The continuous search for improved anaesthetic agents has led to the synthesis of a large number of aliphatic ethers. Of the saturated, unsaturated, and halogen-containing ethers that have been examined, many with anaesthetic properties have been found, but few have survived clinical trial. Few of these newer ethers have any outstanding advantages over diethyl ether.

The five ethers that have been used to any extent in clinical practice are shown in table I. Of these agents, methyl n-propyl and ethyl vinyl ethers have largely passed out of use, whilst the status of fluoroxene is at present being re-evaluated. Divinyl ether and methoxyflurane are considered elsewhere in this number.

Although the use of short-acting barbiturates and neuro-muscular blocking agents has considerably modified the status of potent inhalation agents such as diethyl ether, this agent is still in worldwide use, and a detailed consideration of its properties is still of prime theoretical and practical importance. Other ethers can best be considered in the ways in which they resemble or differ from diethyl ether.

### DIETHYL ETHER

Diethyl ether is a colourless liquid with a boiling point of 34.6°C. It is therefore readily vaporized. The vapour is 2.6 times as heavy as air. The latent heat of vaporization at 20°C is 63 cal/gm. The specific heat of liquid diethyl ether is 0.36 cal/gm. When this agent is vaporized—unless provision is made to supply heat to the vaporizer—the temperature of the liquid diethyl ether may fall considerably, thus reducing the volatility of the drug and the concentration delivered.

Diethyl ether is highly soluble in blood, having a blood/gas partition coefficient of 12.1 (Eger, Shargel and Merkel, 1963). Diethyl ether differs from all other known inhalation agents in being more soluble in water than in blood, the water/gas partition coefficient being 13.1. This high water solubility is due to the ability of diethyl ether to

### Table I

<table>
<thead>
<tr>
<th></th>
<th>Diethyl ether</th>
<th>Divinyl ether</th>
<th>Methyl n-propyl ether</th>
<th>Ethyl vinyl ether</th>
<th>Trifluoroethyl vinyl ether</th>
</tr>
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<tbody>
<tr>
<td><strong>Synonyms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chemical formula</td>
<td>C₂H₅-O-C₃H₇</td>
<td>C₅H₅-O-C₃H₇</td>
<td>CH₃-O-C₃H₇</td>
<td>C₂H₅-O-C₃H₇</td>
<td>CF₃CH₂-O-C₃H₇</td>
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<tr>
<td>Molecular weight</td>
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<td>70</td>
<td>74</td>
<td>72</td>
<td>126</td>
</tr>
<tr>
<td>Boiling point (°C)</td>
<td>34-6</td>
<td>28-4</td>
<td>39-0</td>
<td>35-8</td>
<td>42-7</td>
</tr>
<tr>
<td>Saturated vapour pressure (mm Hg at 20°C)</td>
<td>442</td>
<td>553</td>
<td>442</td>
<td>428</td>
<td>295</td>
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<tr>
<td>Specific gravity of liquid</td>
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<td>0-77</td>
<td>0-73</td>
<td>0-76</td>
<td>1-13</td>
</tr>
<tr>
<td>Blood levels for surgical anaesthesia (mg/100 ml)</td>
<td>50-120</td>
<td>30-40</td>
<td>—</td>
<td>20-30</td>
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<tr>
<td>Partition coefficients</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Water/gas</td>
<td>13-1</td>
<td>1-4</td>
<td>—</td>
<td>—</td>
<td>0-84</td>
</tr>
<tr>
<td>Blood/gas</td>
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<td>2-8</td>
<td>—</td>
<td>—</td>
<td>1-37</td>
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<tr>
<td>Oil/gas</td>
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<td>58</td>
<td>—</td>
<td>—</td>
<td>47-7</td>
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<tr>
<td>Brain/blood</td>
<td>1-14</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1-43</td>
</tr>
<tr>
<td>Oil/water</td>
<td>3-2</td>
<td>41</td>
<td>—</td>
<td>45</td>
<td>91</td>
</tr>
</tbody>
</table>

