The First Use of Divinyl Ether in Humans

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Horace Wells (1815-1848)
The First Operation with Ether

(Painting by Robert C Hinckley. Oil on Canvas 8’ x 10’. Boston Medical Library 1893)
James Young Simpson-Chloroform
Ethyl Chloride
Ethylene

Chemical structure and bond angles:
- C-C bond angle: 121.3°
- C-H bond length: 108.7 pm
- C-C-H bond angle: 133.9 pm
The Evolution of Inhalation Anesthesia

Nitrous Oxide (N2O)
Ethylene (C2H4)
Cyclopropane (C3H6)
Xenon (Xe)

Di-Ethyl Ether (C2H5-O-C2H5)
Di-Vinyl Ether (C2H4-O-C2H4)
Ethyl-n-Propyl Ether
Ethyl-Methyl Ether (C2H5-O-CH3)
Methoxyflurane (CHCl2CF2-O-CH3)
Enflurane (CHFCICF2-O-CH3)
Isoflurane (CF3CHCl-O-CHF2)
Desflurane (CF3CHF-O-CHF2)
Sevoflurane (C3HF6-O-CH2F)

Chloroform (CHCl3)
Ethyl Chloride (C2H5Cl)
Trichlorethylene (CCl2CHCl)
Halothane (CF3CHClBr)
Pharmacological Manipulation

- $\text{CH}_2 = \text{CH}_2$ (Ethylene)
- $\text{CH}_3 - \text{CH}_2 - \text{O} - \text{CH}_2 - \text{CH}_3$ (Diethyl Ether)
- $\text{CH}_2 = \text{CH} - \text{O} - \text{CH} = \text{CH}_2$ (Divinyl Ether)

“Further study of this interesting series of agents is justified and cordially invited.”

## Physicochemical Properties of Inhalation Anesthetics

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From Leake’s essay in The History of Surgical Anesthesia by Thomas E Keys

Introductory Essay

this we attempted to cover as carefully as we could all factors of significance in the pharmacological appraisal of the new anesthetic agent. We had previously established ideal standards for the introduction of new drugs, and we were trying to live up to our own pronouncements!

My colleagues at the University of California Medical Center in San Francisco were not particularly impressed with our studies. We had demonstrations in the laboratory and there was courteous interest, but this was tempered by proper professional caution. Although the first surgical anesthesia with divinyl ether about it.

Meanwhile, our first reports had excited a number of scientists. Dr. Samuel Gelfan in Canada asked for the privilege of studying the effect of divinyl ether 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. In

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“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.”

- Gelfan and Bell

J Pharmacol Exp Therap
1933; 47: 1
Divinyl Ether

- Merck and Co - Vinethine 1935
- Rapid induction and recovery
- Very volatile
- Low incidence of Nausea & Vomiting
- Very useful for short procedures
- Expensive- 60 cents for 25 ml in 1935
- 25 ml of Sevoflurane costs $30 in 2008
New Anesthetic Is Reported to Medical Group

Divinyl Ether Found Most Effective After 2,200 Tests in Pennsylvania

Relaxes Muscles Better

Two Methods of Combating Poisoning Are Revealed

By a Staff Correspondent

PHILADELPHIA, Oct. 21.—A new form of anesthetic, divinyl ether, the closest approach yet found to the ideal anesthetic, was reported here today to the fifteenth annual Congress of Anesthesiologists, being held simultaneously with the annual Congress of the American College of Surgeons. Dr. Isidor S. Ravdin, professor of research surgery at the University of Pennsylvania, explained that the anesthetic is rapid in its action, and that it is more effective in inducing anesthesia in persons who are obese. It is also said to be less irritating to the respiratory tract and to produce a more satisfactory degree of relaxation of the muscle than other anesthetics.

Due to the affinity of the anesthetics for fat, obese persons are much harder to anesthetize than slim people, it was said. The anesthetic is distributed in the fats in the body almost as rapidly as it is administered and it is harder to remove it from these tissues, thus making it likely that fat persons will stay under the effects of an anesthetic longer once it does take effect. Slim persons respond to the anesthetic much more quickly and come out of its effects with equal rapidity, it was reported.

Wound Bacteria Killed

Dr. Frank L. Meleney, assistant professor of surgery at Columbia University, and Miss Balbina Johnson, reported that many of the severe infections in wounds were due to bacteria that could not live in oxygen, and that they had found a chemical compound, peroxide of zinc, which could be supplied to the wound and would release oxygen in sufficient quantities to prove fatal to the bacteria.

Half of the industrial establishments examined by the American College of Surgeons with respect to medical services available for employees have been approved, Dr. M. N. Newquist, of the college reported at the hospital standardization meeting.

