is also no ground for refusing employment in a sanatorium. Since no one is entitled to superannuation benefit until the lapse of ten years the tuberculous staff might be accepted under such schemes without grave risk of bankrupting them, "as a tuberculous man who has survived ten years has an expectation of life not widely different from the normal population" (Dr. Trayer).

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VINYL ETHER AS AN ANAESTHETIC AGENT*

BY

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Although I have had some experience in the use of vinyl ether during the past two years, I cannot claim to be in any way responsible for the great amount of experimental work that has placed this agent upon a scientific basis as an anaesthetic.

This is, I believe, the first occasion upon which vinyl ether has been the sole subject of a discussion at an anaesthetics meeting in Great Britain and Ireland, and I should like to open with a short account of the work which led to its use as an anaesthetic and to give you some of its chemical and physiological properties.

History

Leake and Chen in 1930 demonstrated that vinyl ether possessed anaesthetic properties, and in 1931 a purer and more stable product was prepared in the research laboratories of Merck and Co. by Ruigh and Major and was used as an anaesthetic on dogs by Knoefel, Guedel, and Leake. These investigators found that dogs were more easily anaesthetized by vinyl ether than by chloroform. They also found that the period of recovery was rapid and free from vomiting; moreover, they did not notice any significant pathological effect on the various organs.

The first experiments on human beings were conducted in 1933 by Gelfan and Bell, who after trying vinyl ether upon themselves considered it worthy of clinical study. The first extensive account of vinyl ether anaesthesia in man was published in 1934, when Goldschmidt and his colleagues reported having used it in operations in 461 mixed cases. In all these cases vinyl ether appeared to have no undesirable effect on respiration, the circulation, the liver, or the kidneys.

Since then a number of anaesthetists have recorded their experiences with this agent, and the early claims for its

safety seem to be well founded. Its especial advantages in certain well-defined indications are now being recognized. Wesley Bourne is particularly enthusiastic for the use of vinyl ether as the anaesthetic of choice in obstetric cases. The first report of its use in England occurred in 1935, when Sir Francis Shipway recorded a series of 314 cases. Besides these there are many reports which uphold the claim that it is of great benefit in short anaesthetics, for its rapidity of action and for its use as an adjunct to gas-and-oxygen anaesthesia.

I may here quote from a report by Beach of Philadelphia on a series of 2,630 cases:

"In endeavouring to place vinyl ether in the notch in which it seems most suitable our experience leaves us to suggest that it is most suitable in:

1. Minor surgery in short cases.
2. Major surgery only as a supplementary agent to the gases such as nitrous oxide and ethylene, where increased relaxation is required.
3. As an induction agent, especially in children, in an ethyl ether follow-on.
4. Obstetrical analgesia and short anaesthetics.
5. In dental surgery.
6. For short simple cases in the home or office, of the ambulatory type, and in cases where a gas machine is not available."

It is interesting to note that Beach administers vinyl ether by the open method when using it alone, but, on the other hand, Wesley Bourne, its most enthusiastic supporter, invariably uses a closed system with carbon dioxide absorption. For major operations this appears to be the method of choice, and I feel sure you will agree that this is so when we discuss its administration.

Chemistry of Vinyl Ether

Vinyl ether is a very volatile, clear, colourless liquid. It possesses a characteristic odour, said by some to resemble garlic, while others compare it to acetylene. It has a specific gravity of 0.77, and a boiling point of 28.31° C. (83° F.). Its chemical formula is $\begin{matrix} \text{CH}_2\text{CH} \\ \text{CH}_2\text{CH} \end{matrix} > \text{O}$, from which it is seen that vinyl ether is really a divinyl oxide, whereas ethyl ether has the formula $\begin{matrix} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{matrix} > \text{O}$, and is thus a diethyl oxide.

