Host: Welcome to the Anesthesiology journal podcast, an audio interview of study authors and editorialists.

Dr. James P. Rathmell: Hello. I’m Jim Rathmell, Professor of Anesthesiology at Harvard Medical School and one of the Executive Editors for Anesthesiology. You’re listening to an Anesthesiology podcast that we’ve designed for physicians and scientists interested in the research that appears in the journal.

Today we are going to talk about the discovery and development of propofol, the most common anesthetic agent in use worldwide today. With us today is Dr. Iain Glen. Dr. Glen, who trained as a veterinarian and research scientist and was working at Imperial Chemical Industries or ICI Pharmaceuticals in the United Kingdom in the 1970’s. It was at ICI that Dr. Glen and his team studied a series of compounds to identify those with desirable anesthetic and hypnotic properties and selected propofol for further development in 1973.

We’ll cover much more of the history and Dr. Glen’s role in our discussions today. But it was for his central role in the discovery and development of propofol as an anesthetic that Dr. Glen was recently awarded the 2018 Lasker-DeBakey Clinical Medical Research Award. Dr. Glen, thank you for joining us.

Dr. John Baird (Iain) Glen: Thank you very much. I’m delighted to be here.

Dr. James P. Rathmell: Also joining us today is Dr. Margaret Wood. Dr Wood is the E.M. Papper Professor and Chairman Emerita at Columbia University in New York, New York. Dr. Wood teamed with Dr. Ron Stark, who was formerly the Chief Physician at ICI Pharmaceuticals, to write a special article about Dr. Glen and the discovery and development of propofol as an anesthetic. This special article appears in the December 2018 issue of the journal and is titled “John (Iain) Glen Wins 2018 Lasker Prize for Development of Propofol: An Award for All of Anesthesiology.” Dr. Wood, thank you for joining us today.

Dr. Margaret Wood: Hello, everyone. It’s my pleasure.

Dr. James P. Rathmell: Dr. Glen, congratulations on your receiving the Lasker Award, an extraordinary recognition of your scientific accomplishments and their direct contribution to all of medicine. An explanation is in order for our listeners: The Lasker Awards Program was created in 1945 by Albert and Mary Lasker to shine a spotlight on fundamental biological discoveries and clinical advances that improve human health and to draw attention to the importance of public support of science.

The Lasker-DeBakey Clinical Medical Research Award is given in recognition of a major advance that improves the lives of many thousands of people. As an anesthesiologist, I also want to thank you for giving us propofol, an anesthetic that has done nothing shy of revolutionizing the way we practice today.

Can you tell us a little bit about your childhood and your training and experience before you joined ICI?

Dr. John Baird (Iain) Glen: Yes, certainly. I grew up on a farm on the Island of Arran on the West Coast of Scotland and I decided to study veterinary medicine at Glasgow University. And the undergraduate course there included lectures and practical experience of anesthesia under supervision because if one moves into general practice, one has to be responsible for the anesthesia of the animals that are being presented for surgery.

I decided to stay within the academic environment at Glasgow University in the Department of Surgery and at that time the Head of Department, Professor Sir William Weipers, was also President of the Royal College of Veterinary Surgeons, the regulatory body for veterinary surgeons in the UK.

He felt that it was time that other specializations were introduced into veterinary practice and he encouraged the introduction of a number of diplomas in specialist subjects and one of these was the diploma in veterinary anesthesiology and I was the first person to take that diploma by examination after a couple of the earlier specialists had been granted diplomas and to act as examiners in the diploma.

So, that allowed me to attend classes for medical anesthesiologists in the royal infirmary in Glasgow and a lot of the lectures that they were having for their post-graduate experience included physiology and pharmacology and physics and many of the topics were quite relevant. So, I was very fortunate to broaden my understanding of anesthesia in that way.

And during my work for my day-to-day experience at the university surgery department, I was also able to look at new drugs that had been developed for use in man and be trying them out in animals and working on methods of evaluation of new drugs in animals and all of that experience became very useful later in my career.