Surveys have been made of 1,593 industrial plants, employing approximately 7,000,000.
April 3, 1987

Dear Roy:

In reply to your letter of 25 March, I am afraid I can't be of much help regarding the use of di-vinyl ether except to relate my first (and only) experience with it as a student observer.

I faintly remember the following incident. Wesley Bourne was late in arriving at the hospital (Queen Elizabeth) for the administration of an anesthetic for a minor operation under rectal anesthesiology. Patient appeared to be anesthetized until incision was made when she responded with strong muscular movement. Wesley withdrew a brown bottle and a handkerchief to supplement the anesthetic. Body movements ceased, operation was completed (1 & 1/2 hours) and recovery was rapid and without incident. Wesley said the anesthetic was di-vinyl ether which had been sent to him for clinical trial by Hans Molitor of Merck on the advice of Chauncey Leake. He continued to use it for obstetrical anesthesia at the Royal Victoria Maternity Hospital. Shortly thereafter he went to Montreal (1932) to begin a residency at the University of Wisconsin.

At the University of Wisconsin the anesthesiology department, under Dr. Waters, and the pharmacology department, under Dr. Sewers, were deeply involved in extending the Toronto initiated study of cyclopropane and, at their request, introduce it clinically. As a team member I had no experience with di-vinyl ether but remember a lengthy communication between Arthur Guedel and Ralph Waters regarding its place in clinical anesthesia. Chauncey Leake, a Wisconsin graduate and a highly regarded former teacher, who discovered di-vinyl ether, failed to interest the Wisconsin department in using it clinically because it failed to show the clinical promise compared to cyclopropane. At the University of California there was no interest in the clinical employment of any new anesthetic, however, Chauncey's close friend, Arthur Guedel, located in Southern California, spent time at the University of California where he worked with Chauncey on di-vinyl ether (dogs) and then used it in his private practice at Cedars of Lebanon Hospital in Los Angeles. When cyclopropane became available, Guedel employed it to the exclusion of di-vinyl ether. He said the discovery of cyclopropane "completely loused up the need for Vinetole."
Nevertheless, it is interesting to note the discovery of di-vinyl ether by Chauncey Leake (University of California), ethylene and cyclopropane by Henderson and Lucas (University of Toronto), failed to gain clinical appreciation in the schools of their birth.

Di-vinyl ether was prepared entirely on theoretical chemical structural grounds to design an agent combining the pleasant smell and induction speed of chloroform with the safety of ether.

Fluothane (Ferguson) at I.C.I. is the only newer anesthetic similarly planned.

The Guedel Center has all the correspondence between Guedel and Waters and I believe there are many "off the cuff" references to di-vinyl ether contained in that exchange.

Although I looked upon Chauncey Leake and Arthur Guedel as medical giants in pharmacology and anesthesia, respectfully, I failed to see a place for di-vinyl ether as instructional material when I entered Stanford in 1937.

Ron Stephens might be more helpful since, I believe, he used di-vinyl ether in obstetrics before using the non-flammable trichlorethylene.

As one of the first researchers to use the Guedel Center, I think you will find the new folder and enclosed Bulletin interesting.

All the best,

Bill

WILLIAM B. NEFF, M.D.
Chairman
CSA Liaison-Guedel Memorial Anesthesia Center
for induction anesthesia
there's no "fighting" it
VINETHENE®

Patients rarely fight induction with VINETHENE. Its action is rapid and smooth, seldom causing excitement or nausea. Used prior to maintenance with ether, VINETHENE largely spares the patient from irritation to mucous membranes. Also valuable in short operative procedures by itself and as a supplement to less potent agents such as ethylene or nitrous oxide. VINETHENE has been used with confidence for well over 25 years.

SUPPLIED: in 10-cc., 25-cc., 50-cc, and 75-cc bottles, each with adjustable plastic dropper cap.

VINETHENE is a trademark of Merck & Co., Inc.

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Division of Merck & Co., Inc., Philadelphia 1, Pa.
1930s Advertisements

According to repeated nationwide surveys, More Doctors Smoke CAMELS than any other cigarette!

Doctors in every branch of medicine were asked, “What cigarette do you smoke?” The brand named most was Camel.

You’ll enjoy Camel’s rich taste, no burn, and filling. Camel’s mildness, pack, after pack, and a flavor unmatched by any other cigarette. Make this memorable test: Smoke one Camel and 40 days and you will never again smoke. You’ll see how enjoyable a cigarette can be.

The Doctors’ Choice is America’s Choice!