Data for this table obtained from Sadove, Balagot and Linde (1956), Dundee (1958), and Eger and Larson (1964). (Where gaps are left in this table the data are not available in the literature.)
form \((\text{C}_2\text{H}_5)_2\text{O} \cdots \text{HOH}\) hydrogen bonds with water, the electrophilic oxygen of ether acting as a proton acceptor to attract the relatively positive hydrogen of water. Pauling (1964) has considered the possibility that such hydrogen bonding by diethyl ether in the presence of proton donors is related to its ability to produce anaesthesia. He has, however, concluded that such bonds are not involved in the narcotic action of diethyl ether, but that as with other inhalation agents, narcotic activity is related to a less specific action such as electron correlation attractions. Such a non-specific mode of action is more in accord with the thermodynamic hypothesis of Ferguson (1939).

**UPTAKE, DISTRIBUTION, AND ELIMINATION**

The uptake, distribution and elimination of diethyl ether in the dog was studied by Haggard, who published his findings in a classical series of papers (Haggard, 1924a–e). More recently similar studies have been undertaken in man (Onchi and Asao, 1961; Eger et al., 1962) and theoretical studies with electrical analogues have been performed (Eger and Severinghaus, 1964; Mapleson, 1964). The factors involved in the pharmacokinetics of diethyl ether have been recently reviewed by Butler (1964).

The major factor in determining the pattern of uptake of diethyl ether is its high solubility in blood. As the body has a large capacity for any water-soluble agent, large amounts can be removed from the alveoli into pulmonary capillary blood. Thus during induction the alveolar tension of diethyl ether is appreciably lower than the inspired tension, and the rate at which alveolar tension approaches that inspired is slow. As the alveolar tension of an inhalation agent determines its arterial and brain tensions, during induction with diethyl ether these two latter parameters will also rise slowly.

Being highly soluble in blood, the rate of rise of alveolar tension of diethyl ether will be dependent upon both alveolar ventilation and cardiac output. An increase in alveolar ventilation, by presenting a greater quantity of diethyl ether to the alveoli in unit time, will significantly decrease the time taken for alveolar tension to approach that inspired. Eger (1963a) has demonstrated that a fourfold increase in alveolar ventilation produces after 20 minutes a threefold increase in alveolar tension, when inspired tension is constant. To a much lesser extent alterations in cardiac output affect alveolar tension of diethyl ether. A rise in cardiac output allows more diethyl ether to be removed from the alveoli by the blood and thus increases the inspired-alveolar tension gradient of this agent. Both Haggard (1924e) and Yamamura and his colleagues (1963) have demonstrated the much greater dependence of diethyl ether uptake upon alveolar ventilation than on cardiac output, and because ether is a respiratory irritant its inhalation can lead to breath-holding and reduced alveolar ventilation.

As diethyl ether is used over a wide range of inspired tensions and is also a soluble agent, the rate of approach of alveolar to inspired concentration with this agent will be a function of inspired concentration; the higher this concentration, the more rapidly will alveolar tension approach inspired (Eger, 1963b). This so-called "concentration effect" is due to the removal of significant volumes of gas from the lung by pulmonary capillary blood during the early stages of uptake; the additional gaseous inflow necessary to maintain intrapulmonary pressure increases the total rate of gas uptake.

From arterial blood diethyl ether passes to the tissues. Its rate of tissue uptake is determined by the various tissue/blood partition coefficients throughout the body, and by the vascularity of the various tissue groups. For the first 3 or 4 minutes tissues of the vessel-rich group (brain, heart, kidney, hepatoporal system, endocrines) dominate uptake. For the next 2 hours uptake by muscle and skin plays a dominant role. Fat continues to take up diethyl ether after all other tissues have reached equilibrium, due to the high solubility of diethyl ether in fat (Eger, 1963a). The uptake of diethyl ether by the tissues further delays the rise in alveolar tension towards that inspired, since the lowered venous blood tension permits greater quantities to be removed from the alveoli.

During recovery from anaesthesia, alveolar tension is a resultant of the quantity of anaesthetic released to the alveoli by blood and the quantity removed from the alveoli by alveolar ventilation. Due to the high solubility of diethyl ether and the large quantities present in blood and tissues, high alveolar tensions are maintained for a considerable time after the reduction of inspired tension to zero.
The physical properties of diethyl ether will thus tend to prolong the duration of induction. During maintenance, rapid alteration of depth cannot be easily achieved, as alteration of inspired tension will have a delayed effect on arterial tension. As clearance from the alveoli occurs slowly, recovery from diethyl ether anaesthesia is prolonged.

