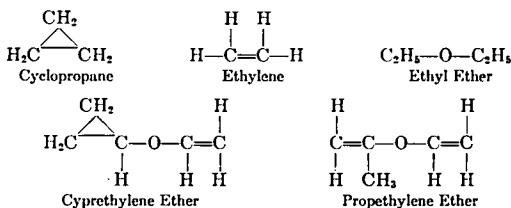


## ANESTHESIA. XII. STUDIES WITH ISOPROPENYL VINYL ETHER (PROPETHYLENE ETHER) IN MAN\*

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It occurred to one of the authors that it would be of interest from chemotherapeutic standpoint to prepare a hybrid molecule between ether and cyclopropane. Pursuant to this concept the anesthetic agents cyprome (1) and cypreth (2) ethers, were synthesized and studied. Later cyprethylene ether (3), containing the essential chemical linkage of cyclopropane, ethyl ether and ethylene, was prepared and studied in animals and man. Although cyprethylene ether appeared to be an excellent anesthetic agent in animals and proved meritorious in producing anesthesia in a limited number of cases in man, difficulties encountered in the synthesis of the compound, at present at least, preclude the possibility of its extensive use. Continuing our studies of similar ethers as anesthetic agents, our attention was directed to an isomer of cyprethylene ether, namely isopropenyl vinyl ether. The relationship chemically among these compounds is apparent from the following formulas:



## PHYSICAL PROPERTIES

Propethylene ether (4) is a colorless, mobile liquid, possessing characteristic odor, slightly resembling cyclopropane. The specific gravity of propethylene ether is 0.786 at 20 C.; the boiling point is 55 C. The compound contains less than 0.1 per cent of acetone as an impurity. It is stable in alkaline and neutral media, but rapidly hydrolyzed into acetone and acetic aldehyde by strongly dissociating acids. Propethylene ether dissolves in water to the extent of 0.4 cc. per 100 cc. of water at 25 C., while 8.6 cc. of ethyl ether dissolves in the same volume of water under the same conditions. The vapor pressure at 25 C. is 256 mm. that of ethyl ether, at the same temperature, is 532 mm. (5).

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The inflammability range of propethylene ether is of the same order of magnitude as that of ethyl ether, namely, between 2 and 3 per cent.

#### PHARMACOLOGY

Propethylene ether exhibited promising anesthetic syndromes (4) in mice, rats, dogs and rhesus macacus monkeys. The potency of propethylene ether is three to four times greater than that of ethyl ether. Its potency approaches that of chloroform. The anesthetic index of propethylene ether, measured on the dog, is 4.32, that of ethyl ether 2.00 and that of chloroform 1.62 (2). The concentration in the blood of the dog and monkey under surgical anesthesia is approximately 200 mg. per cent. In the dog, rat and monkey, long anesthetics of one to three hours produced no kidney or liver damage. The blood pressure remains high and the pulse good in the dog under deep surgical anesthesia with propethylene ether. Under surgical anesthesia with propylene ether in the dog and monkey, there appeared no significant difference in the form or regularity of the electrocardiograms. The heart rate was, as a rule, slightly increased.

#### FIRST ANESTHESIA IN MAN

After the completion of the pharmacologic studies, including anesthetics in more than 100 animals, we deemed that the properties of propylene ether warranted its trial as an anesthetic in man. On June 30, 1943, at 11:30 a.m., one of us (J. C. K., Jr.) administered propylene ether to an anesthetist, Constance Black, by the open drop method. The induction period was about sixty seconds. Light anesthesia was continued for two minutes. The recovery was rapid and uneventful. The subject stated that the vapors did not irritate the upper respiratory tract.