Vinyl ether undergoes certain oxidation changes when exposed to light or air for any length of time, and for this reason 3.5 per cent. absolute alcohol is added and 0.01 per cent. of a non-volatile oxidation inhibitor. If vinyl ether is kept for more than twenty-four hours after the container has been opened it rapidly loses its potency and thus greater quantities are required to effect anaesthesia. No toxic effect has, however, been noticed after using stale vinyl ether.

It is highly inflammable, and the same precautions are essential in its use as would be required for ethyl ether. The following table gives the limits of inflammability of both vinyl ether and ethyl ether (Guedel, 1937).

Vinyl ether and air	..	..	..	1.70-27.00 %
Ethyl ether and air	..	..	..	1.85-36.50 %
Vinyl ether and oxygen	..	..	..	1.85-85.00 %
Ethyl ether and oxygen	..	..	..	2.10-82.00 %

From this it is seen that in anaesthetic proportions vinyl ether combined with air or oxygen produces a highly explosive mixture.

* Read in opening a discussion in the Section of Pharmacology and Therapeutics, including Anaesthetics, at the Annual Meeting of the British Medical Association, Belfast, 1937.

Pharmacology

Vinyl ether produces anaesthesia with great rapidity; surgical relaxation is excellent, and is similar to that obtained with ethyl ether. The relative anaesthetic potency compared with ethyl ether was 4 to 1 when used on dogs and 7 to 1 when used on man. Compared with chloroform the relative potency determined on dogs was 1.3 to 1 (Goldschmidt *et al.*, 1934).

Vinyl ether does not irritate the upper air passages, but it does cause an increased flow of saliva, and for major operations a pre-operative dose of atropine is advisable. It can be mixed with ethyl ether in any proportion, and the resultant mixture will vaporize in approximately even percentages. An experiment has been conducted during which a stream of air was passed through a mixture of 27 per cent. by weight of vinyl ether and 73 per cent. by weight of ethyl ether. The first 25 per cent. of the material that came over analysed 31.5 per cent. vinyl ether and the rest ethyl ether. The last 10 per cent. of the material that was carried over by the air contained 25 per cent. vinyl ether.

Moliter has anaesthetized a series of mice with various mixtures of vinyl ether and ethyl ether, and his results are given graphically in Fig. 1. From this it is seen that

FIG. 1.—The effect of vinyl ether upon the induction time of ethyl ether on mice.

the lowering of the induction time is most marked after the addition of 10, 20, or 30 per cent. vinyl ether. Actually these animal experiments correspond fairly accurately with the clinical findings of anaesthetists who have used mixtures of these two agents. Wesley Bourne (1937) has recently advocated the use of a mixture of 25 per cent. vinyl ether with 75 per cent. ethyl ether by the open method where it is not possible to use a "closed" method with carbon dioxide absorption for long cases, and for obstetric use in the patient's home.

Physiology

Vinyl ether owes its anaesthetic effect to the fact that it is lipid-soluble. In the blood, anaesthesia is produced with a remarkably small concentration; in dogs this is 28 mg. per 100 c.cm., whereas with chloroform it is 37.5 mg. per 100 c.cm. During ethyl ether anaesthesia, however, the concentration is as high as 116 mg. per 100 c.cm. Overdose produces respiratory arrest, but respiration returns rapidly on withdrawing the anaesthetic and inflating the lungs with oxygen.

Peoples and Phatak (1934) have studied the effect of ethyl ether, ethylene, and vinyl ether on the intestinal muscles of rabbits. They found that whereas ethyl ether always caused an immediate and marked loss of tone and inhibition of movement of the gut muscle, and ethylene caused a slight and transitory loss of tone with an occa-

sional increase in the amplitude of contraction, vinyl ether uniformly increased the tonicity of the intestine. Thus we may expect its use to be followed by less post-operative distension than with either ethylene or ethyl ether. This view is supported by the clinical experiences of many observers.

The action of this anaesthetic agent upon the liver has been investigated with extreme thoroughness by several workers, and it has been proved without question that vinyl ether has little action upon liver function, even when administered to patients with toxæmia of pregnancy. As this aspect of the subject is of such importance I shall go into some detail concerning the work that has been done.

