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The Invention and Development of Enflurane, Isoflurane, Sevoflurane, and Desflurane

*Ross C. Terrell, Ph.D.**

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Thirty-six halogenated Me Et ethers have been synthesized for evaluation as volatile anesthetics. Eleven of the ethers were too unstable to test, and, of the remaining 25, 13 had promising anesthetic properties in mice and are suitable for study in larger animals. Those ethers having one H with at least 2 halogens other than F or 2 or more H with at least one Br or Cl were the best anesthetics.

THE anesthetic properties of several fluorinated hydrocarbons were reported by Robbins[1] in 1946. In the period 1946–1959, three fluorinated compounds, two ethers, and one hydrocarbon were introduced into clinical practice: fluoroxene ($CF_3CH_2OCH{=}CH_2$) by Ohio Medical Products (Cleveland, OH) in 1951, halothane ($CF_3CHClBr$) by Ayerst Laboratories (New York, NY) and Imperial Chemical Industries, PLC (London, England) in 1955, and methoxyflurane ($CH_3OCF_2CHCl_2$) by Abbott Laboratories (Abbott Park, IL) in 1959. Although several other fluorinated ethers and hydrocarbons were reported to have anesthetic properties, none were successfully marketed.[2] Halothane was an immediate success because it was potent and nonflammable with a very acceptable anesthetic syndrome. It was especially useful for mask inductions in children. There were, however, three problems associated with halothane, less than ideal cardiovascular properties, the occurrence of rare but serious hepatic toxicity, and a substantial degree of metabolism. Despite these problems, halothane rapidly became the market leader. Fluoroxene and methoxyflurane were less successful because fluoroxene was borderline flammable and caused serious postoperative nausea and vomiting. The high boiling point (102°C) and high lipid solubility of methoxyflurane resulted in long recovery times, and some renal toxicity probably due to a high degree of metabolism.

This was the "state of the art" around 1960 when Ohio Medical Products (a small division of Airco, Inc.) initiated a research project, the goal of which was to synthesize a new volatile anesthetic at least equal to, but hopefully better than, halothane, the market leader at the time. This was a logical project for Ohio Medical Products because they were already in the anesthetic market with nitrous oxide, cyclopropane, medical oxygen, the somewhat unsuccessful fluoroxene, and some other anesthesia-related hardware. A new improved inhalation anesthetic would have been a valuable addition to the product line. Ohio Medical Products assigned two senior chemists, Louise Speers Croix, Ph.D. (1920–1992), and me to the project. I remember that at the time, several of our colleagues told us that we didn't have a chance to compete with the large companies, Abbott Laboratories, Imperial Chemical Industries, or Ayerst, who probably had done or were doing considerable research on new anesthetics. History shows that they had not and were not.

We were not discouraged, and over the next 10 or 15 yr, we synthesized several hundred new fluorinated compounds, four of which—enflurane (CHF_2OCF_2CHFCl), isoflurane ($CF_3CHClOCHF_2$), sevoflurane ($(CF_3)_2CHOCH_2F$, and desflurane ($CF_3CHFOCHF_2$)—are currently used in clinical practice. Some of the most important work on the synthesis of fluorinated methyl ethyl ethers and fluorinated methyl isopropyl ethers, which resulted in the discovery of enflurane, isoflurane, sevoflurane, and desflurane, has been published.[3–6] Most of the other work on fluorinated hydro-

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* Vice President (Retired). Current position: Research Associate.

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Address correspondence to Dr. Terrell: Minrad, Inc., 50 Cobham Drive, Orchard Park, New York 14127-1421. mariposa4@yahoo.com. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

carbons, fluorinated diethyl ethers, and methyl-n-propyl ethers has not been published except in the patent literature, although many compounds were synthesized in these areas.

The research project was unique in several ways. There were four general requirements. First, volatility was necessary. This limited syntheses, with few exceptions, to compounds having no more that four carbon atoms. Second, nonflammability. This limited the number of hydrogen atoms. Fortunately, hydrogen could be substituted with chlorine or fluorine and still retain some anesthetic properties. Third, stability, especially to soda lime. This requirement effectively excluded groups such as CH_2ClO–, generally known to be unstable to base, as well as some other groups. Fourth, a synthesis that could be used to manufacture relatively large quantities at a reasonable price. This is in contrast to the usual pharmaceutical product where the active ingredient is usually measured in pounds. For anesthetics, the quantity is measured in tons. Current annual production of volatile anesthetics is estimated to be well over 2,000 tons. Following this fourth guideline, much of the work was done using readily available starting materials, such as $CF_2{=}CFCl$, the starting material for enflurane; CF_3CH_2OH and CF_2HCl (freon 22), the starting materials for isoflurane and desflurane; and $(CF_3)_2CH{-}OH$, the starting material for sevoflurane. The most valuable synthetic route used was photochemical chlorination, followed by replacement of the chlorine by fluorine. The Swarts reaction, discovered around 1895, which used SbF_3 or HF catalyzed by $SbCl_5$, was the most useful.[7] Chorine could also be substituted using potassium fluoride or other fluoride salts, also a well-known reaction.[7]

It would have been simpler to replace hydrogen directly using elemental fluorine rather than first chlorinating and then replacing the chlorine with fluorine. However, elemental fluorine is so reactive that the reaction is exceedingly difficult to control. Some research was done on this method, and the first sample of desflurane was synthesized by this method.[8] We also produced several fires, and this synthetic route was soon abandoned.

