After You, Please

The Second Annual John W. Severinghaus Lecture on Translational Science

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BEVERLY Philip called and made my day with her invitation to give the second John W. Severinghaus Lecture on Translational Science, noting by way of encouragement that the American Society of Anesthesiologists would pay my way and add an honorarium. “Bev,” said I, “not necessary. I’d pay for that honor.” So, here I am, giving the lecture named for my greatest hero, the man who prompted my career, guided me in my scientific and personal life, and led me to vistas I otherwise would not have seen. And doubling the pleasure, I am introduced by my best friend and colleague of a half century, Larry Saidman, who, although not named, shares the honor of this lecture. As I will write, much of the work I have done resulted because Larry and John pointed the way. “After You, Please” is an apt description of my life with these two dear friends and other colleagues with whom I have worked and whom I have admired. I claim little that is original. As you will see, this is not false humility.

My career in anesthesia began on a pleasant spring day in 1952 as a newly minted first-year medical student who wished to make money as an anesthesia extern. After a 2-month summer apprenticeship in anesthesia, I would take call for my mentor, who could rest secure at home knowing that the care of emergency patients was in my capable hands. On that first day, he showed me how to start an intravenous infusion of 0.2% thiopental, dial a 70% concentration of nitrous oxide, properly hold a rubber mask to the patient’s face, and watch the rebreathing bag. Then, he left the room, rating me for obvious incompetence, he asked if I wanted breathing. With great presence of mind, and instead of breathing me for obvious incompetence, he asked if I wanted to give artificial respiration. “Yes, please.” I responded, voice still squeaky. The surgeon squeezed the chest, the rebreathing bag now moved, and the circulating nurse fetched my mentor, who noted that the rebreathing bag could be used to ventilate the patient’s lungs. I finished the day exhausted and smelling of terror. The epiphany came as I sat thinking of the day’s events. To that moment, I had dreamed of becoming a second Robert Koch, a country physician who would make great medical discoveries as a general practitioner. A wonderfully naïve dream that suddenly vanished as I thought “You nearly killed a patient, today, and if you chose anesthesia as a career, you could do that every day. Every day you could take a patient’s life in your hands. Every day.” To a control freak (me) that image was overwhelmingly seductive. That day changed my life, a change I have never regretted.

I read all the books and journals on anesthesia available to me. I sought out local anesthetic meetings. A revelation! Little was known about anesthesia, particularly about how anesthetics worked and what they did. How appealing! All of the known world of anesthesia could be explored, learned, and assimilated. God knows whether I would go into anesthesia today; the amount of present information is overwhelming.

Fast forward 5 yr to my residency at the University of Iowa and an evening lecture by fellow resident (1 yr ahead of me; he is always 1 yr ahead of me) John W. Severinghaus on inhaled anesthetic uptake and distribution. Afterward, I argued with John, taking the position that if ether were more soluble, then it should act faster than nitrous oxide because more would be taken up. Like all my disagreements with John, he was right, and I was, well, hooked on uptake and distribution. Afterward, I thought of the day’s events. To that moment, I had dreamed of becoming a second Robert Koch, a country physician who would make great medical discoveries as a general practitioner. A wonderfully naïve dream that suddenly vanished as I thought “You nearly killed a patient, today, and if you chose anesthesia as a career, you could do that every day. Every day you could take a patient’s life in your hands. Every day.” To a control freak (me) that image was overwhelmingly seductive. That day changed my life, a change I have never regretted.

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anesthetic movement into the lungs and from the lungs to the tissues of the body. No, I do not know why a dietitian needed a calculator accurate to 21 places. It took a couple of days to calculate the values for an hour or so of anesthesia. Lots of things were not hard to solve, just have a preoxygenated reservoir and measure the carbon dioxide in the rebreathed gases. The answer came in two parts. The increase in carbon dioxide started fast; a 10–12 mmHg increase in the first 30–45 s and then 3–5 mmHg per minute thereafter (fig. 2). Aha! The increase in carbon dioxide was the lung (alveolar gas) catching up with the partial pressure of carbon dioxide in venous blood, and the second slow increase was the carbon dioxide input from metabolism added to the reservoir that the whole body constituted. The practical side of this was that the partial pressure of carbon dioxide would not increase as fast as one might have predicted from the input of carbon dioxide produced into the lung without a body to buffer it. Without that buffer, the increase might have been 70–80 mmHg/min. A patient could be apneic for a long time, with neither hypercapnia nor hypoxia being an immediate consequence. Perhaps that was my first experience with translational research: the focus on end-tidal analysis led to a clinically applicable finding, and John led the way (after you, please).