The slow induction phase of diethyl ether anaesthesia can be shortened by certain manoeuvres. The use of a non-rebreathing technique will eliminate dilution of inspired gas by that expired. At any given inspired tension the rate of uptake can be increased by any manoeuvre that will increase alveolar ventilation. An initial inspired tension in excess of that eventually required for maintenance will also shorten the induction period. Even if alveolar tension was simply related to inspired tension, a high inspired tension would achieve the desired alveolar tension more rapidly.

The significant concentration effect with diethyl ether means that with high inspired tensions, the required alveolar tension can be attained more rapidly than simple calculation suggests. The high solubility of diethyl ether in blood permits "over-pressure" with this agent to be performed with a greater safety margin than with less soluble agents. The gradual reduction of inspired tension, by which a relative overdose might more readily be so produced, towards maintenance tension will tend to produce an approximately constant arterial tension of diethyl ether.

Inhalation agents are usually considered as inert compounds which are absorbed and excreted unchanged. Although the major portion of a given dose of such agents is eliminated in the expired air, recent work has shown that with most inhalation agents metabolism occurs to a measurable extent. Using a radioactive isotope technique, Van Dyke and his co-workers (1964) found that after the administration of 14C-diethyl ether, a measurable quantity of 14C-carbon dioxide and labelled urinary metabolites were produced. It is suggested that the initial step in the metabolism of diethyl ether is cleavage of the ether linkage by hydroxylation, leading to the formation of acetaldehyde and ethanol. Van Dyke and Chenoweth (1965) have pointed out that metabolism of volatile anaesthetics occurs in microsomes, where most of the drug-metabolizing enzymes are found, and that most drug-metabolizing reactions require nicotinamide adenine dinucleotide phosphate as a cofactor for hydrogen ion transfer. The individual enzymes concerned in the metabolism of volatile agents have not been identified.

RESPIRATION

Diethyl ether, in both animals and man, stimulates respiration until the deepest planes of surgical anaesthesia are reached. This respiratory stimulant action can be readily masked by the concomitant use of barbiturates or opiates. Gabbard and his co-workers (1952) found that in twelve patients premedicated with atropine and maintained at plane 4 of stage III of diethyl ether anaesthesia, alveolar ventilation was almost invariably greater than 5 l./min, respiratory rate was increased, \( P_{CO_2} \) was reduced, and \( pH \) was high. Kubota, Schweizer and Vandam (1962) in a study of ten patients under diethyl ether anaesthesia found that all patients had a reduced \( P_{CO_2} \), the mean value being 31 mm Hg. Jones and his colleagues (1962) in a similar study of thirteen patients, found that end-expired \( P_{CO_2} \) was usually reduced; the average blood ether concentration at which elevated \( P_{CO_2} \) levels were observed (148 mg/100 ml) was significantly greater than that at which reductions in \( P_{CO_2} \) occurred (116 mg/100 ml).

Dripps and Severinghaus (1955) examined six possible explanations for this respiratory action of diethyl ether. This effect could be a reflex response to sensitization of pulmonary stretch receptors, lower respiratory tract irritation, or stimulation of extra pulmonary sensory receptors. Respiratory stimulation could be secondary to metabolic acidosis, or result from the increase in circulating catecholamines seen with diethyl ether. Diethyl ether may have a direct biphasic effect on the respiratory centre, initially stimulating and later depressing its activity. Goldberg and Hamilton (1959) have given cogent arguments against accepting any single one of these possible mechanisms. As sectioning of the vagi does not prevent diethyl ether from causing hyperventilation, pulmonary stretch receptor activation cannot be involved. Respiratory stimulation occurs at a time when direct surgical attack on the trachea and bronchi is possible without noticeable respiratory effect; thus irritant actions cannot account for this effect during deep anaesthesia. Extra pulmonary sensory receptors are stimulated when diethyl
ether is injected into the femoral artery of experimental animals; the resulting hyperpnoea is probably due to "pain" impulses originating in or near the arterial wall. This phenomenon is not specific to diethyl ether, being seen with other irritant compounds. Metabolic acidosis, whilst common in the dog, rarely occurs to a significant degree in man. Moreover, the respiratory stimulation produced by diethyl ether occurs at a time when pH is raised rather than reduced (Gabbard et al., 1952). The catecholamine response to diethyl ether is predominantly due to an increase in circulating noradrenaline (Price et al., 1959), which is not a marked respiratory stimulant. Similar catecholamine responses occur during cyclopropane anaesthesia which is characterized by respiratory depression. Finally, no evidence of a direct stimulant effect of diethyl ether on the respiratory centre has as yet been produced. There are no a priori reasons for assuming that diethyl ether differs from all other inhalation agents, which are direct respiratory depressants.