Bourne and Raginsky (1935) administered vinyl ether to normal dogs, to dogs with livers damaged by chloroform, and to partially starved dogs, and the liver function was estimated by means of the bromsulphalein test. The conclusions they arrived at were as follows:

"1. Vinyl ether anaesthesia in normal dogs does not alter the liver function appreciably. In those cases where cyanosis is a feature of the anaesthesia moderate liver damage occurs which is not due to the action of the drug but to the associated cyanosis.

"2. Vinyl ether anaesthesia does not enhance the liver function damage produced previously by the inhalation of chloroform, nor does it delay the period of recovery from this damage.

"3. The effect of vinyl ether anaesthesia upon the liver function in partially starved dogs is not appreciably different from that produced in normal animals."

In addition to experiments upon animals Wesley Bourne has carried out the bromsulphalein test in four obstetrical cases in which vinyl ether was used and in two cases in which chloroform was administered. The results of these investigations are given in Table I. It will be seen that

TABLE I.—Effect on the Liver in Obstetrics in Primiparae

Case No.	Age	Anaesthesia		Dye Retention	
		Method	Duration	%	Hours after
1	17	V.E. closed	51 min.	10	18
2	25	V.E. open	58 "	10	23
3	24	V.E. closed	60 "	10	24
*4	18	V.E. closed	39 "	5	24
5	21	CHCl ₃ closed	30 "	25	24
6	21	CHCl ₃ closed	35 "	20	24

* Case No. 4 was a "toxæmia of pregnancy" with albumin and casts in the urine, and B.P. 160/105.

the impairment of liver function was very much less marked after vinyl ether than after chloroform, and that the toxic case suffered little harm from the inhalation of vinyl ether.

Moliter has approached the problem of the effect of anaesthetics on the liver in a novel but direct manner. Cannulae are inserted into the bile duct and the duodenum of a rabbit. The bile is then collected, measured, and weighed, and reinjected into the duodenum. Before being collected the bile passes through a drop-recorder, so that the slightest change in the amount of bile secretion can be noted. When chloroform is administered there is an immediate decrease in bile secretion, which continues after the anaesthetic has been withdrawn. With ethyl ether there is a very slight initial decrease and a subsequent increase in the flow of bile. When vinyl ether is admin-

istered there is no change in the flow of bile, even though the anaesthetic last for two hours. When a mixture of 95 per cent. nitrous oxide with 5 per cent. oxygen is applied there is an almost complete cessation in the flow of bile, which is apparent immediately. If a change is now made to a mixture of 80 per cent. nitrous oxide and 20 per cent. oxygen, with sufficient vinyl ether to continue deep anaesthesia, the bile commences to flow again and resumes its normal rate within five minutes. All this tends to support the view that anoxaemia is the primary factor in the production of liver necrosis.

Determinations of the coagulation time of the blood following vinyl ether anaesthesia show that the administration of this drug produces little if any change, as may be seen in Table II (Bourne *et al.*, 1937).

TABLE II.—Effect of Vinyl Ether Anaesthesia on Coagulation Time of Blood

Case No.	Before Anaesthesia	Administration	After Anaesthesia
1	3 min. 30 sec.	45 min.	4 min. 45 sec.
2	3 " 30 "	40 "	4 " 0 "
3	3 " 30 "	40 "	3 " 15 "
4	3 " 30 "	23 "	3 " 25 "
5	3 " 35 "	20 "	3 " 23 "
6	4 " 0 "	30 "	4 " 20 "
7	4 " 10 "	20 "	4 " 20 "
8	4 " 0 "	15 "	4 " 15 "
9	4 " 0 "	60 "	3 " 13 "
10	3 " 45 "	19 "	3 " 35 "

The blood sugar is raised at the beginning of a vinyl ether administration, but it falls fairly rapidly; in contrast, ethyl ether produces a considerable and sustained rise in

FIG. 2.—Blood sugar response of male rats to anaesthetics.

the blood sugar. This is seen in Fig. 2, which demonstrates the effect of various anaesthetic agents upon the blood sugar of rats (Emerson *et al.*, 1937).