Dr. James P. Rathmell: So, you joined ICI Pharmaceuticals in 1972. Can you tell us about what attracted you to ICI and about the assignment you were given when you joined ICI and the team you were working with?

Dr. John Baird (Iain) Glen: While I was at Glasgow, I could see the opportunities for improvement in the drugs that were available at the time, but I had no access to any compounds to test. And by accepting a position at ICI Pharmaceuticals, I became a member of a team that comprised both chemists and biologists, and the chemists were synthesizing compounds that they hoped would have anesthetic properties and the search was for something with improvement over existing agents.

The team was comprised of about four chemists and about four of us on the biology side. I had a couple of experimental officers, one of whom had worked earlier with James Raventos who was the developer of halothane at ICI much earlier and he was still working in the anesthesia lab.

The chemists were looking for both new intravenous and inhalational agents at that time; there had been progress in the synthesis of fluorinated hydrocarbons, but we didn’t find anything in that area. It was in the intravenous side that we were more fortunate.

And again, the chemists were making modifications of known intravenous agents in the hope of finding improvements, but nothing came from that speculative work. It was actually looking back at some of the old compounds that had been made much earlier by ICI chemists that we came across the drugs we were interested in.

The overall objectives that we had were very broad: we were asked to look for new anesthetic agents and new methods of studying anesthetic agents.

Dr. James P. Rathmell: I want to tell listeners about a beautiful piece that you wrote for the journal Cell. It appeared on September 20, 2018 and it’s titled “Balancing Tricks and Mini-Pigs: Steps along the Road to Propofol.” And right on the front of this article is a picture of the biology research group and you’re standing in the front of a group of four of your teammates there and holding a vial of what looks to be propofol, so…
Dr. John Baird (Iain) Glen: That’s correct, yes.

Dr. James P. Rathmell: So, how were you actually testing these agents. What was the experimental you were using?

Dr. John Baird (Iain) Glen: Well, our primary screening used intravenous injections in mice. We had a standardized process of doing this such that the rate of injection or the duration of injection was standardized and there was a range of doses that we would administer.

And we were looking for compounds to show evidence of hypnosis where mice would lose their righting reflex and become unconscious. And that simple test in mice could tell us really quite a lot of information not only about the anesthetic potency, the hypnotic potency, we would also see what doses were tolerated so we could get an indication of the safety margin.

But we would also get some information about the speed of onset which was obviously very important for a drug that would be used for induction of anesthesia and also some information on the quality of anesthesia. Many agents would produce unconsciousness, but it would be accompanied by muscle tremors or other excitatory effects which were obviously undesirable.

And compounds that looked promising in the first screen would then be taken into other species and we used the rabbit as a secondary test and anything which was suspicious of causing excitatory effects the rabbit seemed to be particularly good for demonstrating that and many of the compounds that might have looked promising were eliminated from further testing because they were not satisfactory in the rabbit.

So there was thereafter a cascade of tests that would gradually extend, as a compound looked satisfactory in the first couple of tests it would extend into other areas. But most of them, the great majority—in fact, all but one—fell down as we went further with these tests.

Dr. James P. Rathmell: Wow, what a rational well thought-out plan. So, why did you select this compound: ICI 35868 known chemically as 2,6-diisopropylphenol, propofol as the optimal compound for further testing?

Dr. John Baird (Iain) Glen: Yes. It was discovered in our collection of old compounds. The lead compound was actually (2,6-diisophenol) and that prompted Roger James, one of the chemists in the team, to search for related alkylphenols. And we found, again, in the compound collection 2,6-diisopropylphenol was obtained there and it was more potent than the lead compound and it also was faster in onset.

And we looked at many alkylphenols, but none of these showed any improvement over the 2,6-diisopropylphenol. That was very much based on its speed of onset and a balance between potency. Potency was obviously a problem using a large animal model with pigs. Is that correct?