Petersen and Elam (1958) have claimed that diethyl ether anaesthesia is associated with a significant increase in the rate of production of carbon dioxide by the body, ventilation being increased in order to maintain carbon dioxide homeostasis. Their findings have been ascribed to the failure of the subjects investigated to attain a steady state (Dodd, 1962).

Goldberg and Hamilton (1959) examined and rejected the possibility that the elevated blood ammonia level seen during diethyl ether anaesthesia was a factor in the production of respiratory stimulation. In the subjects they studied increases of blood ammonia over control levels were consistently produced by diethyl ether; increases of the same order of magnitude were also produced by cyclopropane.

CIRCULATION

It is classically stated that diethyl ether anaesthesia in man is associated with an elevated cardiac output and a persistent tachycardia, and that blood pressure, after a rise during induction, is maintained at a near-normal level (Wylie and Churchill-Davison, 1960; Dodd, 1962). These assertions are in the main based on random clinical observations and on the results of animal experiments. Blalock (1927) showed that diethyl ether caused a 75 per cent increase in cardiac output in the intact dog. Robbins (1945) in a similar study found that a 50-70 per cent higher concentration of diethyl ether was required to produce cardiac irregularities than that to produce respiratory arrest. This sparing action of diethyl ether upon the circulation of the intact dog is widely quoted as an important safety factor in clinical diethyl ether anaesthesia in man.

Despite its long continued use as an anaesthetic agent, the circulatory effects of diethyl ether in man have only recently been adequately studied. Johnson (1951) showed that diethyl ether in man reduced both cardiac output and arterial blood pressure to below pre-anaesthetic levels. Prime and Gray (1952) found that in man cardiac output and heart rate increased soon after induction with diethyl ether, but fell to below normal subsequently. No correlation was seen between cardiac output and blood ether content. Jones and his colleagues (1962) studied thirteen patients under diethyl ether anaesthesia, and found that in most of their subjects heart rate rose, blood pressure and total peripheral resistance fell, cardiac output tended to rise as the duration of anaesthesia increased, and varied changes occurred in right atrial pressure. Kubota and his associates (1962) in similar studies on ten patients, found no significant alterations in heart rate, blood pressure, cardiac output or total peripheral resistance, but a threefold increase in central venous pressure.

The rather benign cardiovascular manifestations of diethyl ether anaesthesia disguise the fact that this agent is a potent myocardial depressant. In animals the maintenance of a high cardiac output during diethyl ether anaesthesia is due to concomitant stimulation of the sympathetic nervous system; in the absence of circulating catecholamines blood ether concentrations required for surgical anaesthesia will exert a severe depressant action on the heart. Brewster and his co-workers (1953) have shown that the administration of diethyl ether to dogs who had previously undergone bilateral adrenalectomy and total sympathetic blockade caused a fall in cardiac output, a fall in ventricular stroke work, and an increase in mean atrial pressure on both sides of the heart, indicating that circulatory failure was due to direct myocardial depression rather than from peripheral vasodilatation. In these animals deep diethyl ether
anaesthesia caused cardiac failure before respiratory arrest.

