Special Article

Canadian contributions to the introduction and use of divinyl ether

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In 1930, some 90-odd years after the pioneering efforts of Drs. Wells and Morton, the only changes that had taken place in inhalation anesthesia were the introduction of chloroform by Dr. James Young Simpson[1] and the introduction of an ingenious array of delivery systems (vaporizers, inhalers and other apparatus). Initial enthusiasm about the gift of anesthesia began to wane as physicians realized that there was a price to pay for this exceptional advance, and that not too infrequently, patients succumbed to the inherent risks of this process. The discovery of local anesthesia by Dr. Koller[2] in 1884 added a new dimension, and Dr. Bier's discovery of the spinal route[3] in 1898 fully launched the era of regional anesthesia. Despite these new developments, the majority of surgical procedures still required a state of unconsciousness induced by inhalation anesthetics.

How had anesthesia progressed by the 1930s, and what inhalation agents were available by that time? Although more doctors were beginning to take an interest in the subject, probably as a result of their experiences in World War I, anesthesia as a medical specialty was still in its infancy, with most anesthetics in the developed world being administered by general practitioners. Diethyl ether (DEE), chloroform, ethyl chloride, ethylene and, of course, nitrous oxide, were all being used by this time, with clinical testing of cyclopropane underway[4] and the early intravenous barbiturates on the horizon. Although DEE was clearly the most popular agent, it had a very slow onset of action. Anesthetic inductions were often challenging, with recovery prolonged, and frequently marred by protracted periods of nausea and vomiting and, of course, the drug was flammable. Chloroform was very effective with much smoother and faster inductions, but high concentrations caused cardiac depression, and there were a number of fatalities associated with its use, the first recorded anesthetic death having been linked to chloroform in 1848[5] when a young 15-yr-old girl named Hannah Greener died prior to the intended removal of an ingrown toenail. Although not flammable, chloroform was also a known hepatotoxin. Ethylene was not a very effective anesthetic agent and was flammable. Ethyl chloride, often used as an induction agent in combination with DEE, was also flammable, and it had a very narrow therapeutic margin of safety. Nitrous oxide/oxygen combinations could be used for short procedures, but were not very effective unless hypoxic mixtures were used or supplemented by sedation, regional anesthesia or additional inhalation anesthesia. So, in the early 1930s, it was evident that there was significant room for improvement in inhalation anesthesia.

Early investigations related to the pharmacology of inhaled anesthetics

In 1931 Drs. Leake and Chen[6] studied the pharmacology of inhalation anesthetics, and predicted that by combining the pharmacological properties of ethylene and DEE they would produce the "ideal" inhalation anesthetic (Figure 1). Using an impure sample of divinyl ether in mice they found, as predicted, that it had anesthetic properties as good as, if not better than DEE. They concluded their article with the words 'further study of this interesting series of agents is justified and cordially invited'.

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Chemical Structure of Three Previously Used Inhalation Anesthetics

$CH_2 = CH_2$	Ethylene
$CH_3 - CH_2 - O - CH_2 - CH_3$	Diethyl Ether
$CH_2 = CH - O - CH = CH_2$	Divinyl Ether

FIGURE 1 Chemical structure of three inhalation anesthetics
Drs. Leake and Chen tested the potency of a number of chemical compounds combining the chemical qualities of diethyl ether and ethylene in mice. They tested six unsaturated ether compounds, of which only divinyl ether proved to be an improvement on diethyl ether. *Leake CD, Chen MY.* The anesthetic properties of certain unsaturated ethers. Proc Soc Exp Biol Med 1930; 28: 151.

Drs. Samuel Gelfan and Irving Bell at the University of Alberta responded to Dr. Leake and Chen's challenge and tried, but were unsuccessful in their attempt to prepare divinyl ether in their own laboratory. Dr. Leake kept them up to date about experiments he was carrying out with divinyl ether (DVE) in dogs at the University of California. Drs. Ruigh and Major[7] successfully manufactured pure DVE in 1931, and patented it under the name of Vinethene, much to Dr. Leake's chagrin, who rightfully claimed that he played a major role in its development.[8] However, Dr. Leake's claim on the discovery of DVE may also be questioned, as Dr. Semmler[9] had described this chemical years before.