Dr. John Baird (Iain) Glen: That’s correct.

Dr. James P. Rathmell: …marketed as Cremophor EL by Bayer. But that turned out to cause anaphylactic reactions in the initial clinical studies in a small number of patients. And then you, it sounds like always the scientist, went to the laboratory and proved that this was very much a problem using a large animal model with pigs. Is that correct?

Dr. John Baird (Iain) Glen: That’s correct, yes. We were able to show that in the pig the first administration of a Cremophor-containing agent was tolerated well, there was no problem. But if we gave a second administration within one to two weeks, it was a critical interval; then we got a typical response where the animal would show marked, blotchy cyanosis. It became hypertensive rather than hypotensive, histamine release was evidenced and a marked reduction in polymorph count occurred suggestive of complement activation.

And we were able to show that in the case of epontal, it was definitely the Cremophor because if we get the propanidid in a non-Cremophor vehicle, there was no problem. With althesin, the steroid mixture, there was a question mark that even the steroids themselves in some of the animals did cause a problem when they were readministered one or two weeks after the first administration.

So, certainly with propanidid there was a problem and for that reason I certainly formed a view that Cremophor should not be taken further and there was a real need to find an alternative.

Dr. James P. Rathmell: So, tell us more about the discussions that went on at this stage: you’ve got a fantastic drug in all of the animal models, but this problem with the formulation. Was ICI ready to scrap the development program? How'd you convince them to continue and how did you eventually solve the formulation problem? And why were you so convinced that this agent was worth further development?

Dr. John Baird (Iain) Glen: Yes. Well, I had seen how the animals behaved, how anesthesia was induced so smoothly without side effects that they recovered promptly. It just is a very impressive form of anesthesia that I was witnessing and I can remember one day having a pen of pigs laid out in a row all sleeping soundly coming back ten minutes later and they’re all up eating away there.

The quality of recovery seemed to stand out and we also had done studies comparing propofol with thiopentone, the standard agent at the time, and in comparison with thiopentone we could give repeated injections of propofol without a significant prolongation of recovery time whereas with thiopentone the first injection was short, but after two or three repeated injections they were sleeping for three or four hours.
Also, we were able to show that the recovery of coordination in mice we were using occurred much more rapidly after the end of anesthesia with propofol than was the case with thiopentone. We asked mice to balance on a rod after they had recovered from anesthesia and the propofol mice could do that about three minutes after regaining their righting reflex whereas the thiopentone mice, although they were walking about as if they had recovered, continued to slide off the rod for up to about 40 or 50 minutes.

So, there was a marked difference between propofol and the standard agent at the time which certainly gave me the confidence to advocate and continue development of this compound.

Dr. James P. Rathmell: So, how did you eventually solve the formulation problem?

Dr. John Baird (Iain) Glen: It was the formulation of the drug that was one of the – certainly one of the major difficulties in the whole development because after Cremophor, we found that there was a totally synthetic surfactant, polyoxyethylated and polyoxypropylene, which did not produce the response in the pig; it was well-tolerated and we thought we had the answer then. But that fell down in toxicology tests; there were some lesions in the animals’ livers that could not be explained, although that the formulation had apparently been tolerated quite well.

So, that had to be taken no further and at that stage again there was concern that we wouldn’t be able to go further, but we did. We had looked at emulsions in the early days and emulsions were not particularly useful then because I think the particle size was too large and the properties of the drug were not maintained in emulsions because they were slower in onset and had lost potency.

But by this time that we were looking for a third formulation, emulsion technology had improved quite a bit; it was possible to get emulsions with much smaller particle sizes. We were given the go-ahead to work with our pharmaceutical department. They looked for materials that would be compatible with propofol and would solubilize it as an emulsion and I looked at the tolerance of the various emulsion materials in animals and together we came up with the soybean oil emulsion that is the present one today. So, that was another couple of years in development along the way.