The fact that diethyl ether resembles other anaesthetic agents in producing myocardial depression has been demonstrated in the dog heart-lung preparation by Price and Helrich (1955) who showed that the anaesthetic agents tested produced approximately equal depressant effects on the heart in concentrations producing approximately equal degrees of anaesthesia, and that depression of a similar degree was produced by a fall in pH of 0.5 units in the perfusing fluid. Boniface and his associates (1955) implanted strain gauges into the myocardium of intact dogs and found that diethyl ether caused a progressive fall in myocardial contractile force to 50 per cent of the control value at the time of respiratory arrest. Sporadic increases in myocardial force were seen during stage II and the first plane of stage III. A direct myocardial depressant action of diethyl ether in man has been demonstrated by Malt (1958), who has shown by ballistocardiographic studies that during the third plane of surgical anaesthesia with this agent myocardial contractile force is reduced to one-third of its initial control value.

Price and his colleagues (1959) suggested that in man the adrenal medulla does not participate to any significant degree in the sympathetic nervous system response to diethyl ether. In patients anaesthetized with this agent there was a marked though erratic rise in circulating noradrenaline, whereas only occasionally did the amount of circulating adrenaline increase. In three patients who had previously undergone bilateral adrenalectomy diethyl ether produced similar changes in circulating noradrenaline.

Li and his colleagues (1964) have criticized the use of plasma levels of catecholamines as a criterion for the activity of the sympato-adrenal system, pointing out that changes in circulating catecholamine represent combined processes of biosynthesis, liberation, binding and metabolism at various body sites. They measured the catecholamine content of the dog myocardium after exposure to various anaesthetics. Diethyl ether (and cyclopropane) increased noradrenaline content and reduced adrenaline content. Myocardial abrenaline depletion did not occur when reserpinated animals were exposed to these anaesthetics. They suggest that myocardial adrenaline depletion may indicate the exhaustion of adrenaline mobilization from the adrenal medulla. In man, evidence of adrenaline mobilization by diethyl ether in patients undergoing open-heart surgery has been presented by Anton and his associates (1964).

**METABOLIC EFFECTS**

Liver damage, varying from fatty infiltration to central necrosis, has been produced by diethyl ether in experimental animals (Bunker, 1962). These changes may be largely prevented by administering a high carbohydrate intake and a high inspired oxygen concentration, and occur less often than with chloroform, halothane, divinyl ether or trichloroethylene. In man, slight changes in liver function have been noted following diethyl ether anaesthesia. Fairlie and his co-workers (1951) noted that the majority of the patients they studied showed abnormal findings in at least one of a battery of liver function tests following diethyl ether anaesthesia, and that such abnormalities persisted for several days. French and his colleagues (1952) showed that in patients with pre-existing abnormalities of liver function, unfavorable hepatic effects of diethyl ether were more frequent, more intense, and longer in duration than in those patients with normal pre-operative liver function, and were directly related to the initial degree of hepatic dysfunction. In both studies no differences were noted between the hepatic effects of diethyl ether and cyclopropane.

Urinary output in man is diminished by diethyl ether anaesthesia. Renal plasma flow and glomerular filtration rate fall, and tubular reabsorption of water is increased. Increased tubular activity is related to an increased blood level of ADH. The fall in renal blood flow and glomerular filtration are related to renal vasoconstriction; this is probably neurogenic, as it cannot be reproduced in animals after renal denervation (Habif et al., 1951; de Wardener, 1955).

The effect of diethyl ether on the sympathetic nervous system has already been noted. Diethyl ether also causes a two-fold increase in circulating 17-OH corticosteroids (Hammond et al., 1958) and an increased secretion of ADH (Ames and Van Dyke, 1952). Price (1960) has suggested that these hormonal effects of diethyl ether indicate a site of action at the posterior hypothalamus.
The most striking metabolic effect of diethyl ether is the production of hyperglycaemia. This is due to an increased rate of formation of glucose from hepatic glycogen (Annamunthodo et al., 1958). Hyperglycaemia does not occur in hepectomized animals (Bollman et al., 1925), and is less pronounced in man with liver disease (Cantarrow and Gehret, 1931). The increased liver glycogenolysis is related to increased sympathetic activity. Brewster and his colleagues (1952) showed that experimental animals with a total sympathetic blockade did not develop hyperglycaemia during diethyl ether administration.