Dr. Leake contributed an introductory essay to "The History of Surgical Anesthesia" by Thomas Keys[10] and refers to Dr. Samuel Gelfan in that essay: "Meanwhile, our first reports had excited a number of scientists. Dr. Samuel Gelfan in Canada asked for the privilege of studying the effects of DVE on human beings. I arranged for samples to be sent to him and for his publication to appear with the extended pharmacological report which we made."...and therefore, one may speculate that this is why he approached the Canadian researchers. There is additional corroboration of this story in correspondence from Dr. William Neff, in which he stated that: "At the University of California there was no interest in the clinical employment of any new anesthetic".[A]

Open drop divinyl oxide, so-called at that time to avoid confusion with the well established DEE, was

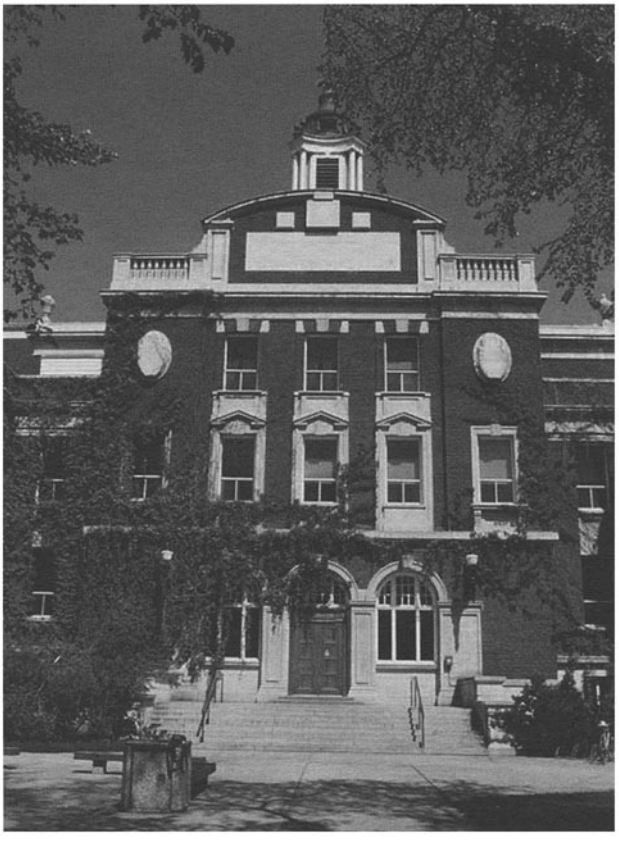

FIGURE 2 Dentistry/Pharmacy Building, University of Alberta 2008
Drs. Gelfan and Bell conducted their clinical trials on divinyl ether in 1932 in a laboratory in this building, which was then the conjoined Departments of Physiology and Pharmacology at the University of Alberta.

administered by Dr. Bell to his co-worker Dr. Gelfan for a period of ten minutes at the University of Alberta, sometime in 1932. This work was carried out in the then-conjoined Departments of Physiology and Pharmacology at the University of Alberta,[B] in what is now known as the Dentistry/Pharmacy Building (Figure 2). Dr. Bell gave the following description: "Divinyl oxide is not unpleasant to inhale. It is sweetish in taste but lacks the burning pungency of diethyl ether, and does not apparently irritate the respiratory passages. The induction with divinyl oxide is impressively smooth, prompt, and even, and the recovery rapid". Two minutes after removal of the mask, Dr.

A Letter from Dr. William Neff to Dr. Roy Humble dated April 3rd 1987. Original correspondence retained by the author.

B Dr. Humble presented a paper entitled: The first use of di-vinyl ether as an anesthetic agent in humans at the 2nd International Symposium on the History of Anesthesia at the Royal College of Surgeons of England (London 1987) and in that paper he indicated the site of the first human administration of DVE.

Gelfan had fully recovered and was able to converse intelligibly. Several days later, he again received the anesthetic, this time for 18 min.

The effects on respiration, pulse, blood pressure, eye reflexes and pupillary activity were recorded throughout. Blood pressure varied by no more than 5–10% from pre-induction levels, and the pulse did not vary significantly. A fair degree of relaxation of the abdominal muscles was obtained, and the presence of complete analgesia was confirmed by the application of electrical current to the foot and leg. There was once again a rapid recovery, with complete absence of nausea and vomiting.