For 30 days, test Camels in your “J-Zone” (V for Throat, V for Taste).

www.StrangeCosmos.com
Connection between Gelfan and Leake
Dr. Irving Bell
Commemoration

DIVINYL ETHER
WAS FIRST ADMINISTERED TO MAN
BY
DR. SAMUEL GELFAN
AND
DR. IRVING R. BELL
IN THIS BUILDING 1932
ALBERTA ANAESTHETISTS’ SOCIETY
Acknowledgements

- Dr. Roy Humble (Retired Anesthetist at U of A)
- The Board and Staff of the WLM
- Archives, Merck & Co., Inc.
Mr. President, Members of the Academy, Ladies and Gentlemen. Thank you very much for inviting me to speak at the Academy this year. The title of my presentation is The first use of Divinyl Ether in humans. This event took place in the 1932.
The discovery of anesthesia was a very contentious issue and several individuals have claimed to be the first. Today I am going to talk about a pivotal event that led to the widespread use of anesthesia.

Horace Wells was a Dentist from Hartford, Connecticut who successfully anesthetized a number of patients for dental extraction with Nitrous Oxide between December 1844 and February 1845, but a demonstration of nitrous oxide anesthesia at the MGH was so decidedly a failure that his method was discredited. Well's own explanation for this failure was that the inhalation was interrupted when the gas had barely begun to take effect on the patient—an error of judgement on Well's part probably due to his being flustered by the presence of a highly critical audience. Several expressed their opinion that it was a “humbug” affair. Wells actually used a bellows with a wooden tube which he stuck in the patient's mouth and pinched off the nose for more effective inhalation. However he was so anxious to demonstrate his technique to his very distinguished audience that he did not wait long enough for the nitrous to work and the patient screamed out during the dental extraction. Actually to this very day life in the goldfish bowl is the plight of ever anesthetist. Unlike our surgical colleagues who frequently work in dark anatomic recesses, our actions are there for everyone to see and even 180 odd years after the discovery of anesthesia we first of all do not know how anesthesia works nor do we know for sure when our patients are completely anesthetized. This is not to say of course that patients remember. In fact it is very rare that a patient will remember however the body does respond to noxious stimuli with increases in blood pressure and heart rate and even withdrawal in some cases. I don’t know if any of you saw the recent movie called ‘Awake’
This is a very famous painting entitled The first Operation with Ether. That is not true but this was the first public demonstration of Etherization at the MGH. This is one of the most popular paintings in Medical history.
James Young Simpson Professor of Midwifery at Edinburgh introduced the use of Chloroform into anesthesia practice in 1847. Chloroform had some major advantages over ether. 1. it was non-explosive. 2. It had a rapid onset. It was pleasant to inhale. It also had some major disadvantages one of them being sudden death and actually the first reported anesthetic death occurred with chloroform and it occurred in a young girl named Hannah Greener undergoing a relatively minor procedure that had not even begun. Despite some drawbacks with chloroform it's use continued even up to the 1950s. Therefore for more 100 years Ether and Chloroform were the main stay of inhalation anesthesia.
Ethyl chloride produced from ethanol and HCL is a general anesthetic and was tested as a GA as early as 1847 but it never really evolved as a GA. It is used on the sports fields to quell the pain various bumps and bruises. In my reading I discovered that it was a recreational drug referred to as Duster and it is used to enhance sexual activity. In Brazil it is taken during Carnaval parades and is referred to as lança perfume.
Was also a general anesthetic but obviously not a very good one.
Let me briefly review this chart of the Evolution of Inhalation anesthesia. The only agents available at that time were DEE, Chloroform, Ethyl chloride, Ethylene and of course nitrous oxide. Cyclopropane was being tested at that time and the science of Pharmacology was beginning to flourish.
Chauncey Leake was one of leading Pharmacologists in the U.S. at that time. There was a great deal of interest among pharmacologists in the relationship between chemical constitution and biological action. Leake was particularly interested in the action of anesthetics. He predicted that the unsaturated carbon atom of ethylene would enhance the anesthetic properties of ether if it was part of the ether molecule.
Using an impure sample of DVE Leake and his colleague Chen tested this new compound in mice and demonstrated that it had anesthetic properties that were as good as if not better than DEE.
"Further study of this interesting series of agents is justified and cordially invited."