It has been claimed that diethyl ether has a direct effect upon carbohydrate utilization (Bunker, 1963), possibly by interfering with the entrance of glucose into peripheral tissues via phosphorylation. The effect of glucose infusions during diethyl ether anaesthesia in man have been studied by Drucker and his associates (1959) and by Henneeman and Bunker (1961). Both these groups of workers asserted that the rise of blood sugar seen in these circumstances was greater than could be predicted from the rate of glucose infusion and the known effect of diethyl ether alone, and concluded that carbohydrate utilization had been impaired. Both the design of these experiments and the conclusions drawn from them have been strongly criticized by Greene (1963), who holds the view that all the effects of diethyl ether upon carbohydrate metabolism can be explained by activation of the sympathetic nervous system. Galla and his co-workers (1962) found that carbohydrate utilization by the dog heart was not significantly impaired by diethyl ether anaesthesia.

Diethyl ether anaesthesia is associated with a rise in blood lactate level, which is again dependent upon increased sympathetic activity. Pyruvate rises to a lesser extent, there thus being an elevation of both excess lactate and lactate-pyruvate ratio. Whereas Bunker (1963) has suggested that this increased lactate is another manifestation of deranged carbohydrate metabolism, due to a direct action of diethyl ether, Greene (1961) infers that the increased lactate-pyruvate ratio is indicative of a tissue oxygen debt, secondary to impaired tissue perfusion. Greene and Spencer (1963) have demonstrated that diethyl ether will inhibit lactate dehydrogenase in vitro, but believe that this action is of little or no significance in vivo.

Ether Analgesia

The first stage of diethyl ether anaesthesia has been divided into three planes (Artusio, 1954). The third plane of the analgesic stage, characterized by total analgesia and amnesia, has been used for major surgical procedures in conscious and co-operative patients (Artusio, 1955). In this plane of analgesia arterial ether concentrations range from 16 to 33 mg/100 ml. Electroencephalographic studies have shown that third plane analgesia is associated with a dominant 24 c.p.s. activity of 30-40 microvolt amplitude (Bellville and Artusio, 1955); this fast activity rapidly diminishes as depth of anaesthesia increases (Bellville and Artusio, 1956).

Neuromuscular blocking agents may be used during ether analgesia when profound muscular relaxation is required, e.g. monitoring being then essential to maintain a steady analgesic state (Tiers and Artusio, 1960).

The main advantages claimed for ether analgesia are that the low ether concentrations required cause minimal disturbances of body function, and that the necessary inspired concentrations (0.6-1.6 per cent) are below the lower limit of flammability of diethyl ether in oxygen. Although the initial description of this technique aroused wide interest, ether analgesia has not become widely practised. No critical studies of the technique have been reported.

Methyl n-propyl Ether

Methyl n-propyl ether (Neothyl, Metopryl) is an isomer of diethyl ether. Its anaesthetic properties were described by Krantz and his colleagues in 1946, and its use as an inhalation anaesthetic in man was first reported by White and her co-workers (1946). The physical properties of methyl n-propyl ether closely resemble those of diethyl ether. It has a boiling point of 39°C, is somewhat less soluble in water than diethyl ether, and has a higher oil/water partition coefficient. The vapour is inflammable and explosive over a similar range to that of diethyl ether: 1.8-36.5 per cent in air; 2.1-82.5 per cent in oxygen (Dundee, 1958; Leonard, 1960).

The major advantage claimed for methyl n-propyl ether over diethyl ether is a reduced irritant action on the respiratory tract. Higher concentrations may thus be used during induction and high blood levels more rapidly attained.
Recovery from this agent is said to be smoother than with diethyl ether, and postoperative analgesia is said to persist for several hours. Although the vapour of methyl n-propyl ether is less irritant than that of diethyl ether, it has an unpleasant smell and a reputation for causing frontal headaches in theatre staff. For these reasons and to reduce cost, closed circuit administration has been advocated (Barnet, 1954).