After two such administrations, Dr. Gelfan sought to observe the effects of the anesthetic in a more objective way. A member of the Zoology Department, at the University of Alberta, Dr. Winifred Hughes, happened to be walking in the corridor outside the laboratory at the time, and she was invited to volunteer for the third successful administration of this new anesthetic. It is noteworthy that all three trials were made within two to three hours of a meal, and both subjects were found to have no difficulty in continuing their teaching duties shortly after the anesthetic. The rapid induction and recovery with the absence of nausea and vomiting, which these early subjects found, were to be the hallmarks of anesthesia with DVE.

The reports by Drs. Gelfan and Bell[11] and the animal experiments carried out by Dr. Leake *et al.*[12] from the University of California were both published in the same journal in 1933, Drs. Gelfan and Bell's article, concludes with the words "on the basis of the experiments performed by Leake and his associates and our tests of the anesthetic in the human, we feel that divinyl oxide is worthy of clinical trial and evaluation."

Divinyl ether was further tested clinically in the United States after Dr. Gelfan and Bell's report. The first successful use of DVE for a surgical patient was carried out in 1934 by Dr. Dorothy Wood at the University of California Hospital, San Francisco, in an obese patient undergoing a cholecystectomy [13] The first major clinical description of the use of DVE in patients was reported by Goldschmidt *et al.*[14] at the University of Pennsylvania in 1934. Merck Inc. released DVE for commercial use in early 1935.

On October 22nd 1936, a report was published in the New York Herald Tribune, with a headline that stated: "New Anesthetic is Reported to Medical Group. Divinyl Ether Found Most Effective after 2200 Tests in Pennsylvania." The report also mentioned that DVE was "the closest approach yet found to the ideal anesthetic" (Figure 3; available as Additional Material at www.cja-jca.org). In 1941 there was a report published indicating that approximately 36,000 anesthetics using DVE had been conducted, and that approximately 50% of the cases were dental anesthetics.[15] The drug had mostly been administered using the open drop method.

TABLE A comparison of selective physicochemical properties of new and old inhaled anesthetic agents

Property	*Diethyl ether*	*Divinyl ether*	*Halothane*	*Desflurane*	*Sevoflurane*
Boiling point	34	28	50	24	58
Vapour pressure at 20°C (mmHg)	442	553	241	669	160
Molecular weight	74	70	198	168	200
Blood/gas solubility coefficient	12.1	2.8	2.4	0.42	0.65

Conway CM. The anaesthetic ethers. Br J Anaesth 1965; 37: 644–54; *Black GW.* A review of the pharmacology of halothane. Br J Anaesth 1965; 37: 688–705; and Barash *et al.* Clinical Anesthesia, 2nd edition. Philadelphia: JP Lippincott Co.; 1992: 441.

The main reported advantages of this new agent were its rapid onset, its low pungency and rapid recovery, with a reduced incidence of side effects (nausea and vomiting). Like DEE, it too, was flammable. DVE was a clear, colourless liquid with a sweet ethereal, non-irritating odour. It was quite unstable and was dispensed in 25 mL, 50 mL and 75 mL brown bottles. The 25 mL bottle of DVE cost 60 cents in 1935, upon release for commercial use by Merck[C] A similar quantity of sevoflurane in 2008 costs about $30 Can.

It is interesting to compare the physicochemical properties of DVE with the other agents in use at the time, and to also compare DVE with halothane (still widely used in developing countries) and some of the newest agents available today (Table). The boiling point of DVE was very close to room temperature, and it could readily boil in a warm climate. The manufacturers added 3.5% absolute alcohol to the liquid to prevent ice formation on the mask, and to reduce the risk of burns. The other interesting physicochemical attribute of DVE was its moderate blood /gas solubility coefficient of 2.8, which is quite similar to that of halothane, and about one third that of DEE. This is one of the most distinguishing properties of DVE. In a report by Finer *et al.*[16] the induction of anesthesia in a child was reported to be less than one minute, using approximately 10 mL of DVE. It is important to

C Archives, Merck & Co., Inc.