Leake published this preliminary report and concluded his paper by saying Further study etc
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This may be a good time to discuss the physico-chemical properties of DVE and to compare them with DEE and just for completeness sake I have added in halothane and desflurane. It is obvious from this comparison that DEE is the odd man out. It is interesting to note the similarities between DVE and Desflurane for example. The bottom line is that DVE is much more insoluble in blood than DEE and therefore one can predict that the onset of action with DVE would be much faster.
In Leakes introductory essay in Thomas Keys’ book entitled the history of surgical anesthesia, he mentions that his colleagues at the U of C were not that interested in what he was doing with anesthetics, but also mentions that some Canadian scientists were interested and he mentioned Dr. Gelfan in particular and he arranged for samples of DVE to be sent to him and this is how the Canadian scientists became involved. So this is when the Canadian investigators became involved in this endeavor. The investigators names were Samuel Gelfan and Irving Bell both from the University of Alberta.
Open drop DVE was administered by Dr Bell to his colleague Samuel Gelfan for 10 minutes in this laboratory at the University of Alberta in 1932. This was in fact the first time DVE was used in a human.

Bell described the induction as smooth, prompt and even, with no signs of excitement or struggling. Two minutes after removal of the mask Gelfan had fully recovered. Several days later Gelfan agreed to inhale DVE again. This time the trial lasted for 18 minutes. Bell tested the depth of anesthesia by applying an electrical current to the foot and leg. Upon withdrawal of the agent Gelfan recovered rapidly with complete absence of nausea and vomiting. After being the guinea pig for two sessions, Gelfan was keen to see the effects of this new agent in a more objective way. A colleague named Dr. Winifred Hughes happened to be walking in the corridor outside the laboratory when she was invited to volunteer for the 3rd successful administration of DVE. It is noteworthy that all three trials of this new anesthetic were carried out within 2 or 3 hours of a full meal and both subjects returned to their duties shortly afterwards.
Gelfan and Bell published their report of DVE in humans in the same issue of the Journal that Leake et al published their animal findings. Gelfan and Bell concluded their paper with the following remarks

“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.”

- Gelfan and Bell
J Pharmacol Exp Therap
1933; 47:1
Merck and Co commerically produced DVE for clinical use in 1935 and it was marketed in the US under the name of Vinethine. It was characterized by a rapid onset and offset. It was a very volatile substance and was quite pleasant to inhale. One of the hallmarks of this agent was the low incidence of nausea and vomiting. It was very useful for short procedures e.g. Dental, Obstetrics and pediatrics. I contacted Merck Archives to find out how much it cost and they provided documentary evidence that it cost 60 cents for 25 ml. It was far more difficult to find out how much Sevoflurane cost. I contacted Abbott and they would not release the information unless I had purchased Sevoflurane from them. So I had to go underground to get that information. Even with inflation over 70 odd years this is a huge increase in the price of inhalation anesthesia.
You might be interested in a newspaper report in the New York Herald Tribune in 1936 about DVE. In the first paragraph it said that DVE was the closest approach yet to the ideal anesthetic.
This is a copy of a letter that my colleague Roy Humble received from William Neff. Dr. Humble was interested in finding out more about divinyl ether and wrote to Neff in 1987. On this first page of Neff’s response, he mentions Guedel’s experience with DVE and how the discovery of cyclopropane spoiled the potential success of DVE as an inhalation agent. The actual words used by Guedel were that the discovery of cyclopropane “completely loused up the need for Vinethine.”
In the second page of the letter from Neff I would like to draw your attention to the first paragraph which I thought was very interesting
DVE was used for close to 40 years right up to the time Halothane was introduced. This is a copy of an advertisement in A & A in 1960
This is an example of the kind of advertisements you might have seen in those days. Some of you might even recognize some of the doctors in this ad. However I’m not here to talk about cigarette smoking today. Instead I’d like to talk about other types of inhalants.
I was curious to know if there was any connection between Gelfan and Leake and I discovered that there were both Faculty Members at the University of California in 1928 and very likely met there before Gelfan joined the FOM at the University of Alberta. Gelfan left the U of A in 1932 and went to New York College where he became Professor Neurobiology and died in 1975.
Irving Bell on the other hand remained at the U of A. He was an internist with a joint appointment in Pharmacology and Therapeutics. He administered anesthesia at the 2 major teaching hospitals in Edmonton up to the beginning of WW 2. He was invited to become an honorary member of the CAS in 1953 and he died shortly after that.
This plaque was erected in the foyer of this building in 1955 by the Alberta Anaesthetists’ Society and over time with changing administrations and Departments the plaque was displaced and is now safely in my possession. The U of A celebrates its 100th anniversary this year so I think this is an appropriate time to celebrate this event which has now become part of the heritage of Canadian Anesthesia.
Before I finish I would like to acknowledge Dr. Roy Humble who told me part of this story. I would like to acknowledge the BOD for allowing me to serve as a Paul Wood fellow at the WLM where I researched this topic and also the Patrick Sim and the staff at WLM for all their help whilst I was there.

Finally I would like to acknowledge Archives, Merck & Co., Inc. for the information they provided.