Initial enthusiasm for this agent was tempered by reports of alarming cardiovascular side effects during its administration. Marked hypotension, bradycardia, and arrhythmias under moderate depths of anaesthesia have been recorded by a number of workers (Redgate and Bannister, 1950; Rees and Gray, 1950; Dundee and Lawson, 1952). Deep anaesthesia is associated with marked tachypnoea (Rees and Gray, 1950). Hunter (1950) showed that methyl n-propyl ether caused similar changes in blood sugar to those caused by diethyl ether; suggesting that sympathetic stimulation is a prominent feature of methyl n-propyl anaesthesia.

A mixture of methyl n-propyl ether and halothane containing 31-3 per cent v/v (15-25 per cent w/w) methyl n-propyl ether is azeotropic (Howat and Walsh, 1962). This mixture distils at 53-5°C, the vapour containing the agents in the ratios of 0-324 moles methyl n-propyl ether to 0-676 moles halothane. The lower limit of flammability of the vapour is 8-15 per cent in oxygen and 4-25 per cent in 75 per cent nitrous oxide in oxygen. In clinical use anaesthetic concentrations necessary will often exceed these lower limits of flammability. Howat (1963) has suggested that this azeotrope produces less respiratory depression than halothane alone; the data he presents are not sufficient to evaluate such a claim.

**ETHYL VINYL ETHER**

The anaesthetic properties of ethyl vinyl ether (Vinamar) were described by Krantz and his associates (1947), although it is of interest that this compound was one of a number discussed by Leake and Chen (1930) in their work on the anaesthetic properties of divinyl ether. Chemically and physically this agent occupies a position midway between diethyl and divinyl ethers, and its anaesthetic properties also lie between those of the two parent ethers. Ethyl vinyl ether has a boiling point of 35-8°C, and is readily vaporized. The vapour is inflammable throughout the whole range of anaesthetic concentration, the lower limit of flammability in oxygen being 2-1 per cent (Lawrence and Bastress, 1959). Ethyl vinyl ether resembles divinyl ether in being unstable, decomposing readily on exposure to air, light or heat.

Animal experiments have shown that this agent is about 10 per cent more potent than diethyl ether, but has only 80 per cent of the potency of fluroxene, its fluorinated derivative (Park et al., 1957). Few clinical reports of the use of this agent have appeared. Dornette and Orth (1955) and Sadove and his colleagues (1955) showed the resemblance of clinical anaesthesia with this agent to that produced by diethyl or divinyl ethers. It is less irritant than diethyl ether, though salivation is less. Induction is more rapid than with diethyl ether, and though this is not so rapid as with divinyl ether, inadvertent apnoea is less likely to occur. No hepatotoxic effects of ethyl vinyl ether have been recorded.

Ethyl vinyl ether must not be confused with the mixture of 25 per cent divinyl ether and 75 per cent diethyl ether known as Vinesthene Anaesthetic Mixture (VAM).

**FLUROXENE**

Trifluoro-ethyl vinyl ether was synthesized by Shukys in 1951 and initial evaluations of its anaesthetic properties were published in 1953 (Krantz et al., 1953; Lu et al., 1953). Introduced for clinical use in 1954 as Fluoromar, it aroused little interest, due to the almost simultaneous introduction of halothane. As fluroxene it was reintroduced in 1961. Whilst it has gained some popularity, the information at present available does not allow full evaluation of the place of this agent.

Fluroxene is a colourless liquid with a boiling point of 42-7°C, its volatility being midway between those of diethyl ether and chloroform. The vapour is heavier than air (specific gravity 1-13) and has a not unpleasant smell. Fluroxene contains 0-01 per cent N-phenyl-α-naphthylamine, a stabilizer which prevents polymerization.

Fluroxene vapour is both inflammable and explosive. Lawrence and Bastress (1959) showed lower limits of flammability of 4 to 4-4 per cent (depending on the vaporizing gas). Miller and Dornette (1961) claimed that water vapour present
during closed circuit administration raised this lower limit of flammability to 7.5 per cent, and that explosions did not occur until 12-14 per cent fluroxene was present. The experimental methods used by these workers are open to some criticism. Gramling and Volpitto (1963), using more accurate methods of measurement, showed a lower limit of flammability during closed-circuit administration in oxygen of 4.5 per cent; 73 per cent of concentrations measured during the first 40 minutes of anaesthesia, and 59 per cent of those measured after this time exceeded this lower limit. An azeotropic mixture of fluroxene (52 per cent v/v) and Freon 113 (1,1,2-trichloro-1,2,2-trifluoroethane) with reduced flammability has been described (Krantz et al., 1960). This mixture boils at 40.5°C, and has a lower flammability limit of 7.2 per cent. Clinical anaesthesia with this agent is said not to differ from that with fluroxene alone (Sarangi et al., 1962).

