the time of firing, allowing rapid dissipation of the pressure. (3) All parts were malleable and nonbreakable. It was thought that this simple system closely imitated the type of ignition usually seen in operating room explosions.

Using Fluothane, Fluothane-ether mixtures, and ether, with oxygen at 4 liters per minute through the Fluotec, these results were obtained (table 4). Flu-ether did not flame up to 3.5 per cent (by volume) in oxygen.

Gas Chromatography. Since Flu-ether cannot be separated into its components by fractional distillation, other means were sought that might perform this separation. Gas chromatography was attempted. Two different instruments were used, the Beckman GC-2 and Perkin Elmer 154-C. Twenty micro-liter samples were injected with a calibrated syringe into a 12-foot benzyl ether column (at 40 C.) in the Beckman. Twenty micro-liter samples were injected with a calibrated pipette into a 2-meter diisodecalphthalate column at 40 C. in the Perkin Elmer. Helium was used as the carrier gas in both. Both utilized thermal conductivity cells for detection. Ether, Fluothane, Fluothane-ether mixtures of different composition by weight, and Flu-ether prepared by weight and by distillation were used.

Figure 5 shows typical curves obtained with

TABLE 4

FLAMMABILITY OF TWO DIFFERENT MIXTURES OF FLUOTHANE AND ETHER

% Mixture in about 100% Oxygen	Mixtures		Flammability
	Mole Fraction Fluothane	Mole Fraction Ether	
2.2	0	1.00	no response
3.0	0	1.00	light "poof"
3.7	0	1.00	"bang"
5.3	0	1.00	explosive shock
2.2	0.67	.33	no response
3.5	0.67	.33	no response

Column 1 indicates % by volume (determined— see text) of the mixture in oxygen. Columns 2 and 3 indicate the compositions of the 2 mixtures: (top 4 lines, pure ether; and bottom 2 lines, Flu-ether). Column 4 indicates an arbitrary scale of flammability from "light poof" to "explosive shock."

Fluothane, ether, and Flu-ether. The elution time (not shown) identifies the component, and the area under the curve indicates the quantity of each. Since the quantitative aspects of the chromatograph have not been perfected yet, in our laboratory, this will not be presented in detail here. This is shown only to demonstrate that the azeotrope can be completely and easily separated into its components by gas chromatography. Further work using the gas chromatograph for quantitative determinations of Fluothane will be reported later.

Errors. The data presented here were the results of some exploratory experiments and were not necessarily intended to represent very accurate quantitative factors for "Handbook reference." This was particularly true for the heat of formation experiments which were only attempts to ascertain the order of magnitude.

A few of the major sources of errors not mentioned elsewhere in this paper will be discussed here. In general, temperatures were considered accurate to ± 0.2 degree centigrade, although the boiling point determinations were probably slightly better than this. Barometric corrections were accurate to ± 1.0 mm. of mercury. All weights are considered accurate to ± 1.0 gram, except the specific gravity measurements which were accurate to ± 1.0 mg. The *precision* (reproducibility of a given experiment) of the specific gravity determinations was ± 0.001 sp. gv. unit, which was much better than the *precision* of preparing the various Fluothane-ether mixtures (± 0.01 sp. gv. unit). The specific gravities of two known substances (Fluothane and ether) agreed with other authorities giving an *accuracy* (error when compared with accepted data) of ± 0.003 sp. gv. units. The specific heat of Fluothane was considered accurate to about ± 0.01 calorie/gram/degree centigrade. All above figures were maximum limits, not statistically predicted limits.

The large error (about 18 per cent *standard deviation*) in the heat of formation experiments was due to the relatively small amount of heat change compared with the total heat content of the system, which greatly magnified small errors of weighing, evaporation, etc. This assumption was substantiated by the smaller error (about 3 per cent *maximum*) in the specific heat experiments using the same apparatus and techniques.

DISCUSSION

The experiments reported here on the physical chemistry of Fluothane-ether mixtures confirm the findings of Boivin and others that an azeotrope occurs.[9] The evidence for this is a boiling point curve with a maximum (fig. 2), a mixture inseparable by fractional distillation, and a mixture less volatile than either of its components (fig. 4).

