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SPECIAL ARTICLE

From the *Journal* archives: Early clinical evaluation of enflurane: the cost of progress

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Editors' Note: Classics Revisited

Key Articles from the *Canadian Journal of Anesthesia* Archives: 1954-2013

As part of the *Journal's* 60th anniversary Diamond Jubilee Celebration, a number of seminal articles from the *Journal* archives are highlighted in the *Journal's* 61st printed volume and online at: www.springer.com/12630. The following article was selected on the basis of its novelty at the time of publication, its scientific merit, and its overall importance to clinical practice: *Virtue RW, Lund LO, Phelps M Jr, Vogel JH, Beckwitt H, Heron M*. Difluoromethyl 1,1,2-trifluoro-2-chloroethyl ether as an anaesthetic agent: results with dogs, and a preliminary note on observations with man. Can Anaesth Soc J 1966; 13: 233-41. Dr. Orlando Hung provides expert commentary on this early clinical evaluation of enflurane.

Hilary P. Grocott MD, Editor-in-Chief
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Summary

Virtue RW, Lund LO, Phelps M Jr, Vogel JH, Beckwitt H, Heron M. Difluoromethyl 1,1,2-trifluoro-2-chloroethyl ether as an anaesthetic agent: results with dogs, and a preliminary note on observations with man. Can Anaesth Soc J 1966; 13: 233-41.

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While a fluorinated compound, such as halothane, had substantial advantages over the earlier volatile agents (ether and chloroform), cardiovascular instability associated with the use of halothane was a major concern. Difluoromethyl 1,1,2-trifluoro-2-chloroethyl ether (enflurane) was developed in the early 1960s with some promising anesthetic properties. The goal of a series of experiments conducted by R.W. Virtue *et al*'s research group was to determine the efficacy and safety of enflurane for general anesthesia in animals and humans. The first set of experiments involved investigating the anesthetic effects of enflurane and the resulting physiological changes in dogs, including organ toxicity and biochemical alterations following enflurane anesthesia in some of these dogs. In a separate set of experiments using four dogs, the comparative anesthetic effects (including enzyme changes) of halothane, methoxyflurane, fluroxene, and enflurane were determined using a Latin square design. After obtaining favourable results from animal experimentation, physiological and biochemical changes under enflurane anesthesia were examined in eight healthy human volunteers. Enflurane was then administered to eleven surgical patients for a variety of orthopedic and gynecological procedures. From the results of this series of experiments, the investigators concluded that enflurane had a potency of about half that of halothane and that enflurane could produce smooth anesthesia without salivation, irritation, or nausea in dogs. While enflurane did not appear to have any significant changes on cardiovascular, renal, or liver functions in dogs, 19% of the dogs under enflurane anesthesia developed ventricular fibrillation following an intravenous bolus dose of epinephrine. The anesthetic and analgesic effects of enflurane in humans appeared to be comparable with that of halothane. Unfortunately, three of

eight volunteers were nauseated for a short time during recovery.

Commentary

I did not have the nerve to tell my wife that I had paid $5,000 for my first cellphone in 1990. It was the new Motorola "Flip Phone". I had just finished my research fellowship in California. Money was very tight, so this would be an outrageous purchase. Today, a top-of-the-line smartphone with a quad-core CPU, stunning display screen, and high-resolution camera can easily be purchased for $599 or less. Over time, as technology has advanced, costs have decreased. In contrast, medical advances and discoveries that have led to improved health outcomes have been met with huge escalations in cost.

In an effort to highlight the most significant medical advances, the *British Medical Journal* (BMJ) conducted a readership survey in 2007 to gather opinions as to the most important medical milestones since the BMJ was first published in 1840.[2] The summary of the responses from more than 11,300 clinician and layperson readers worldwide showed that the introduction of clean water and sewage disposal (sanitation) topped the list (15.8% of the votes), followed closely by the discovery of antibiotics (15%) and the development of anesthesia (14%). Despite the fact that Edwin Chadwick first identified the necessity of sewage disposal and piping clean water into homes, John Snow was considered "The original champion of the sanitary evolution" because of his discovery of the source of the 1854 cholera outbreak in London.[2]

While the identity of the founding father(s) of anesthesia remains controversial, it is accepted that John Snow was certainly one of our pioneers. He published two books about inhalational anesthetics.[3,4] More importantly, he made anesthesia history on April 7, 1853 when Queen Victoria asked him to administer chloroform analgesia for the delivery of her eighth child, Prince Leopold.[5] Bestowed with the blessing of the Queen, John Snow positioned obstetrical anesthesia in history, established a benchmark in medicine, and challenged religious beliefs enshrining pain in childbirth as the will of God! In another survey conducted by *Hospital Doctor Journal* in March 2003, John Snow was voted the "greatest doctor" of all time; Hippocrates came in second.

