John (Iain) Glen Wins 2018 Lasker Prize for Development of Propofol

An Award for All of Anesthesiology

Margaret Wood, M.B., Ch.B., F.R.C.A., Ron Stark, M.D., Ph.D., F.R.C.P.

ON September 11, 2018, the Lasker Foundation announced the award recipients for 2018, with Iain Glen named winner of the Clinical Medical Research Award for his central role in the development of propofol. The Lasker Clinical Medical Research Award (www.laskerfoundation.org) is awarded annually to recognize individuals who have made innovative contributions to medical science that have improved the lives of many thousands of people. The Albert and Mary Lasker Foundation has made the awards since 1945 recognizing the most important discoveries in medical science, such that the awards are frequently described as "America's Nobels." Many Lasker recipients have subsequently received Nobel Prizes. It was our honor to nominate Iain Glen for this year's award in recognition of the vast number of patients who have benefited from the use of propofol.

When one of us (M.W.) graduated from medical school in 1970 and started specialty training in anesthesiology, thiopental was the intravenous anesthetic induction agent of choice, maintenance of anesthesia was with an inhalation anesthetic agent, and a frequent specialty board examination question was to discuss the relative complications of intravenous anesthetic induction agents. I (M.W.) vividly remember, as a young trainee, anesthetizing a patient for a repeat incision and drainage of a breast abscess and electing to administer *Althesin* for induction of anesthesia. Althesin was a mixture of two water-insoluble steroids—alphaxalone and alphadolone—that were solubilized in Cremophor EL. Immediately after administration, my patient became hypotensive and developed severe bronchospasm. Although my patient fully recovered, additional such anaphylactic reactions to Althesin eventually resulted in its removal from the market. Propanidid, another induction agent solubilized in Cremophor EL, was also withdrawn following the incidence of anaphylactoid reactions, although at the time, the relative contribution to the reaction of the drug itself or the Cremophor EL was hotly debated. In the 1970s, Dr. Glen, working at ICI Pharmaceuticals in Alderly Park, Cheshire, England, studied a large series of compounds to identify those with desirable anesthetic and hypnotic properties, eventually selecting 2,6-diisopropylphenol (propofol first tested on May 23, 1973)

to progress.[1] He chose propofol because of the characteristics that subsequently made it so widely used—limited effects on both the respiratory and cardiovascular system, rapid and complete recovery after administration, and lack of accumulation after multiple doses.[2] However, propofol is an oil and therefore, solubilization—a problem that others had tried to solve by solubilizing previous novel induction agents in Cremophor EL—was a problem. Solving this led to a more than 10-yr delay before the new agent could be introduced into anesthetic practice. It was initially hoped, and against Dr. Glen's advice, that propofol could be formulated in Cremophor EL. After clinical studies in 1,000 patients made it clear that the Cremophor EL formulation caused anaphylaxis, the clinical trials were stopped. At this stage the whole project might have been shelved and we would still be using thiopental in 2018. However, impressed by the promising clinical efficacy, Dr. Glen persuaded the company's management to continue the search for a formulation that would be safe. Dr. Glen was able to show that an emulsion formulation containing soybean oil and purified egg lecithin did not

Image: Ellen Jaffe.

This article has an audio podcast.

Accepted for publication September 14, 2018. From the Department of Anesthesiology, Columbia University, New York, New York (M.W.); and the Division of Applied Medicine, University of Aberdeen, Aberdeen, Scotland (R.S.).

 Anesthesiology 2018; 129:1055-6

<zdoi;10.1097/ALN.0000000000002481>

produce the anaphylaxis-like reaction in pigs—a species that had shown anaphylaxis-like reactions to Cremophor EL.[3,4] Thus, the "milky white" formulation that we know today was born. The clinical evaluation of the emulsion formulation of propofol began in 1983, and regulatory approvals for induction and short-term maintenance of anesthesia were received in 1986. Clinical anesthesiologists quickly recognized the potential for this new drug, and following clinical trials in a myriad of settings, subsequent approvals broadened the use of propofol to its ubiquitous use today. The successful development of propofol, like so many projects in life, required a visionary committed individual who was able to "stick with" the project in the face of challenges that frequently threatened to sink the project.

As is often the case, the development of one paradigm-changing discovery (propofol) made possible multiple other discoveries and innovations, which, though apparently independent, required the first innovation for their implementation and, importantly, could not have occurred without the first. The explosion of imaging technology in the 1980s and its subsequent widespread adoption in medical imaging was made possible by the ability to use propofol-induced sedation for diagnostic and therapeutic radiologic procedures; many of these studies would not have been possible without propofol. Of particular importance is the role that propofol has had in the safe use of imaging studies in young children. Such studies often require prolonged immobility for adequate imaging, and became possible in the large number of children undergoing such imaging only after propofol became available. The administration of propofol, using techniques developed by Dr. Glen, has saved and improved countless patient lives. In the procedural arena, screening colonoscopy and cataract extraction have a huge impact on the quality of life…and propofol is a major anesthetic for these two frequently performed procedures, allowing not only a reduction in patient morbidity and mortality but also an increased volume of procedures to be performed per session—improving patient access to life-enhancing procedures.

An additional impact of Dr. Glen's development of propofol is illustrated by the laryngeal mask airway, which was introduced by Dr. Archie Brain in 1983,[5] with the first commercial laryngeal mask airway made available in the United Kingdom in 1987. The laryngeal mask airway is a device that provides excellent airway patency, protects the airway, and has in large part replaced mask/inhalational anesthesia. When the airway cannot be secured due to difficulty in intubating the trachea, the laryngeal mask airway allows the patient to be rescued. However, the laryngeal mask airway could never have been introduced or used with only intravenous barbiturate agents available as anesthetic induction agents. It was indeed serendipitous that both propofol and the laryngeal mask airway appeared on the scene at the same time in the mid-1980s. Propofol, with its special pharmacodynamic properties, allowed its safe and efficient use.

Propofol has revolutionized anesthesia throughout the world and affected countless patient lives. In the developed world, almost every person who undergoes a surgical procedure, screening colonoscopy, or complex imaging study may receive propofol—meaning that most of us have received, or will receive, propofol at some point in our lives. All of those who have undergone procedures—surgical, imaging, and screening—in the modern era have received propofol, perhaps without recognizing the enormous impact its discovery has had on medicine and the public's health. This impact was made possible by Dr. Glen's vision in recognizing the potential impact and importance of developing a novel anesthetic such as propofol. There are few families who have not benefitted from Dr. Glen's discovery. In spite of the challenges, it was Dr. Glen's vision, creativity, and persistent stewardship that gave us a drug whose advantages, safety, and ease of use have benefitted vast numbers of patients and remains a standard of care today. However, Dr. Glen did not do this alone. The notion that propofol could be more than an induction agent was carried forward by a successful collaboration between anesthesiologists and drug developers. This award underlines the importance of our specialty to medicine as a whole, and we both congratulate Dr. Glen on this award and celebrate our specialty and its contributions to medicine, science, and our patients.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Wood: mw218@columbia.edu

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