#### SUBSEQUENT ANESTHESIAS IN MAN

The authors wish to emphasize that this report of the first 34 cases of surgical anesthesia with propylene ether is purported to convey only a first approximation of the value of this anesthetic in man. In these anesthetics, the primary consideration was the safety of the patient and frequently complete relaxation was sacrificed for a lighter anesthetic plane, owing to the solicitude of the anesthetist. The cases, however, cover a large number of surgical procedures and serve to demonstrate the availability and safety of the new agent. The operations performed under propylene ether anesthesia were as follows:

Hemorrhoidectomy .....	1	Incision and Drainage of Abscess .....	1
Cholecystectomy .....	1	Uterine Suspension .....	1
Appendectomy .....	5	Excision of Skin Tumors .....	1
Prostatectomy .....	1	Dilatation and Curettage .....	2
Varicose Vein Excision .....	2	Perineal Repairs .....	2
Herniotomy .....	10	Release of Abdominal Adhesions .....	2
Hysterectomy .....	2	Colon Anastomosis .....	1

In this group the longest administration of propethylene ether was one hundred twenty-five minutes.

#### ANESTHETIC TECHNICS

Propethylene ether was administered by a variety of methods, e. g. open drop; open drop with oxygen under the mask; closed circuit with oxygen; closed circuit with nitrous oxide and oxygen; cyclopropane and oxygen and pentothal sodium. The agent was administered with and without preoperative medication. The potency of propethylene ether as measured in laboratory animals is far greater than that of ethyl ether. This appears to hold true for man and is manifested by a shorter period of induction and a lesser amount of the agent required for given anesthesia. The higher boiling point of propethylene ether reduces the amount of the anesthetic agent disseminated through the surrounding air during the induction period, when the open drop method is employed. A large evaporating surface on the mask was found advantageous to facilitate rapid volatilization. A tight fitting mask was found especially beneficial. Breath-holding and laryngeal spasm occurred very infrequently.

#### RELAXATION DURING SURGICAL ANESTHESIA

In the foregoing anesthetics, relaxation of the abdominal musculature was comparable to that obtained during the same plane of ethyl ether anesthesia. In 2 negroes with a history of alcoholism, suitable relaxation was obtained only with some difficulty.

#### BLOOD PRESSURE, PULSE AND RESPIRATION DURING SURGICAL ANESTHESIA

The data assembled on 34 cases of surgical anesthesia with propylene ether show that the blood pressure remains significantly unaffected during the anesthesia. The pulse is not usually affected in rate or volume. The respiration is deep and regular under the anesthetic agent, and like ethyl ether, propethylene ether appears to be a mild reflex respiratory stimulant during the induction period.

#### POSTOPERATIVE SEQUELAE

In a series of 34 cases it is impossible to draw any significant comparative conclusions with regard to postoperative sequelae. Many of the patients had no symptoms whatsoever. The recovery period approaches that of cyclopropane anesthesia in its rapidity. Vomiting occurred in about one-third of the cases. Many of the patients were given premedication with morphine which many times vitiates any significance that may be attached to postoperative nausea.

Tests of renal and hepatic function were not performed on these patients.

## POTENCY

The pharmacology of propethylene ether in many species of animals showed it to be more potent than ethyl ether and to exhibit much shorter induction period. The former was shown to obtain in man since from one-quarter to one-third the amount (measured by volume) of propethylene ether was required as would probably have been required of ethyl ether. Its potency permits a high concentration of oxygen in the respired air, and hence the avoidance of hypoxia. The induction period with a closed system in man appears to be definitely shorter than that when ethyl ether is employed.

## SUMMARY AND CONCLUSIONS

1. Isopropenyl vinyl ether, so-called propethylene ether, an isomer of cyclopropylene ether, is an anesthetic agent in man, as has been shown previously (4) in many other species of animals.

2. Human beings under propethylene ether anesthesia exhibit an anesthetic syndrome similar to that produced by ethyl ether anesthesia.

3. The authors refrain from drawing conclusions with regard to the relative advantages or disadvantages of this anesthetic agent. That propethylene ether is less volatile (boils at 19 C. higher) and is more potent than ethyl ether is observed from the data assembled. The 2 anesthesias in man herein reported in conjunction with pharmacologic experiments indicate that propethylene ether in skilled hands is a safe anesthetic agent.

4. The authors wish to emphasize again that our knowledge of the action of this agent on man is still inadequate and our data are fragmentary. More work, which is in progress, will be necessary to establish the position merited by propethylene among the general anesthetic agents.

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