Despite the limitations of surveys and polls, these findings suggest that anesthesia as a discipline and one of its founding fathers, John Snow, made the most significant contributions to the advancement of medicine and patient care in the last two centuries. We are proud of the many discoveries and advances promulgated by anesthesiologists and the critical role that scientific and scholarly publishing, including the *Canadian Journal of Anesthesia* (the *Journal*), has played in disseminating these discoveries to practitioners and translating knowledge to practice.

As the *Journal* approaches its 60th year of publication, its Diamond Jubilee (1954-2014), it is fitting to recall the many seminal works published in its pages which have shaped the modern practice of anesthesia.

The discovery of ether and other vapours has largely shaped the delivery of anesthesia. From 1946-1959, three fluorinated compounds, fluoroxene, halothane, and methoxyflurane, were introduced.[6] The next generation of promising halogenated ethers (enflurane, isoflurane, sevoflurane, and desflurane) developed during the 1960s and the early 1970s moved the discipline to the modern frontiers of inhalational anesthesia. In 1966, the *Journal* (formerly known as the Canadian Anaesthetists' Society Journal) published a landmark paper by Dr. R.W. Virtue and his research group regarding the efficacy and safety of enflurane.[1] Virtue's work was the first published report on the clinical use of enflurane and likely provided the basis for the approval of the use of enflurane in the USA in 1972. While the use of enflurane was popular during the 1970s, problems related to enflurane anesthesia arose following its introduction. These drawbacks included the fluoride metabolite which might be damaging to the kidneys,[7,8] the potential for hepatotoxicity,[9-11] and the possibility of seizures.[12,13] Interestingly, apart from the "spontaneous twitches" observed in both the animal and human experiments, there were no signs of renal or liver toxicity reported in Virtue's series of experiments. One could well ask how the investigators could miss these adverse effects of enflurane, and why the American Food and Drug Administration (FDA) approved the clinical use of enflurane. Both circumstances probably came about due to a combination of factors, including limitations of the study designs of these experiments, lack of a rigorous peer review process, and a less than ideal regulatory approval process. With regard to Virtue's study, there were no well-defined outcome measurements for these experiments. For example, the investigators did not measure physiological changes at specific end points, such as minimal alveolar concentration or percentage of enflurane. While it was reported that there were no significant hemodynamic changes under enflurane anesthesia, there was no integration of precise hemodynamic measurements within the context of a spectrum of anesthetic depth. Furthermore, there was no estimation of sample size in Virtue's experiments. In fact, some of the tissue toxicity studies involved only two dogs. The most important difference between studies conducted during the 1960s compared with present day studies is the monumental evolution in the understanding and acceptance of clinical trials

methodology, reporting guidelines, and a more advanced editorial peer review process. It is uncertain that the protocol for Virtue's study would have been approved by today's institutional research ethics board, and the scientific scrutiny of the current peer review process would have mandated more detailed description of various aspects of the study methodology and results.

Over the last 60 years, scientific communities have improved the processes of evaluating and disseminating scientific knowledge. The editorial peer review process is one such example, though it can be argued that the peer review process is not without its flaws and can be overly prohibitive. Notably, many discoveries were "casualties" of the peer review process of the journal, *Nature*,[14] but later they merited the Nobel Prize. Nonetheless, the peer review process is an accepted standard in judging scientific evidence, though it is still "a work in progress".[15]

Institutional research ethics board (REB) review is another important development in scientific investigations. Research ethics boards were established in the wake of human rights abuses perpetrated by Nazi physicians during the Second World War and by the United States Public Health Service in the Tuskegee Syphilis Study.[16] These infamous studies spearheaded the development of the Nuremberg Codes, the related Declaration of Helsinki, and the subsequent adoption of the first and second iterations of the Canadian Tri-Council Policy Statement regarding ethical conduct for human research in academic institutions. It would not have been possible in today's research environment for R.W. Virtue's research group to have conducted the aforementioned human studies as they did not indicate that they had obtained REB approval or written informed consent from volunteers and patients.