Even with the somewhat strict guidelines and the limited synthetic methods available, it was possible to synthesize several hundred fluorinated compounds for testing as anesthetic agents. Most of the compounds failed when tested in mice, but three did not— enflurane, isoflurane, and desflurane.[9,10] These three were all patented as anesthetics and are currently approved and marketed. Sevoflurane was patented only as a composition of matter[11] but was not further developed by Ohio Medical Products as an anesthetic because it failed the soda lime stability requirement. All of the compounds having the $(CF_3)_2CHOR$ structure were unstable to soda lime and were abandoned.

One of the compounds in the group abandoned because of instability to soda lime, $(CF_3)_2CHOCHF_2$, may well be as good an anesthetic as sevoflurane. Stability to soda lime should be similar and possibly better because the $-OCHF_2$ group should be more stable than the $-OCH_2F$ group in sevoflurane. This structure may be related to the decomposition of sevoflurane caused by iron oxide and aluminum oxide.[12] There has been one product recall of sevoflurane because of decomposition caused by iron oxide.

There are several other compounds that were not developed by Ohio Medical Products, not because of instability to soda lime but rather because of low potency resulting from low solubility. There are four compounds of possible interest, $CHF_2OCF_2CF_2Cl$,[2] $CHF_2OCF_2CF_2H$,[3] $CF_2ClOCF^2CHF_2$,[3] and $CH_2FOCF_2CHF_2$,[3] which is claimed to have good analgesia at subanesthetic concentrations.[13]

There were also many other compounds, diethyl ethers, methyl propyl ethers, and assorted hydrocarbons, which were volatile and stable to soda lime. None had acceptable anesthetic properties. The data on most of these have not been published.

Data on the large number of fluorinated compounds synthesized allow some general structure–activity relations to be deduced. For example, fully halogenated compounds are usually poor anesthetics or are convulsants. Other correlations can be made, but there are no really definite structure–activity relations that can be used to accurately predict whether a compound will be a good anesthetic. It is fortunate and somewhat amazing, at least to me, that there is any correlation at all between pharmacologic activity and a structural formula as written on paper.

Predictions of activity based on structural formulae often fail. A striking example of this is hexafluorodiethyl ether, $CF_3CH_2OCH_2CF_3$, which might be predicted to be anesthetic because the structure is similar to that of diethyl ether. It is not and is, in fact, a potent convulsant marketed by Ohio Medical Products as an alternative to electroshock therapy.

Are there other compounds possible that have not yet been synthesized and tested? To possibly answer this question, I did the following study, which I believe is unique to the anesthetic project because one can calculate the total number of compounds possible, both ethers and hydrocarbons having four carbon atoms or less and any combination of hydrogen, fluorine, chlorine, and bromine. This could never be done for any other group of pharmaceutical products. The total number of possible one carbon hydrocarbons is 35, two carbons is 210, three carbons is 2,100, and four carbons is 36,900. The total for two carbon ethers is 210, three carbon ethers is 4,000 and four carbon ethers (diethyl ethers, methyl propyl ethers, and methyl isopropyl ethers) is 186,900. These are large numbers and are, of course, impossible to deal with. They can be reduced as follows using the methyl ethyl ether group as an exam-

ple. First, all compounds judged to be too high boiling can be eliminated. This is easily done because boiling points can be predicted quite accurately. Next, compounds expected to be unstable to soda lime or to be flammable can be eliminated. By using these three criteria, the total possible structures can be reduced from 4,000 to only 50, some of which have already been synthesized. Thus, there do not seem to be many new products possible in this group.

Using the same three criteria for excluding structures, the numbers of possible compounds in the other groups are the following: One and two carbon hydrocarbons is none, three carbon compounds is 58, and four carbon compounds is 122. Similarly, the number of two carbon ethers is 4, and four carbon ethers is 204.

Although there are a number of possible new compounds, there do not seem to be reasonable syntheses or manufacturing processes for most of them. For example, many compounds have the CF_3O– group, which is difficult to synthesize. Therefore, research to discover a new volatile anesthetic is a much less attractive project than it was in 1960. This is especially true because there are four generally acceptable anesthetics available today, whereas in 1960 there was only one, halothane.

Although synthesis of new volatile anesthetics may presently be unattractive, there is the interesting possibility of using the currently approved products, especially sevoflurane and desflurane, for conscious sedation. This project is currently under development by Minrad, Inc.[14]

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