The composition of this azeotrope is about 0.65 mole fraction Fluothane, 0.35 mole fraction ether; 66 per cent Fluothane, 34 per cent ether by volume; or 83 per cent Fluothane, 17 per cent ether by weight. This data is taken from a boiling point curve (fig. 2) with a very broad flat maximum, so the exact peak indicating the concentration of the azeotrope is difficult to determine. This agrees fairly well, however, with the figures of Boivin, *et al.*, of 68 parts of Fluothane by volume. By observing the mole fractions, one immediately sees that the azeotrope contains roughly 2 molecules of Fluothane for one of ether. The type of bonding involved is still highly speculative, but it must be a relatively loose bond because of the small amount of energy involved (1,200 calories/mole [*]) and the moderate ease of separation by some techniques (gas chromatography, figure 5).

It was found that the boiling point of the azeotrope was 52.7 C. Boivin, *et al.*, reported a boiling point of 51.5 C., but did not mention a barometric correction. Perhaps this correction would bring these two figures closer together.

Boivin stated that there is a decrease in volume with the admixture of Fluothane and ether, but he did not state how much. In a crude experiment, mixing Fluothane and ether in a graduated cylinder (in azeotropic proportions) produced a slight decrease in volume of about ½ of one per cent. The specific gravity experiments were then done as described above to determine more accurately if

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[*] *E.g.*, a few bond energies: H-H = 103,400 calories/mole; C-H = 87,300 calories/mole; C-O = 70,000 calories/mole.[12]

there is a significant decrease in volume. Any decrease in volume of the azeotrope would be expected to show a maximum on this graph (table 3) that is, an increase in density out of proportion to the increase in Fluothane

content. Since this did not appear here, the decrease in volume must be minimal. This would seem to concur with the work of Boivin although this is difficult to compare, as he did not indicate temperatures, nor state whether
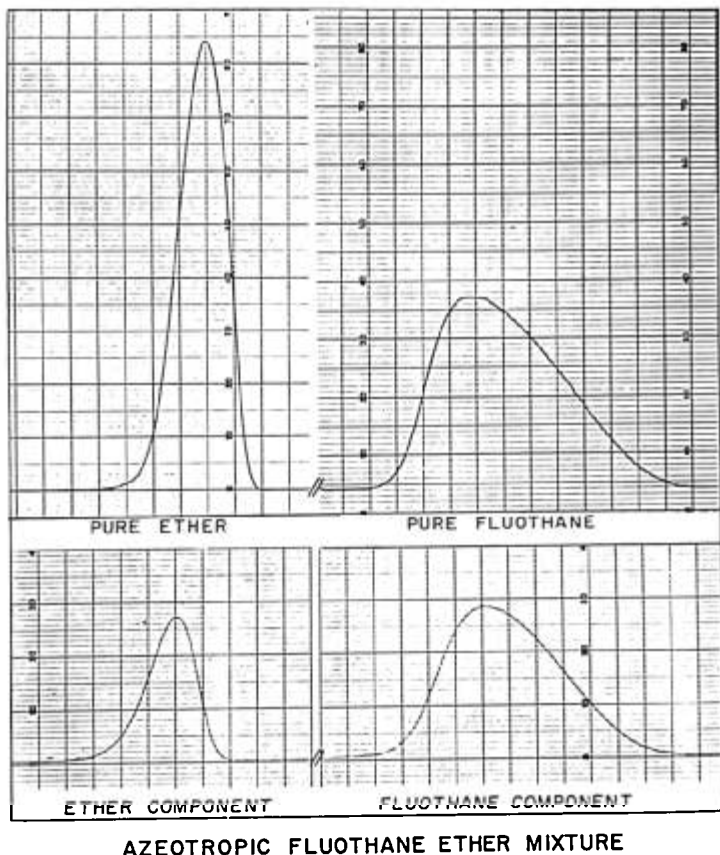

FIG. 5. Three sample chromograms. Top left: pure ether. Top right: pure Fluothane. Bottom: ether and Fluothane component of Flu-ether (same Chromogram with break to conserve space for illustration purposes). Injection times not shown. Same size samples in all three injections.

TABLE 5

SUMMARY OF VARIOUS PROPERTIES OF FLUOTHANE, ETHER, AND FLU-ETHER

	Fluothane	+	Ether $\xrightarrow{\Delta}$ "Flu-ether" +1,200 calories	"Flu-ether"
Mole Fraction	0.654		0.346	1.000
Specific Heat (25 C.)	0.42		0.54	—
Specific Gravity (25 C.) (22 C.)	1.861 1.863*		0.715 0.714*	1.487 —
Boiling Point (760 mm. of Hg)	50.62 50.2*		34.20 34.5*	52.70

* Indicates accepted authorities (Raventós and Suckling, for Fluothane; Handbook of Chemistry, for ether). All other figures are original data of authors.

the "per cent" was by weight, volume, or mole fraction.

