Arthur E. Guedel Memorial Anesthesia Center

Dr. Chauncey Leake and the Development of Divinyl Oxide from Bench to Bedside

By Matthew J. Mazurek, M.D.

Chauncey Leake, Ph.D., spent much of his professional career as a pharmacologist investigating anesthetic agents, and, in this capacity, he collaborated with Arthur E. Guedel on a number of projects. After the death of Arthur E. Guedel in 1956, Leake was one of the individuals who helped organize a West Coast Anesthesia History Museum, and he suggested the name of the museum that is now the Arthur E. Guedel Memorial Anesthesia Center. Leake was also a historian and collector. The Kalmanovitz Library on Parnassus Avenue (UCSF) has a large collection of Leake's papers and books. One notable example is a signed copy of Humphrey Davy's book (1800), wherein Davy described the analgesic properties of nitrous oxide.

While an anesthesia resident at UCSF, Matthew J. Mazurek, M.D., wrote a short essay on Chauncey Leake to compete in the essay contest of the Sixth International Symposium on the History of Anaesthesia. For his essay and oral presentation, he won third prize and was presented with an award at the last meeting of the Symposium, held in Cambridge, England, in September 2005. The following essay is an abbreviated summary of his presentation. If residents are interested in the history of anesthesia, there are cash prizes for top-rated essays from the Anesthesia History Association and from the International Symposium on the History of Anaesthesia.

—Merlin D. Larson, Coordinating Editor of the Guedel Section of the CSA Bulletin

The first anesthetics were discovered through random trials of experimental inhalation in humans with little or no regard for chemical structure or long-term toxicity. By the 1930s, however, it was clear that toxic side effects, explosions and hypoxic mixtures from the available agents posed significant problems and new directions were needed. An approach that succeeded eventually was the introduction of pharmaceutical chemistry into the quest for new agents, a process that began in the 1930s and continues today. Through an analysis of molecular structure and synthesis of potential agents, we now have safe anesthetics with low toxicities and favorable pharmacokinetics.

One of the central figures in introducing new anesthetics based upon an analysis of chemical structure was Chauncey Leake, Ph.D., a pharmacologist who founded the first Department of Pharmacology at the University of California, San Francisco in 1928. (Figure 1) Leake was not a physician, but during his career he developed an interest in the pharmacology of anesthesia. His research demanded extensive correspondence with the leading anesthesiologists of his

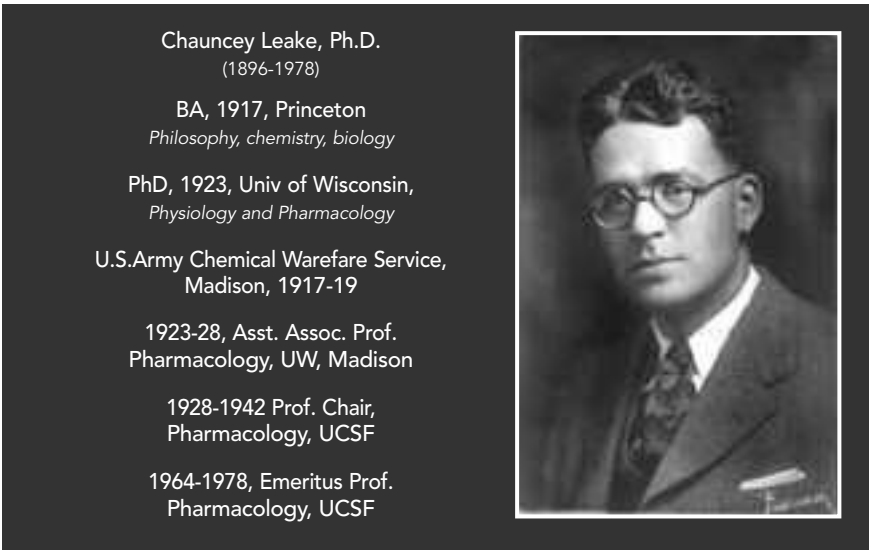

Figure 1. Chauncey Leake, Ph.D.
Courtesy of University of California, San Francisco.

era, and these records provide a unique historical repository to examine the origins of our specialty.

