H. Eversole; Dr. A. William Friend; and Dr. Stevens J. Martin. Since that time, Drs. McCuskey, Eversole, and Friend have been replaced by Drs. Albert M. Betcher, Nicholas G. DePiero, Ralph Sappenfield, and Scott M. Smith. In 1968 Drs. Perry P. Volpitto and John Parmley were nominated by the ASA as its representatives. In 1970 Dr. Albert Faulconer was nominated to replace Dr. John Parmley.

Meetings are held twice a year, one in the spring and the other session at the time of the annual meeting of the American Society of Anesthesiologists. In addition to usual Foundation business, applications from residents in anesthesia for outright grants or loans are given consideration for definitive action. Final selection is based not only upon the application, but also on letters of reference from residency program directors. In our 15 years of existence, more than 322 applications have been processed, of which 39 have been approved for Mead Johnson grants and 205 for loans. Only one candidate failed to repay his loan, and that because of serious illness. It is gratifying to report that to the best of our knowledge those supported financially by us have done well in anesthesia; several have become directors of programs.

The Anesthesia Foundation was originally funded by a loan of $5,000 from the ASA, some years later changed to an outright grant. From 1956, donations have been received from various individuals (some other than ASA members), component and regional societies, and manufacturers and suppliers of anesthesia equipment. Special funds have been received from a bequest of the estate of Oscar Schwidetzky and by a gift from Mr. and Mrs. H. D. Burnside. Annually, gifts are received from a score of other friendly supporters, so that by now a modestly large capital sum has been realized.

The Mead Johnson Company has provided the ASA with funds designated to be used for grants to deserving residents. The sum over the years has amounted to $39,000. The Anesthesia Foundation has acted as a screening committee in selection of recipients and a repository for these funds throughout their distribution and subsequent repayment. In 1970 the Mead Johnson Company notified the ASA and the Anesthesia Foundation that it was discontinuing grants in the fields of anesthesia and several surgical specialties.

During the past two years, requests for financial assistance have exceeded by far the ability of the Anesthesia Foundation to provide funds to worthy residents. Although the assets of the Foundation have steadily increased to a total of approximately $130,000, most of the aforementioned funds are presently outstanding, preventing the Foundation from processing many new applications. It is hoped that additional funds will become available to help the Foundation carry on with a program of financial assistance in the training of young anesthesiologists.

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A History of Forane

THE DISCOVERY of the first general anesthetics, nitrous oxide, diethyl ether, and chloroform, probably contributed as much to man's welfare as the discovery of any other new class of drugs. No major advancements in this field appeared for more than 80 years, until Lucas and Henderson[1] reported the anesthetic properties of cyclopropane, and Waters demonstrated its usefulness in man.[2] During the late 1930's and 1940's, J. C. Krantz, Jr.,

working in an industry-supported research program, developed several useful anesthetics, among which were isopropenyl vinyl ether (Propethylene),[3] propyl methyl ether (Metopryl),[4] and ethyl vinyl ether (Vinamar).[5] None was widely used. None was significantly better than cyclopropane, and all were flammable.

Advances in chemistry necessary for the development of the atomic bomb contributed to the discovery of present-day nonflammable inhaled anesthetics. Purification of uranium isotopes necessitated a new fluorine chemical technology,[6] which provided the background for the synthesis of fluroxene (Fluoromar), halothane (Fluothane), methoxyflurane (Penthrane), enflurane (Ethrane *), and Forane.* Fluroxene, discovered by J. G. Shukys in 1951, was the first of this series. Fluroxene failed to represent an important advance over more explosive predecessors because it was flammable. In contrast, halothane was an immediate success because of its nonflammability.[7] In addition, it possessed such virtues as ease and rapidity of induction and recovery, minimal side-effects, little postanesthesia nausea, and moderately good muscle relaxation.

For a time the success of halothane discouraged further search for better anesthetics. It gradually became apparent that halothane, too, had limitations. It was a respiratory and circulatory depressant. It sensitized the myocardium to arrhythmias induced by epinephrine or isoproterenol. It caused uterine relaxation and increased bleeding during delivery. Its use was occasionally followed by hepatic necrosis and, rarely, by death from hepatic failure.