Dr. James P. Rathmell: The emulsion: soybean oil and purified egg lecithin, the milky-white propofol we know so well. So, once you had a workable formulation, how did the development program proceed? And I want you to go back in time and tell us, where did you think propofol would fit into modern anesthesia as it was initially being tested in humans?

Dr. John Baird (Iain) Glen: By the time the emulsion formulation was developed, there had been probably about 1,000 patients who had had the Cremophor formulation in earlier trials before that program was halted so that we already by that time knew quite a bit about the profile of the drug in patients.

And the clinical trials of the emulsion formulation, they were masterminded by Dr. Stark who’s the co-author with Dr. Wood on her editorial. Dr. Stark planned and carried out a very efficient and fairly quick program of clinical studies with the emulsion formulation.

And with all of these regulatory programs you tend to start with a minimal degree of exposure and as you develop confidence in the drug, you extend the length of exposure. So, the first set of trials were for induction and short-term maintenance of anesthesia mainly by a repeated injection for outpatient procedures.

After that was approved, we were then able to move onto studies looking at the use of propofol for maintenance of anesthesia for longer procedures gradually extending the experience. We were confident that this could be achieved from the animal results that showed that we didn’t get the sort of cumulation that was found with thiopentone.

And thereafter the next step was to move into sedation using the drug for sedation as a complement to regional or local anesthetic techniques. I think what you would call MAC sedation in the US and also sedation for patients requiring controlled ventilation in intensive care environments. That proved to be a very important and useful application of the drug is well.

So, it gradually extended. All of these were envisaged at the early stage when we struggled to convince the ICI management that this was more than a replacement for thiopentone; it was a drug that could be used much more extensively.

Dr. James P. Rathmell: Wow. So, you really had a good idea about the usefulness of this drug from the very beginning.

Dr. John Baird (Iain) Glen: Indeed.

Dr. James P. Rathmell: And I want to elaborate a lot of your – the latter part of your work was in developing infusion pumps and computer-controlled targeted infusion pumps that are now widely available in Europe. So, much of your extension beyond your initial work in animals. And you described that again in the article in Cell.

So, I want to talk to Dr. Wood now. Maybe you can start by telling us a little bit about your role in the development of propofol and your interactions with Dr. Glen over the years.

Dr. Margaret Wood: Delighted to. I was very fortunate in being a Scottish graduate, University of St. Andrews and one of my pharmacology lecturers joined ICI and saw him frequently at pharmacology conferences and so on, (Mike Turnbull), and talked to him when he told me about this new drug propofol that was being developed, if I could be involved with propofol when the studies would start in the United States. So, I was very pleased via (Mike) to have the opportunity to do that.

And, of course, at meetings where the results were reported and then advisory panels as to how Iain’s—and I’ll talk about it later on—how the drug was going to perhaps be used beyond an induction agent and maintenance of anesthesia; being involved with Iain and the American team and the UK team is a very, very exciting time.

I’m not sure I realized just how extensive propofol was going to be used. We surely knew it had a greater indication than just for induction and maintenance of anesthesia, but I don’t think any of us realized how imaging, technology and how radiology would change. And I don’t think it would have changed if sedation with propofol had been available.

And then also some of the technical tools that we now use in anesthesia: the LMA mask, for example, and some of the intubating laryngoscopes and video airway management that we have I think has eased incredibly with the use of propofol.

Dr. James P. Rathmell: Let’s turn to your special article. You detail much of the history behind the development of propofol and Dr. Glen’s role in the program. You describe the impact that propofol has had on modern medicine, some of the things you just hinted to. And I know you teamed with Dr. Ron Stark to write this wonderful tribute to Dr. Glen in the development of propofol.

We’ve heard that Dr. Stark was the lead physician on development of the final formulation, the emulsion formulation. Tell us a little bit more about your co-author Dr. Stark.