I had only loved one of the schools I had attended, The Hyde Park School for Little Children, where I learned to read and write and add and subtract at age 3. I think. Maybe four. Show and tell every day! That was John’s laboratory on Monday morning. Show and tell, and I loved it. Everyone got to detail what he did the previous week and what they would do this week. The lively discussions taught us the nuts and bolts of research, how to think research, and the fun that research was. There was little serious. It was just as Edna St. Vincent Millay wrote:

There rings a hammering all day,
And shingles lie about the doors;
In orchards near and far away
The gray wood-pecker taps and bores;
The men are merry at their chores,
And children earnest at their play.

—from “Song of a Second April”

We would defend our reasoning with citations from the literature. I remember one such defense that John ques-
figures are reprinted from figs. 1 and 2 from ANESTHESIOLOGY 1961; filling of the body with carbon dioxide—the buffering by the body. The sequent 3–5 mmHg/min increase in carbon dioxide reflected the rate of resulting partly from initial ventilation/perfusion inequalities. The sub-

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**Fig. 2.** The upper figure (A) illustrates the closed apparatus used to measure the rate of increase in alveolar carbon dioxide (CO₂) in preoxygenated, anesthetized (thiopental) normocapnic or hypocapnic (previously hyperventilated) patients. Exchange of gases was ensured by intermittent compression of the rubber bag. Volume constancy was assured by adjustment of the inflow of oxygen (O₂) (~200 ml/min). The gas volume, primarily the 300-ml rubber bag, was too small to act as a significant reservoir, and thus the increasing carbon dioxide in the apparatus, as measured by the carbon dioxide analyzer, reflected the rate of increase in alveolar carbon dioxide. The lower figure (B) provides the results. In both the normocapnic and hypocapnic patients, carbon dioxide increased by 10–12 mmHg in the first 30–60 s, reflecting the change in the alveoli from equilibra-

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**A**

**B**

Normocapnic Patients

Hypocapnic Patients

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in the early 1960s, John suggested that I must come to hear a speech by a fellow named Tom Hornbein about altitude, actually about climbing Mt. Everest. I came, Tom gave his inspiring talk, and I was never the same. I got off the couch, bought a backpack, and headed for the Sierras, and Tom and I became friends.

John showed me a brown bottle containing halopropene, a new volatile anesthetic made by the E.I. du Pont de Nemours and Company (Wilmington, DE). John asked whether Giles Merkel and I would like to test halopropene’s properties? We were both John’s fellows, so of course, we said yes, and then asked what we should do, what tests should we apply? John’s response, as I recall, was go figure it out. That was not as flippant as it might seem. John knew we would apply some form of end-tidal analysis (after all, we were in John’s laboratory) and correlate that with some standard physiologic measurements. “Piece of cake,” but what was not clear was how we might determine whether halopropene was better or worse or the same as the then most popular anesthetic, halothane. How might we compare the two anesthetics? We needed a yardstick, a measure of anesthetic potency. OK, so end-tidal analysis would be part of it, and it would be the measure of anesthetic “dose” because the end-tidal concentra-

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**Fig. 3.** After you, please. But we had a more august predecessor: John Snow had given us the basis for MAC. From his book published a century earlier, he described five degrees of anesthesia representing progressively deeper levels of anesthesia. “In the third degree, there is no voluntary motions occur, but muscular contrac-

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becomes a tool for exploring how anesthetics work. Again think translational research: a clinical measure (MAC) underlies studies of mechanisms of inhaled anesthetic action, something that presently has my attention. It underlies research—it provides a measure of how much anesthetic to give and what changes and does not change that requirement.10 It has led to many forms of translational research—it provides a measure of how much anesthetic action is taking place.10

EC50. The details do not matter. What mattered was that Ed Munson and I set about trying to determine the nitrous oxide sometimes take place.66(pp1,2) That is, in the third degree, if you cut a patient with a scalpel, he may move. "In the fourth degree, no movements are seen except those of respiration, and they are incapable of being influenced by external impressions." If Snow had possessed an end-tidal analyzer and been in John’s laboratory, MAC would have been born in the 1850s. After you, please.

And after Larry presented his work on the determination of MAC in humans at the New York Postgraduate Assembly, Louis Orkin, one of the grand old men in anesthesia, got up and told Larry that he had been scooped. "Yes," said Lou with his distinctive dismissive nasal New York accent, "When the surgeon makes an incision and the patient moves, the surgeon yells ‘Hey, Mac.’" After you, please?