Increasing awareness of some deficiencies of halothane revived the search for a better anesthetic. Primary criteria sought were nonflammability and chemical stability. It was believed that compounds with greater chemical stability would not be metabolized; therefore, possible toxic effects attributable to their metabolites would be eliminated. Also sought was a compound which would produce minimal respiratory and cardiovascular depression, provide rapid and pleasant induction and recovery, cause good muscle relaxation, and not sensitize the myocardium to catecholamines. Obviously, the compound should induce no cellular toxicity. Last, but certainly important, the drug would have to be economical to produce.

Several series of compounds were synthesized and discarded. Halogenation, essential for nonflammability, also influenced boiling point, chemical stability, and potency. Totally fluorinated compounds were without anesthetic effect. Compounds with iodine and bromine tended to be unstable. As a series, the alkanes tended to be arrhythmogenic. Halopropane,[8] teflurane,[9] and norflurane[10] appeared and then vanished—victims of their overwhelming propensity to produce cardiac arrhythmias. Methoxyflurane[11] appeared, and enjoyed success, but its advantages and disadvantages were similar to those of halothane and its high boiling point and tissue solubility rendered it less flexible.

Ethers seemed to hold the greatest promise as useful anesthetics. They appeared to provide better muscle relaxation, normal cardiac rhythm with or without epinephrine, and less cardiorespiratory depression. Some ether series were more promising than others. The dimethyl series was hard to synthesize and tended to be unstable. Instability also plagued the isopropyl methyl and isopropyl ethyl series. Surprisingly, investigation of the diethyl series was unsuccessful. Mice anesthetized with many compounds of this series, as well as others, developed convulsions and gasping respiration, with immediate or delayed death. Flammability, acute and delayed toxicity, and problems in synthesis eliminated many others. The most promising seemed to be the methyl ethyl ethers.

Both enflurane (Compound 347) and its isomer, Forane (Compound 469), are methyl ethyl ethers, discovered by R. C. Terrell in 1963 and 1965. Forane is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether (CF_3–CHCl–O–CHF_2), while enflurane is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether (CFHCl–CF_2–O–CHF_2). Enflurane, because it was easier to synthesize and purify, preceded Forane. The problem of purifying Forane

* Trademark, Ohio Medical Products, A Division of Air Reduction Company, Inc.; no USAN Council name has yet been given to Forane.

TABLE 1. Comparative Properties of Anesthetics

	Forane (469)	Enflurane (Ethrane) (347)	Halothane (Fluothane)	Methoxyflurane (Penthrane)
Chemical name	1-chloro-2,2,2-trifluoroethyl difluoromethyl ether	2-chloro-1,1,2-trifluoroethyl difluoromethyl ether	1-bromo-1-chloro-2,2,2-trifluoroethane	2,2-dichloro-1,1-difluoroethyl methyl ether
Structure	$CF_2ClHCl–O–CF_2H$	$ClHFCCF_2–O–CF_2H$	$CF_3CHClBr$	$CHCl_2CF_2–O–CH_3$
Molecular weight	184.5	184.5	197.4	165.0
Boiling point (C)	48.5	56.5	50.2	104.65
Vapor pressure at 20 C (torr)	250	180	243	22.5
Flammability	None	None	None	7.0 in air 5.4 in oxygen
Partition coefficients:				
Oil–gas at 37 C	99	98.5	236	825.0
Blood–gas at 37 C	1.4	1.91	2.3	13.0
Water–gas at 37 C	0.61	0.82	0.74	4.5
Stability to:				
Soda lime at 40 C, 2 hours	Good	Good	Good*	Good*
Soda lime at 40 C, 20 hours	Good	Good	Good*	
Six months in 1 N sodium methoxide–methanol solution†	No change	No change	54 per cent base consumed	75 per cent base consumed
Chemical stabilizer necessary	No	No	Yes	Yes
Storage in clear glass	Two years no change†	Five years no change	No data	No data

* But new compound formed and detected by gas chromatographic analysis.
† Test still in progress.

was sufficiently great that the compound was almost abandoned. In time, however, the work of Louise Speers solved this problem, permitting biological testing of Forane.