As I reflect on this research, it is not my intent to criticize some of the limitations of the research conducted by Virtue *et al.*'s research group or the decision of the *Journal* to publish the study. Rather, I am reminding readers that the research communities have made significant progress in improving the quality and integrity of the scientific research and the Journals that publish those discoveries.

One of the downsides of these advances is the cost associated with new scientific progress. According to a report by Forbes,[A] the average development cost incurred by a major pharmaceutical company for a new drug is at least $4 billion and can reach as much as $11 billion. Arguably, the numbers vary depending on how the research and development data are interpreted and manipulated. Nevertheless, it is clear that the cost of drug development has increased dramatically over the years.

While the increasing costs of medical discovery are multifactorial, it is the price we pay for high-quality research, high standards of scientific scrutiny, and the laborious drug approval processes. The costs of funding these developments are eventually passed on to the consumer. Roy reported that the pharmaceutical industry spent the equivalent of $100 million in today's dollars for research and development of the average drug approved by the FDA in 1975.[B] By 1987, the figure had tripled to $300 million, and by 2005, the figure had more than quadrupled to $1.3 billion. Reforming this drug approval process is desperately needed to bring down the costs of modern scientific pharmaceutical research and to expedite the delivery of safe and effective medications to those who need them.

Let me give you a real-life example. Some years ago, I was working on the inhaled liposomal fentanyl delivery system.[C,17] The FDA insisted that we conduct a 24-hr Holter monitor study with healthy volunteers to ensure that this inhaled fentanyl delivery system did not cause QT prolongation, even though fentanyl had been used clinically since the 1960s and had never been shown to affect cardiac impulse conduction. Such unscientific demands impose unnecessary costs and delays on new drug development.

So, how can the scientific community assist in containing the cost of medical discoveries? Clearly, we need to continue to embrace high-quality research with sound methodology and study design as well as to employ the peer review process to examine and disseminate accurate scientific information. There is no going back! This is a minimum standard.

While it may not be the only way to contain the cost, reforming the drug approval process is an important beginning. In my view, the academic community, industry, and regulatory bodies need to work closely together to reform the drug approval process while maintaining the balance between ethics, safety, liability, and risk when it comes to new drug discovery and its clinical applications.

Let's go back to the first cellphone I purchased almost 25 years ago. Was it really worth $5,000? My wife might not be convinced. But in 1990, I thought it was worth every

[A] *Herper M*. The Truly Staggering Cost Of Inventing New Drugs. Forbes 2012 Feb 10, 2012. Available from URL: http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/ (accessed August 2013).

[B] *Roy AS*. Stifling New Cures: The True Cost of Lengthy Clinical Drug Trials. Manhattan Institute For Policy Research; 2012 April 2013. Available from URL: http://www.manhattan-institute.org/html/fda_05.htm (accessed August 2013).

[C] *Mezei M, Hung OR*. Pain Management with liposome-encapsulated analgesic drugs. US Patent Office 1995; 5451408. Available from URL: http://www.directorypatent.com/US/5451408.html (accessed August 2013).

penny because there were no alternatives. Then again, even by today's standards, it was an outrageous price. Time advances in technology, competition, and the marketplace have conspired to reduce the cost.

It is my contention that we cannot judge the cost of progress without consideration of the context of time, i.e., how events evolve and conspire over time, how unplanned and seemingly unrelated factors can affect cost. And then, like any responsible industry, we need to look back to see how we can improve processes, connections, and communications with a view to manage things better, more efficiently, and with reduced risks and costs.

In 1966, Virtue *et al.* reported a series of carefully conducted experiments to show the safety and efficacy of enflurane in a manner that was perfectly acceptable according to the standards of the 1960s. Forty-eight years later, our methodology and standards related to the conduct and reporting of clinical trials and the ethics and peer review processes have advanced considerably, and these should not be abandoned. Nevertheless, the trajectory of the cost of progress in medicine is out of control and we owe it to ourselves, to our profession, and to our descendants to reverse this trajectory. While we rightfully accept our current research standards, we must also accept our responsibility to take the necessary corrective action in our roles as scientists and clinician-scientists. If we do nothing, how will history judge us?

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