In 1930 Leake and Mei-Yu Chen surmised that if a new compound—divinyl oxide (divinyl ether, vinyl oxide, vinyl ether, and Vinethene®)—could be synthesized, it would combine the anesthetic properties of ether and ethylene, thereby providing a more desirable agent. Their idea was that if an unsaturated carbon atom, present in ethylene, was introduced into the ether molecule, it would improve its anesthetic properties. (Figure 2)

Ethylene: CH2= CH2
Ether: CH2CH3-O-CH2CH3
Divinyl Oxide: CH2=CH-O-CH=CH2

Figure 2. The Chemical Structure of Ethylene, Ether, and Divinyl Oxide Compared

Leake's pivotal role in the development of divinyl oxide had its roots planted firmly in his work with ether and ethylene at the University of Wisconsin, Madison. In a personal interview with Leake in 1977, he states:

> When I was at Wisconsin I had worked on ether, among other things; also on a new anesthetic agent, namely ethylene. Now ethylene has a double-bond in the carbons; ether does not. Ethylene is an excellent anesthetic agent, and is better than nitrous oxide, and has certain advantages over ether. So, I thought: Why don't we combine the chemical configuration of the double-bond carbon? Well, there wasn't any such thing at the time.

Leake, however, was not the first to suggest synthesis of divinyl oxide. It had been synthesized in very small, impure quantities by several organic chemists. With the seeds for this potentially new anesthetic planted firmly in his mind before he left Wisconsin, Leake then had the challenge of obtaining divinyl oxide for study.

After Leake's move to establish the new Department of Pharmacology at the University of California, San Francisco, it was logical for him to approach the organic chemists at the University of California, Berkeley to synthesize divinyl oxide. Leake's colleagues at Berkeley were unable to synthesize divinyl oxide, and he finally received some impure samples from Randolph Major, a graduate chemistry student working with Professor Lauder Jones at Princeton University.

After obtaining the samples from Major, Leake and Chen studied it briefly in mice and published their report in 1930 on its anesthetic properties, concluding with the statement, "Further study of this interesting series of agents is justified and is cordially invited." Leake then collaborated with Arthur Guedel on further work with animals that was published in 1932.

Although Guedel did not seem interested in using the drug on humans, Chauncey Leake and Ralph Waters were close personal friends, so it comes as no surprise that Leake asked Waters to study divinyl oxide. In a letter to Waters dated November 14, 1931, Leake states:

> As you probably know we have been fooling with divinyl oxide…We obtained a very pure sample of this substance from Dr. Randolph T. Major…While it is inflammable like ether, it is much more rapid in its action and has apparently a wider margin of safety than ether. It does not cause the salivation or the mucous flow so characteristic of ether inhalation. It seemingly has much less effect on the metabolic functions of the body ha [sic] reflected in pH or blood gas changes as any of the common anesthetic agents. In other words, I am altogether convinced it is a damn good anesthetic. How would you like to study a little of it in dogs, maybe to check up on me, and then try it out in the hospital?

Waters received his first supplies of divinyl oxide from Major and immediately had trouble with the agent while attempting to anesthetize a few dogs. One suffered from cardiac arrest after much salivation, and the other was successfully resuscitated. Correspondence between Waters and Leake led to the mutual conclusion that the samples that Waters obtained were contaminated with impurities, either formaldehyde or formic acid.

In January 1933, Samuel Gelfan and Irving Bell, anesthesiologists from the University of Alberta, Canada, published a paper on the anesthetic action of divinyl oxide in humans. They were extremely fortunate to have **pure** divinyl oxide to use. This brief study was published in the *Journal of Experimental Pharmacology and Therapeutics* and describes the anesthetic experience of Samuel Gelfan as he was administered the agent with the open-drop technique.

According to Leake, Dr. Mary Botsford, chief anesthesiologist at the University of California, San Francisco, was the first to administer divinyl oxide for a clinical case. This first use of the agent in the operating room was for a hysterectomy in early January 1932.

Unfortunately, the political climate at the University of California undermined Leake's efforts to perform a large clinical study, and many of the anesthetists at the University of California were not impressed with divinyl oxide. This must have disappointed Leake, as it was studied extensively at other institutions.

Leake's divinyl oxide had some success, but questions arose regarding liver toxicity, and there were other concerns about purity of the agent during storage. Several colleagues were blunt in their assessment that it was not a good anesthetic and could not be recommended. Of course, the agent suffered from the flammability problem common to that era.

However, Leake and Chen made important contributions in their approach to the development of safer agents. With their analytic methods, they paved the way for others who used chemical synthetic methods to fluorinate the hydrocarbon molecule and produce nonflammable agents.

(References available on request)

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