The chemical and physical properties of Forane, enflurane, halothane, and methoxyflurane are compared in table 1, which lists them in order of increasing solubility in blood. Although solubility in blood is related to rapidity of induction and recovery, a mild pungency of Forane, unlike that of enflurane, limits the rate at which induction may be achieved. A striking feature of Forane and enflurane compared with halothane and methoxyflurane is their chemical stability. All are nominally stable in soda lime, but at 40 C for 20 hours both halothane and methoxyflurane undergo slight dehydrohalogenation. Exposure to a strong base, 1 normal sodium methoxide in methanol, produces more striking differences. No reaction is evident at six months with Forane or enflurane, but halothane and methoxyflurane have reacted chemically to consume 56 and 75 per cent of the base, which indicates halogen lability. Similarly, Forane and enflurane are unaffected by light and have no corrosive action on metals such as aluminum, tin, copper, and iron despite the absence of chemical stabilizers. The greater stability of Forane and enflurane may be reflected in a lesser metabolism by body tissues.

The testing of Forane in animals showed promise. This work was carried out by A. B. Dobkin and P. H. Byles at the State University of New York, Upstate Medical Center, and by W. C. Stevens and colleagues at the University of California, San Francisco. Anesthesia was smooth and recovery rapid, without significant organ toxicity. No change was noted in renal and hepatic function (including enzyme studies) in sets of dogs and monkeys exposed for either three hours daily for 15 hours or four hours on alternate days for 16 hours. The same results were observed in dogs exposed to four hours of anesthesia with concomitant hypoxia (Pa_{O_2} 50 torr) and hypercapnia (Pa_{CO_2} 70–80 torr). Hypoxia and hypercapnia in Forane-anesthetized dogs produced what appeared to be fat vacuolization in some kidney specimens. However, both light and electron microscopy failed to reveal hepatic or renal lesions in normoxic or normocapnic sets of beagles and monkeys exposed to 16 hours of anesthetic concentrations of Forane.

These results encouraged extension of studies to man, and five of the seven papers in this issue present some of the initial findings. These

results suggest that Forane neither depresses the human heart nor predisposes to arrhythmias. In miniature swine the metabolism of Forane is less than that of halothane or methoxyflurane. Muscle relaxation is good, and compared with halothane, Forane markedly potentiates the effect of *d*-tubocurarine. On the other hand, Forane is a profound respiratory depressant.

Does Forane possess other defects? Does it produce hepatic or renal toxic effects in man? Although 500 human exposures have failed to reveal any such toxicity, thousands of exposures may be necessary to uncover a "sensitization" phenomenon or a subtle toxic effect. Is Forane metabolized in man? What are its uptake, distribution and excretion characteristics? How soluble is it in body tissues? Does it enhance uterine bleeding? Does it have adverse effects on the fetus? Are there unfavorable or favorable interactions with other drugs patients might receive concomitantly? The list of unanswered questions is long. If initial results are confirmed by further studies, Forane may constitute a major advance in the search for the perfect anesthetic.

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Drugs

HALOTHANE HEPATITIS Halothane-induced stimulation of lymphocytes was observed in ten of 15 patients for whom diagnoses of drug-induced hepatitis were made following halothane (nine patients) or methoxyflurane (one patient) anesthesia. Stimulation of lymphocytes was measured serologically by the incorporation of ^{3}H-thymidine into the DNA lymphocytes. Three patients exposed to halothane who did not develop jaundice, nine patients with hepatic disease and six healthy persons served as controls. None of the control patients showed any evidence of stimulation of lymphocytes in the presence of halothane. These data support the hypothesis that sensitization to halothane may be involved in the pathogenesis of hepatic damage following halothane and methoxyflurane. (*Paronetto, F., and Popper, H.: Lymphocyte Stimulation Induced by Halothane in Patients with Hepatitis Following Exposure to Halothane, New Engl. J. Med. 283: 277 (Aug.) 1970.*)