In 1965, Dr. Cullen asked me what I was going to do now that I had explored all of MAC’s possibilities?7–9 I mumbled something, but it was not memorable, and I have never gotten away from MAC, and it has led to many forms of translational research—it provides a measure of how much anesthetic to give and what changes and does not change that requirement.10 It underlies studies of mechanisms of inhaled anesthetic action, something that presently has my attention. Again think translational research: a clinical measure (MAC) becomes a tool for exploring how anesthetics work.

Studying for boards, I noted that nitrous oxide should move into a gas space within the body faster than oxygen or nitrogen or other atmospheric gases or gases made in the bowel (hydrogen and methane, but not carbon dioxide) could move out. By now, Larry and I were a team, and we showed that this notion was correct, and that the result was that a gas space in the bowel or in a pneumothorax would expand if a subject breathed nitrous oxide, and that the expansion was linearly related to the concentration of nitrous oxide.11 Then, Larry had his epiphany (as I recall, he blurted this out in a stairwell as we were climbing to John’s laboratory on the 13th floor).12 "Expansion presumes that the walls surrounding the gas space are compliant. If the walls aren’t compliant then the volume won’t expand, but the pressure will increase!" and we proved all these predictions in a series of experiments in dogs (fig. 4). Our findings moved quickly into clinical practice (another experience with translational research). Surgeons took up the cry—do not use nitrous oxide if I am operating on the bowel, or if I am putting air into the brain or the eyeball. Larry and I get much of the credit for this, but in fact, Ray Fink’s description of diffusion anoxia presented the idea in one form in 1955,13 and John Nunn had predicted this effect of nitrous oxide in 1959 in an obscure letter to the editor.14 After you, please.

Nitrous oxide figured in another experiment John set us to. We thought we could estimate the time constant of the site of anesthetic action by defining an anesthetic endpoint and then determining the rate at which that endpoint could be achieved with a concentration slightly greater than the EC50. The details do not matter. What mattered was that Ed Munson and I set about trying to determine the nitrous oxide
concentration that made us lose consciousness as reflected in an inability to keep air pressure in a closed space constant at 50 mmHg in the face of a slow air leak. I went first and lost consciousness at 35% nitrous oxide, but with Ed, it took 40%. Not to be outdone, I tried again and stayed awake to 45%. Ed upped the ante to 50%, and I countered with 55%. Perplexed, we went back to John who volunteered to be the next subject. John inclined on a gurney, and we wired him up. We put on a blood pressure cuff and electrocardiograph and electroencephalograph leads; we did not want to miss anything. Then, we started the nitrous oxide, inching it up as John held the pressure at 50 mmHg. All went well until John sat bolt upright, wild-eyed, the electrocardiograph and electroencephalograph leads suddenly dislodged, scaring the bejesus out of Ed and me. The experiment was over. We did not say much, and John went back to his office. Later, we asked him whether he knew what had happened. He said that suddenly he had "come on the answers to all the important questions." "And?" "I forgot."

I had come to the University of California, San Francisco, to sit at John’s feet and learn all there was to know about uptake and distribution. We took up measuring the uptake and solubilities of old and new inhaled anesthetics with a vengeance: ether, halothane, methoxyflurane, fluroxene, xenon, and cyclopropane. John showed me how to mimic uptake with capacitors and resistors and that approach was also used by Tom MacKrell and William Mapleson who with John presented their results at the conference where I made my uptake and distribution debut. The capacitors and resistors were great; they could predict the effects of tissue groups on uptake—just as Hal Price had done with thiopental. Hal had scooped us all with that insight (After you, please), but none of the programs could do what my iterative program could—they did not predict the concentration effect. So, there I was in the Big Apple. John and Tom presented first, I followed, and Bill stood up to make his presentation. He opened by saying that his presentation was in tatters: Severinghaus and Mackrell had scooped him and Eger said they—and he—were wrong.

We went beyond uptake and determined the effects of these anesthetics on vital functions, on breathing, and the cardiorespiratory effects such as pungency or produce arrhythmias.
Specific molecular demands followed from some of these considerations. The ideal anesthetic must be an ether because alkanes tend to produce ventricular arrhythmias. It must be halogenated with fluorine because heavier halogens increase solubility, vulnerability to degradation, and toxicity, but it must not be completely fluorinated because complete fluorination unduly decreases potency and produces convulsant compounds.27 And, as in the Goldilocks story, it must not be too small or too big because too small or too big diminishes potency and increases the tendency to convulsions.27,28

These thoughts resulted from our various physical and animal studies. They were in my mind in the mid-1980s when Ross Terrell and I examined the summary sheets for more than 700 compounds that Ross had made in the 1960s in his search for a better inhaled anesthetic.29 The anesthesia community had already gotten two widely used clinical anesthetics (enflurane and isoflurane) from the work of this genius in synthetic chemistry.30 He and I wondered whether there was something that had been overlooked in his 700 compounds, something that met the criteria listed in the preceding paragraph. We found four or five compounds that looked possible. Of these, one succeeded—desflurane. Desflurane had been dismissed because it was hard and dangerous to make (the synthesis of the time involved elemental fluorine), it was expensive to make, and it was not as potent as we might have liked. But, indeed, desflurane has turned out to have much of what is ideal in an anesthetic. Ross led the way (after you, please).