Cardiac irregularities have not been noticed in any of my cases, and there has been little if any fall in the blood pressure. The chart of a typical case is seen in Fig. 3. The patient was a boy aged 13, who was admitted to

hospital for a tibial graft to the left radius on account of fracture. The physical findings were normal. He was given as premedication 1/100 grain of atropine at 1.30 p.m. The anaesthetic used was 22 c.cm. of vinyl ether by the closed method with absorption by Wilson soda lime. Consciousness was regained at 3.20 p.m.

FIG. 3.

Methods of Administration

Vinyl ether may be given by the open or closed method, and as an adjuvant to gas and oxygen, as follows:

(a) *Open*.—Vinyl ether. Mixtures with ether.

(b) *Closed*.—To-and-fro for minor surgery; absorber added for long cases.

(c) As an adjuvant to gas-and-oxygen: In a Boyle or a McKesson machine, diluted with ether; with drip regulator; with Rowbotham's chloroform bottle.

The administration of vinyl ether by the open method has not proved a success in my hands, although Saghirian reports a series of 150 dental cases in which the method was used successfully. I have found that the extreme volatility of vinyl ether makes it difficult to maintain an even plane of anaesthesia for prolonged cases, and for short cases considerably more vinyl ether is used than by a "closed" method. On the other hand, a mixture of one part of vinyl ether to three parts of ethyl ether, when used on an open mask, gives excellent anaesthesia. Induction is rapid and relaxation adequate; in fact this mixture has all the advantages of a chloroform-ether mixture without its dangers. With regard to the closed method of administration for dental and other minor operations, I do not propose to go into detail here; it has already been described (Goldman, 1936). Since its introduction in March, 1936, the method has been in daily use at the Eastman Dental Clinic, and up to April 30, 1937, a total of 1,342 children had been anaesthetized with vinyl ether. Only five of these cases were sick after the administration, and not a single child has had to be detained for any post-anaesthetic complication. It is the opinion of the nurses at the clinic that the children who have had vinyl ether recover as uneventfully as after a "straight" gas, and many are fit to leave the clinic sooner than those who have had gas. Ramage has reported the use of this method in a school dental clinic, and seems to be equally satisfied with it.

For major operations with vinyl ether anaesthesia the closed system, combining carbon dioxide absorption, is the method of choice. We prefer the to-and-fro system of Waters (1931), in which the soda-lime canister is fitted between the face-piece and the rebreathing bag, with a small tube on the face-piece mount for the anaesthetic gas supply. A small "bubble-through" bottle, holding 25 c.cm., is attached to the oxygen supply coming from a

gas-and-oxygen machine fitted with a finely calibrated oxygen flow meter. During induction oxygen is bubbled through at the rate of half a litre a minute, and in three to four minutes the third stage of anaesthesia will have been reached. The oxygen flow is now reduced to between 200 and 300 c.cm. a minute, according to the patient's metabolic rate. As soon as the required depth of anaesthesia has been attained the by-pass on the vinyl ether bottle is opened, so that only pure oxygen is now given to the patient. Only at occasional intervals when anaesthesia becomes lighter is it necessary to add more vinyl ether. By this method we average about 20 to 30 c.cm. of vinyl ether an hour for an abdominal operation, and, in addition to the economy of the method, the patient derives all the benefits of a closed system of anaesthesia. There is no reason why induction should not be carried out with gas-and-oxygen or evipan, and there is no contra-indication to the use of a basal anaesthetic with vinyl ether.