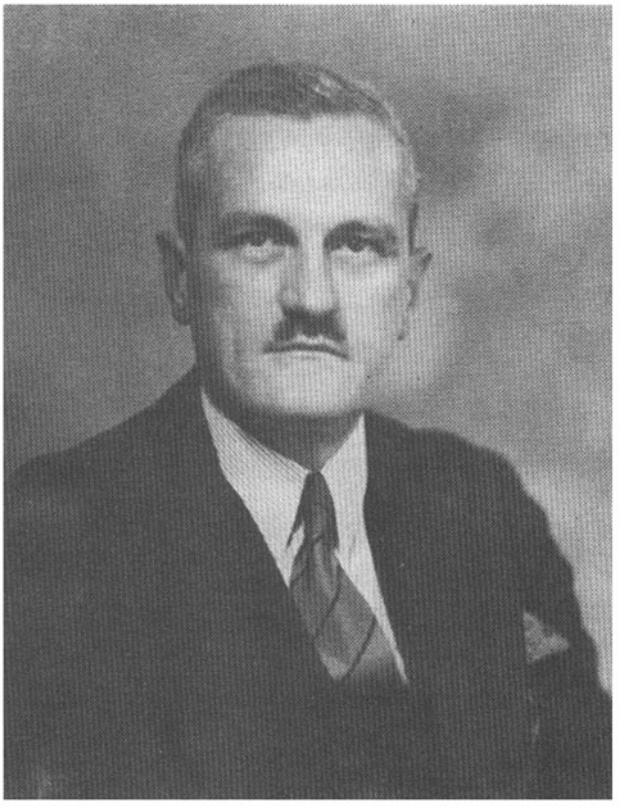

FIGURE 4 Dr. Wesley Bourne (courtesy of Mr. Patrick Sim, Wood Library Museum)

bear in mind that most anesthetics in the 1930s were administered by the "open drop" method. It should also be remembered that very little patient monitoring was carried out at that time, and indeed, the most frequent monitor used was "the finger on the pulse".

Dr. Wesley Bourne (Figure 4), a very prominent anesthesiologist at McGill University in Montreal in the 1930s, had considerable experience using DVE in obstetric patients. Dr. Bourne published a number of scientific and clinical articles describing the use of DVE in obstetric patients, the first appearing in the Lancet in 1934.[17] In a subsequent article published in JAMA[18] he stated the following: "when vinyl ether is used to produce anesthesia sufficient for obstetric procedures, it apparently does not cause liver damage nor does it interfere with muscular activity in the intestine and in the uterus. Vinyl ether (DVE) seems to be particularly suitable for obstetric anesthesia in general practice on account of its safety for mother and child, its ease of administration, the rapidity of its action, the satisfactory maintenance of any desired degree of narcosis, and the early uneventful recovery". Dr. Bourne was awarded a prize for the best essay by the British Journal of Anesthesia in 1935[19] for his paper entitled: Vinyl ether (vinesthene) anaesthesia in dogs: effects upon normal and impaired liver. This accomplishment was somewhat tarnished by the judges' comments, which were as follows: "They would have been happier, perhaps, if the winning essay had been of a nature to be of greater clinical or practical benefit...the exact nature of the subject matter was only one of the considerations to be taken into account in awarding merit and those essays, which in this particular case were preferred to the winner, were too far behind in other respects to replace it." It should be mentioned that the judges' selection for this prize was unanimous.

Drs. Bevan and Pacelli,[20] in their book written about Dr. Wesley Bourne, commented that this was an unenlightened view by the judges, especially when one considers that hepatotoxicity was a significant problem in anesthesia at that time, related to the use of chloroform. It is also interesting to note that Dr. Bourne was awarded the first Henry Hill Hickman Medal in the following year. This medal is awarded no more frequently than triennially, for original work of outstanding merit, and the award was made by the Royal Society of Medicine on the recommendation of the Section of Anaesthetics. The Henry Hill Hickman award is today considered to be one of the most prestigious awards in anesthesia in the world. Bourne[21] also deserves credit for promoting the use of mixtures of 25% DVE and 75% DEE, "... hence the solution of the problem of tremendous waste from rapid volatilization which occurs when vinyl ether alone is used by the 'open' method." In this same report, he said the following: "in teaching it should be just as necessary to repeat the advantages of a new drug as it is to tell again and again the story of the poisonous effects of chloroform, or that of the value of oxygen. Even now this good food is not used sufficiently in anesthesia, and that perfidious compound is still being employed despite advice and warnings which are being given never so loudly. May these provocative thoughts represent a votive offering to Thoth!"