Sometimes little things can change the world—a little. A case report found that oxygen delivery became inadequate despite a reasonable balance of inflowing oxygen seen on the flowmeter readings. The problem lay in two things. One was a leak in the oxygen flowmeter. The second was the position of the flowmeter—last in the carburetor scheme.31 The solution: simply change the order of the flowmeters, a system universally adopted with no reported recurrence of a problem.

Two decades ago, Hank Bennett called. I had foolishly said publicly that an anesthetizing concentration (meaning 1 MAC) of any inhaled anesthetic would prevent a patient from remembering anything, and Hank (who I did not then know) asked whether that was correct. "Yes," I said. "How do you know?" Hank asked. "Well," I said lamely, "I have never seen a case." "Have you looked?" "No." "Then how do you know?" He had me, and the result was a series of studies with what turned out to be a delightful and unusual set of people who helped me understand that the problem of learning and memory during anesthesia might be more complicated than I had realized. They taught me that remembrance could be unconscious (implicit) as well as conscious (explicit). Our studies supported my initial hunch that anesthetizing (MAC) concentrations of inhaled anesthetics prevented both explicit and implicit memory, at least in most patients.32 And subanesthetic concentrations down to roughly a half MAC also suppressed learning, even implicit learning.33 But, these were studies of the suppression of learning of irrelevant information, information of no immediate concern to the patient.

The psychiatrist Bernard Levinson prompted a crucial experiment. Bernard argued that patients would remember information presented during anesthesia if the information were relevant to their lives.34 To prove this, he presented a crisis drama to 10 dental patients anesthetized to burst suppression with ether. The anesthetist spoke to the patient, reading from a script: “Stop the operation. I do not like the patient’s color. His (or her) lips are too blue. I am going to give a little oxygen.” At this point, he pumped the rebreathing bag for a few moments and finally announced: ‘There, that’s better now. You can carry on with the operation.’” The patients had no explicit memory of this staged crisis postoperatively, but under hypnosis, four of the 10 patients remembered portions of the script verbatim and others became frightened and broke out of the hypnotic trance. This seemed to convincingly demonstrate the capacity of some patients to remember relevant material presented at surgical levels of anesthesia.

But Bernard’s experiment was unblinded, lacked a control group, and used an anesthetic no longer available. So, with Bernard’s help, we repeated it using a larger group (21) of subjects anesthetized twice—once with desflurane and once with propofol.35 At 1.5 or 2.0 times their MACawake value (MACawake is the alveolar concentration—or its equivalent—that suppresses appropriate response to command in 50% of subjects), we staged the crisis drama during one of the anesthetic administrations but not the other (random selection), using a recorded message that only the subject received. Bernard and Hank (blinded to the receipt or nonreceipt of the crisis drama) interviewed the subjects after each anesthetic. No volunteer had an explicit memory of the drama. Bernard then interviewed each subject under hypnosis. Finally, he and Hank (and Robert Block who saw the interview through the marvels of television) had to guess when the crisis drama had been given. Bernard guessed correctly 11 of 21 times (i.e., he did as well as a coin flip would have done).

And how does this relate to translational research? My involvement with a clinical problem subsequently prompted exploration of the mechanistic basis by which anesthetics suppress learning and memory, including posttraumatic stress disorder. We do not know the complete answer yet, but we are getting closer. In these works, I find myself a fascinated voyeur.36,37 After you, please.

There is a human side to translational or any research. Research should equal fun. I am in my office in San Diego, where I have gone to write my book on anesthetic uptake and action. Eric Wharenbrock knocks on my door and asks whether I want to measure the uptake of inhaled anesthetics in one California Gray whale? "Of course," I say! Here is the experiment no one will ever be able to repeat and say you have erred. (John says that the experiment that produces the most fun is the one proving that a colleague has made a dreadful mistake and you get to tell the world; no one would...
ever/could ever repeat this experiment.) So, we did the experiment and no one has ever repeated it (fig. 5).

The study of the whale is one of the so many that have brought me pleasure, pleasure from the research itself, pleasure from the people I have met because of the research. All sorts of people. They have changed my life, and I thank them for that, perhaps the best kind of translation in research, and I have been led by the grandest man in all of anesthesia. After you, John.

References

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