Fluroxene is poorly soluble in blood and water. Partition coefficients are: water/gas 0.84, blood/gas 1.37, oil/gas 47.7 (Munson et al., 1964). It is to be expected from the low blood solubility and high volatility that induction with fluroxene will be rapid, that depth of anaesthesia can be readily altered, and that recovery will be rapid. Munson and his colleagues (1965a) have studied fluroxene uptake in man and have shown that alveolar concentration of fluroxene rises rapidly towards that inspired. With a constant alveolar concentration, uptake falls to one-third of its initial rate within 9 minutes. These workers have also shown (Munson et al., 1965b) that an alveolar concentration of 3-4 per cent is necessary for light anaesthesia, that premedication with 10-12 mg of morphine reduces this minimum anaesthetic concentration to 2-7 per cent, and that a reduction to 0.8 per cent occurs if fluroxene is administered with nitrous oxide.

**Pharmacological Actions.**

Fluroxene has depressant actions on respiration and the circulation. Clinical concentrations of the vapour are not irritant to the respiratory tract, but tachypnoea frequently occurs. As with trichloroethylene, this is associated with a reduced tidal volume and alveolar hypoventilation. Premedication with opiates (but not with barbiturates) reduces the severity of this tachypnoea (Dundee and Dripps, 1957).

Fluroxene commonly causes hypotension, the degree of blood pressure fall being related to the depth and duration of anaesthesia (Gainza et al., 1956; Dundee et al., 1957). Hypotension is probably due to peripheral vasodilatation, as it has been shown that fluroxene has little effect on cardiac output (Virtue et al., 1962). Cardiac arrhythmias are not a prominent feature with this agent. Sinus tachycardia is seen occasionally; more rarely bradycardia, nodal rhythm or a wandering pacemaker occur (Dundee et al., 1957; Sadove et al., 1957). Fluroxene does not greatly potentiate the effect of exogenous adrenaline on cardiac excitability. Israel and his colleagues (1962) showed that dangerous arrhythmias can occur when adrenaline is given during fluroxene anaesthesia, but the risk of such arrhythmias occurring is less than with halothane or cyclopropane. Price and Dornette (1965) claim that this risk is negligible.

Few effects of this agent upon metabolism have been demonstrated. Gainza and his co-workers (1956) showed that after 1 hour of fluroxene administration some increases occurred in blood sugar and BSP retention, whilst renal function was unaffected. Sadove and his associates (1957) showed slight changes in BSP clearance and urea clearance. Nausea and vomiting occur no more frequently after fluroxene than after any potent inhalation agent.

**Applications.**

It has been suggested that fluroxene possesses a broad usefulness as an inhalation agent, and may be the agent of choice for such situations as cardiac surgery, neurosurgery, paediatric surgery, and obstetric analgesia and anaesthesia (Martin and Bosnak, 1962; Miller et al., 1962; Dornette, 1963). The chief advantages of fluroxene are its low blood solubility, lack of irritant properties, and its analgesic action. Against these must be set the flammability of this agent and the liability to
respiratory depression with any depth of anesthesia. The cost of administration is of the same order as that of halothane, the lower cost of fluoroxyne being offset by the higher concentrations required. It is possible that the most useful future application of this agent will be for minor surgical procedures of limited duration.

REFERENCES


THE ANAESTHETIC ETHERS


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**NORTH-EAST OF SCOTLAND SOCIETY OF ANAESTHETISTS**

**Syllabus for 1965–1966**

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Meetings are held at 8 p.m. in Aberdeen Royal Infirmary, Dundee Royal Infirmary, or in Strathclyde Hospital, Brechin.