Dr. Margaret Wood: Ron is a Scot, he was born in Stonehaven and he’s a medical school graduate of the University of Aberdeen in Northeastern Scotland. He gained his PhD in cardiovascular research and he worked
in universities in the UK and Canada. And I think his academic career gave him a certain rigor, a discipline, a special way of thinking about things that I think continued when he decided to move to industry.

He chose ICI Pharmaceuticals which later on became AstraZeneca, a huge, large global pharmaceutical company today. I don’t know for sure, but he may have been influenced by the fact that Jimmy Black, Sir James Black, the discoverer of beta blockers and a winner of the Nobel Prize, had also worked there.

So, ICI, especially with the development of halothane also I think had a reputation for innovation and Ron decided that this was the place to work. He eventually became, as you have said, the Chief Physician of the company and fast-forward to when Iain was at ICI and he was working on his pigs, the time came that propofol was to undergo clinical development and Ron was given the responsibility for the clinical development of propofol. And really after that I think the rest is history.

Dr. James P. Rathmell: So again, I want to direct listeners to Dr. Glen’s September 2018 article in *Cell* and you’ll find a photo of Dr. Glen in the clinical trials group including Dr. Stark that were responsible for the clinical development of the emulsion formulation of propofol.

So, Dr. Wood, take us back to 1970. What were the most common anesthetic agents used for induction for anesthesia at the time? And what were their limitations?

Dr. Margaret Wood: Thiopental was the gold standard. One limitation that I will never forget was that you had to mix it up on the spot; it was a powder that came in a very heavy glass ampule in a box with another vile, another ampule to dilute the thiopental in and shake it around. And in the box was a serrated blade to break this glass ampule. And I can’t even begin to tell you how many times I cut my fingers on the glass ampule in the rush to get a case started.

So, I think that was a huge limitation and I think all of us, all anesthesiologists, felt that if we could get an IV induction agent that we didn’t have to mix on the spot that would be a huge advantage.

Another drug that was available at the time was methohexital and these were both barbiturates and at the time we thought that thiopental was ultra-short acting. But determination of action was due to rapid redistribution and excretion—as Iain has described—took much, much longer, many more hours. And after two to three doses, cumulation occurred.

We all knew that cardiovascular and respiratory depression was a serious limitation, a serious side effect. Thiopental was often called a drug that was fatally easy to give. Indeed, during the Pearl Harbor attack during World War II when thiopental was given to seriously compromised patients during the war who obviously were in shock, had blood loss and so on, thiopental was a very, very dangerous drug. So, there were huge limitations to thiopental.

Other drugs on the scene at the time were ketamine and then the droperidol-fentanyl combination, neuroleptanesthesia which was something that we did use in neuroradiology; certainly couldn’t have used thiopental.

So, the steroid anesthetics and the eugenols that Iain described that were diluted in Cremophor EL came along a little later.

Dr. James P. Rathmell: You already hinted at this but tell us about how propofol has impacted the practice of anesthesiology and also made multiple other discoveries and innovations possible.

Dr. Margaret Wood: Well, I think one thing you have to recognize with thiopental was that if a patient was stimulated surgically, although the patient might look deeply anesthetized, laryngeal spasm could occur or the patient might move. So, thiopental might render a patient unconscious, but if the inhalation anesthetic was not fully onboard and the patient wasn’t to the right anesthetic depth, the patient was considered to be hypersensitive, if you will. I don’t think excitatory side effects was really the right word for it.

And in fact, you had to do — introduce the inhalation anesthetic very slowly and gradually increase the concentration; all very old-fashioned anesthesia, and the surgeons knew this. They always—and I mean always—had the courtesy to ask permission to start the operation, even to touch the patient so that you could imagine in a situation like this an LMA certainly would not have worked. It wouldn’t have been impossible to insert the LMA quickly and efficiently.