As an adjuvant to gas-and-oxygen, vinyl ether has many uses, such as a difficult nasal gas case, or to obtain just that extra amount of relaxation that is so helpful in an abdominal operation. It can also enable a gas-and-oxygen anaesthetic to be given to a heart case without reducing the oxygen to a dangerous level. The simplest method of adding vinyl ether to a gas-and-oxygen anaesthetic is to put some of the 1:3 vinyl ether in ether mixture in the ether bottle provided on most gas machines.

A more accurate method is to fit a drip device between the rebreathing bag and the mask. Such a device has been made for me, and has recently been described (Goldman, 1937). Dr. Rowbotham has devised an excellent vaporizer which serves the same purpose, although it was introduced originally as a means of giving chloroform with a McKesson machine, and this is the method in use in the obstetric unit of the Royal Free Hospital.

The following tabular statement, which gives my personal experience with vinyl ether, shows that although the number of major operations is not large these cover a wide field of surgery.

Methods of Administration

Vinyl ether alone ; major and minor ..	1,150
Vinyl ether-ether mixtures ; major ..	4
Gas-and-oxygen plus vinyl ether ; major ..	37
Total to May 30, 1937 ..	1,191

Operations Performed

Dental cases ..	1,093
Minor operations, etc. ..	24
Major abdominals ..	27
Major orthopaedic ..	17
Major ear, nose, and throat ..	13
Major gynaecological ..	5
Thyroidectomies ..	2
Amputation of breast ..	2
Other major operations ..	8
Total ..	1,191

The longest case so far was that of a woman aged 54 who had a partial gastrectomy performed. She had, as premedication, a hypodermic injection of 1/6 grain of morphine and 1/150 grain of hyoscine. Vinyl ether was given in a closed system by means of a Waters canister ; after induction an endotracheal tube was passed by means of a laryngoscope, and the whole operation took 105 minutes, during which time 45 c.cm. of vinyl ether were used. The patient made an excellent recovery and she did not vomit.

I have had no death due to the anaesthetic, and there have been few complications ; the only one of note was a gastro-enterostomy, in which a parotitis developed on

the second day. This may have been due to increased salivation caused by vinyl ether. However, this cleared up in a few days. The other patients all had uneventful recoveries ; only a few vomited after the anaesthetic.

Summary

Vinyl ether is a potent anaesthetic for major and minor surgery.

It has been used in a large variety of cases, and it is suggested that its sphere of usefulness is a wide one.

Administration by means of a closed inhaler has advantages over the open method.

A series of 1,191 cases is reported, without a death or serious complication.

In conclusion I should like to thank the surgeons and anaesthetists on the honorary staff of the Royal Free Hospital and Eastman Dental Clinic for their help and encouragement ; and also Mr. H. Tally of Messrs. A. Charles King for his assistance in the manufacture of the apparatus necessary.

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H. Brockmann (*Klin. Wschr.*, October 2, 1937) points out that it has long been known that substances containing vitamin D vary considerably in their effect in the treatment of rickets—for example, cod-liver oil is more effective than irradiated ergosterol. These variations have been explained as follows: (1) irradiated ergosterol contains, besides the antirachitic factor, one which raises the phosphorus content of the blood ; (2) human rickets is a combined D- and A-avitaminosis, and the administration of vitamin D alone (ergosterol) fails to relieve all symptoms as does cod-liver oil, which contains D and A. Brockmann believes, however, that the real reason is that the vitamin D of ergosterol differs in characteristics from that of cod-liver oil. The former is D₂, the latter D₃. He was able to obtain vitamin D₃ in pure form and to prove that it was far more effective than D₂ in the treatment of rickets. Twenty-one infants were examined before treatment and a record made of the clinical features, the phosphorus content of the serum, and the x-ray findings. Two daily doses of 0.07 mg. of D₃ (which is one-half to two-thirds of the threshold dose of D₂) were administered, the infants being treated in hospital. In every case a complete cure was obtained after a two to three weeks' course. No butter was included in the diet, and ultra-violet ray therapy was withheld. The errors occurring during ambulant treatment by other investigators were avoided.