Some of the results of these experiments are summarized in table 5 along with some figures from other sources.

The specific heat of Fluothane (0.42 calories/gram/degree centigrade) is in the same range as ether but increases more sharply than ether does with a rise in temperature. This might be expected of this more complex molecule.

It may be concluded from the flammability experiment that the azeotrope Flu-ether is free from explosive hazard in usual anesthetic concentrations, simply because of the small concentration of ether vapor present. The presence of Fluothane in the Flu-ether mixture probably does not alter the flammability of the ether vapor. In higher concentrations (above 8 per cent) it might be flammable.[13]

What clinical value Flu-ether may have remains to be seen. It might be predicted from its composition, however, that the ether, being present in such a small proportion, acts mostly as a diluent for the Fluothane, rather than contributing any pharmacological properties of its own.

SUMMARY

The physical chemistry of Fluothane ether mixtures was investigated. The work of others which showed that Flu-ether is an azeotropic mixture was confirmed. This mixture has a composition of 0.65 mole fraction Fluothane, a

boiling point of 52.7 C. at 760 mm. of mercury, and a specific gravity of 1.49 at 25 C.

Admixture of Fluothane and ether liquids produces an exothermic reaction with a heat gain of 1,200 calories per mole of Flu-ether. The specific heat of Fluothane was determined separately and found to vary with temperature, it being 0.42 calories/gram/degree centigrade at 25 C. (table 5).

Flu-ether cannot be separated into its components by fractional distillation but can be separated by gas chromatography. The mixture is nonflammable in pure oxygen in anesthetic concentrations. Flu-ether is less volatile than ether or Fluothane as shown by calibrations of Fluotec and F.N.S. vaporizers.

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DRUG REACTIONS Some of the drugs
commonly used in the medical management
of disease have been shown to have deleterious
effects on homeostatic mechanisms. Patients
treated with cortisone may develop adrenal
cortical insufficiency. Reserpine or rauwolfia
alkaloids tend to deplete adrenal glands of
adrenaline and noradrenaline as well as reduc-
ing stores of noradrenaline in the myocardium
and vessel walls. Chlorothiazide may produce
profound hypopotassemia. Long term use of
tranquillizers may prolong the action of nar-
cotics and relaxants, potentiate the hypoten-
sive action of thiopental, and modify the re-
sponse to vasopressor drugs. When medical
history reveals that a patient has been treated
with these drugs, appropriate prophylactic
measures must be undertaken to avoid unex-
pected morbidity. (*Minuck, M.: Reaction to
Drugs during Surgery and Anaesthesia, Canad.
M. A. J. 82: 1008 (May 14) 1960.*)

**LOCAL ANESTHESIA WITH PRO-
METHAZINE** Promethazine (Phenergan)
has been used successfully as a local anesthetic
in minor surgery, a 2 per cent solution roughly
equalling that of 1 per cent procaine. No
amounts larger than 2 cc. were given; a gen-
eral sedative effect should be anticipated with
larger dosage. Injections must be given
subcutaneously since intradermal application
causes necrosis. (*Kalz, F., and Fekete, Z.:*

*Use of Promethazine as Local Anesthetic.
Canad. M. A. J. 82: 833 (April 16) 1960.*)

DRUG TOXICITY Procaine hydrochloride
and 2-chloroprocaine (Nesacaine) hydrochlo-
ride, 1.0 mg., lidocaine (Xylocaine) hydro-
chloride, 0.5 mg., and tetracaine (Pontocaine)
hydrochloride, 0.1235 mg. per kilogram of
body weight per minute were administered
intravenously to 12 unanesthetized human
subjects who served as their own controls.
The intravenous infusion of chloroprocaine was
tolerated the best, and that of lidocaine hydro-
chloride the least well of the 4 compounds.
After discontinuation of infusion, the signs and
symptoms of systemic toxicity disappeared
most rapidly with chloroprocaine and most
slowly with lidocaine hydrochloride. The low
systemic toxicity of chloroprocaine hydrochlo-
ride is primarily due to its rapid enzymatic
hydrolysis in plasma. The findings of this
study confirm the clinical experience that, of
the available local anesthetic agents, chloro-
procaine hydrochloride is the safest and, con-
sequently, it should be the preferred drug
when large volumes of relatively concentrated
local anesthetic must be used (caudal
and lumbar epidural block and conduction
anesthesia of large nerve trunks). (*Foldes.
F. F., and others: Comparison of Toxicity of
Intravenously Given Local Anesthetic Agents
in Man, J. A. M. A. 172: 1493 (April 2)
1960.*)