So, I think it was really extremely fortunate that Archie Brain introduced the LMA just as the same time as propofol was being introduced into anesthetic practice and I think that had a tremendous effect on the way anesthesia has evolved; mask inhalation anesthesia has almost disappeared and the innovation of an LMA has become standard of care with all the advantages and safety features that we all know that the LMA possesses.

It’s also allowed other procedures to become routine, especially in outpatient ambulatory surgical practice; many of these procedures involve technology that needs an instant on-off anesthetic. It’s used in radiology, it’s used in pediatric practice, it’s used in the intensive care units. It’s really used everywhere.

And I think if you recognize that the two most frequently commonly reported anesthesia CPT codes are for screening colonoscopy and for cataract removal, I think it gives you an idea of just how much propofol is used today. But not only that, how many lives it saved; screening colonoscopy has a – had a tremendous effect on colon cancer. You just speak to anybody who’s a little older and they will tell you that having their cataracts removed has absolutely revolutionized their daily quality of life.

So, I really believe that it’s had an incredible effect on medical practice, not just anesthetic practice.

Dr. James P. Rathmell: So, I want to read a section from your article that nicely ties all this together. You point out that almost every person who undergoes a surgical procedure will receive propofol. And I want to quote, “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 benefited vast numbers of patients and remains a standard of care today.”

Can you tell us a bit about the Lasker Award itself and why this recognition of Dr. Glen underlines the importance of our specialty to medicine as whole?

Dr. Margaret Wood: The Albert and Mary Lasker Foundation has made these awards since 1945 and the award is to recognize individuals who have made innovative contributions to medical science. But I think what’s also just as important is that the contribution should have impacted and improved the lives of many thousands of people. These awards are extremely prestigious and they’ve been described as America’s Nobel Prizes. And, indeed, many of the Lasker Award winners have later on gone on to win a Nobel Prize.

You ask the question, why does this award also recognize our specialty? Anesthesiologists recognize that we’re often underappreciated. I think, in part, because we do such a great job very quietly in the background making sure that everything goes well. But I think in the case of propofol, I think anesthesiologists, when we were part of the first clinical trials, we recognized that this was a drug that wasn’t just for induction and maintenance of anesthesia in healthy patients.

But to go back to the Pearl Harbor analogy, but it also has the potential to be valuable in many subspecialty areas: in cardiovascular anesthesia, in neuroanaesthesia, obstetrics, pediatrics, the ICU, sedation practice. And I think we all worked as a team to expand the development of
I think AstraZeneca and Iain knew exactly where the drug was going to be useful and worked as a team with clinical anesthesiologists. And I think it was an incredible partnership that changed medicine. I think just as many years ago ether anesthesia produce the abolition, the removal of pain and really allowed the specialty of surgery to advance. I think, Jim, you know all about that being in Boston with the Ether Dome there.

But I really truly believe that in a similar way propofol changed modern medicine. It was a quantum leap forward to change medicine, both the surgery and also procedures in the intensive care and acute hospital practice. And we congratulate Iain Glen for that. But I think anesthesiologists should also be very proud of how very quietly we’ve also been involved in changing medicine and acute hospital practice.

**Dr. James P. Rathmell:** Dr. Glen, again, congratulations. Do you have any advice for young scientists as they face challenges similar to those you faced in the early work with propofol?

**Dr. John Baird (Iain) Glen:** Well, I think it’s highly likely that anybody doing research will come across problems along the way; hopefully one appreciates the satisfaction of overcoming the problems. Problems can be expected and are a challenge that researchers will always face.

**Dr. James P. Rathmell:** Perfect. Perseverance is the message of the day. I hope today’s discussion will lead many of you listening to read the special article about Dr. Glen, the Lasker Award and the discovery and development of propofol that appears in the December 2018 issue of *Anesthesiology*.

Drs. Glen and Wood, thank you for joining me today and for the wonderful discussion about propofol.

**Dr. John Baird (Iain) Glen:** Thank you very much.

**Dr. Margaret Wood:** Thank you.

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