In another report published in the British Journal of Anesthesia, Bourne wrote: "It seems fair to say that at long last we have a substance which is safe for common use. This substance is vinyl ether (called Vinethene)."[22]

Divinyl ether was widely used in Europe and North America for at least 30 years, until it was replaced by halothane. Divinyl ether was marketed under the name of Vinethine in the United States, Vinesthine in the United Kingdom, and Vinydan in continental Europe. In the 1960s, the distributors of Vinydan in Europe indicated that 8,000 L of Vinydan was sup-

FIGURE 5 Dr. Irving Bell (University of Alberta Archives)

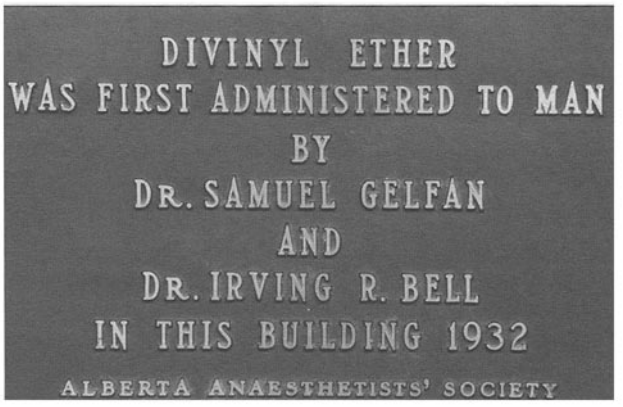

FIGURE 6 Plaque (University of Alberta Archives)
This plaque was first erected in The Old Medical Building on the University of Alberta campus in 1955. It was removed when that building was renamed, and is now in the author's possession.

plied annually to Austria, France, Germany, Holland, Hungary, Scandinavia and Switzerland.[D] The drug may have had a much wider application in North America were it not for the introduction of cyclopropane around the same time. Despite the competition between these two inhalation agents, DVE outlasted many of the inhalation agents introduced in recent years, and served a very useful purpose until safer, non-flammable agents, became available in the mid-1960s.

Historical interpretation

What was the connection between the researchers at the University of Alberta and Professor Leake? Upon reviewing Dr. Gelfan's curriculum vitae, he was born in Bogopol, Russia in 1903 and he became an American citizen in 1927, the same year in which he graduated from the University of California, with degrees in Arts and Biology. He worked as a research associate in that same institution in 1927 and 1928. Professor Leake joined the University of California in 1928, where he was charged with the task of organizing the Pharmacology Laboratory at that institution. Therefore, it is possible that Dr. Gelfan may have met Dr. Leake, or that he was familiar with his work at the University of California, as Dr. Leake was a very high profile pharmacologist in the United States at that time. Dr. Gelfan was subsequently appointed assistant professor of physiology and pharmacology at the University of Alberta in 1930. Dr. Gelfan left the University of Alberta in 1932, and subsequently, became Professor of Neurophysiology at New York Medical College. He died in New York in 1975.

Although he was an internist with a joint appointment in Therapeutics and Pharmacology at the University of Alberta, Dr. Irving Bell administered anesthetics at two major medical centres in Edmonton for many years leading up to World War II, and he was elected subsequently to honorary membership in the Canadian Anaesthetists' Society (as it was named at that time) (Figure 5). He died in Edmonton in 1953. Two years after his death, the Alberta Anaesthetists' Society erected a plaque in the foyer of The Old Medical Building in Edmonton, to commemorate this first use of DVE in humans (Figure 6).

Conclusions

In conclusion, Dr. Gelfan and Bell's early work was a brief practical study, typical of the uninhibited work of many of the pioneers in anesthesia, who willingly par-

D This information was mentioned in a publication by Dr. B. Finer (Br J Anaesth 1965; 37: 661–6) and Dr. Finer's source was courtesy of W. Hougs, Lundbeck, Copenhagen (no other reference provided).

ticipated as "guinea pigs" in their continuing search to advance the body of medical knowledge in the pharmacology of anesthetic agents. Their work provides inspiring examples of how Canadian researchers have quietly contributed to advances in anesthesia for many decades. Drs. Gelfan and Bell deserve considerable credit for taking that very important first step to evaluate the use of DVE in humans, as Dr. Bourne deserves credit for popularizing the use of this historically important inhaled anesthetic in clinical anesthesia, in Canada and the United States.

Acknowledgements

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