

## After You, Please

### *The Second Annual John W. Severinghaus Lecture on Translational Science*

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**B**EVERLY 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, and I was in trouble. The rebreathing bag moved less and less and finally stopped. I knew little of anesthesia, just information supplied in a few lectures in pharmacology, but I knew that breathing was good and not breathing was bad. My

squeaky voice told the surgeon that the patient had stopped breathing. With great presence of mind, and instead of berating me for obvious incompetence, he asked if I wanted him 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. For years thereafter, I spent many waking hours thinking about uptake and distribution and what factors governed the movement of inhaled anesthetics into, through, and out of the body. Two years in the Army followed residency, two wonderful years where the world mostly left me alone to muse and develop my thoughts on uptake. I invented an iterative program that predicted uptake from a knowledge of anatomy, physiology, and the gas laws. I borrowed the dietitian’s calculator, a hulking device that calculated to 21 significant places, to estimate the time course of

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Received from the Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California. Submitted for publication November 23, 2009. Accepted for publication November 24, 2009. Supported by NIH grant 1P01GM47818 for part of this work. Dr. Eger is a paid consultant to and speaker for Baxter Healthcare Corporation.

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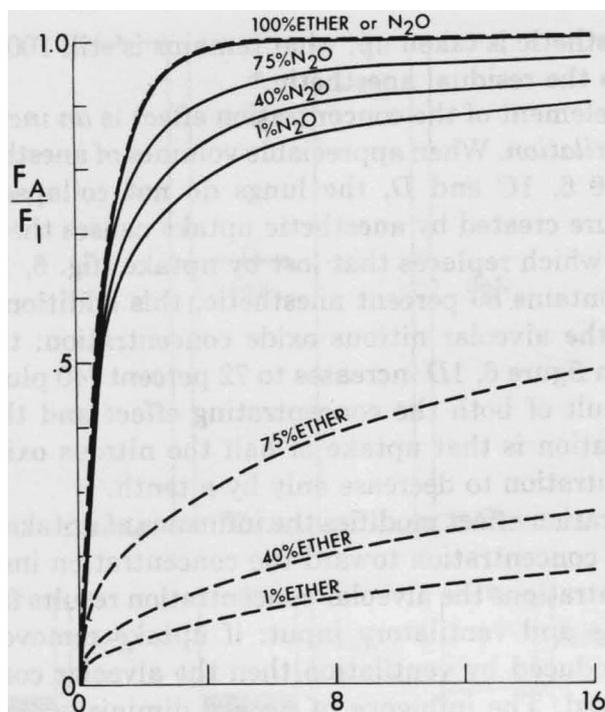


Fig. 1. These graphs illustrate the effect of the concentration effect for two gases that differ significantly in solubility and, therefore, uptake characteristics: the poorly soluble nitrous oxide and the highly soluble diethyl ether. At a 1% inspired concentration, the alveolar concentration (each graph gives the alveolar concentration as a percentage of the inspired concentration) increases faster with nitrous oxide than with ether. However, this differential decreases as the absolute inspired concentration (the values associated with each graph) increases, and at 100% inspired concentration, the increase is fastest and is the same for nitrous oxide and ether. Uptake does not influence how rapidly the alveolar concentration increases. These computer simulations are used with permission from figure 6.2 of *Anesthetic Uptake and Action*, 1974, 1–371.

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 fell out of this work, including the concentration effect (fig. 1).<sup>1</sup> I did not predict the concentration effect; indeed, I initially thought my program erred. I tried to figure out what I had done wrong, but my persistent efforts gave the same result with every anesthetic, not just nitrous oxide.

My tour in the Army approached an end. What would I do with my life? By now, my infatuation with uptake and distribution had become an addiction. Who knew more about uptake and distribution than John, now Director of Research at the University of California, San Francisco? John had made the first and (up to then) only measurement of uptake of an inhaled anesthetic (nitrous oxide) in a human in an ingenious experiment using the simplest of tools. So, with the encouragement of another of my heroes, William K. Hamilton, I applied to Stuart C. Cullen (third hero and Chair at the University of California, San Francisco) for a fellowship. Cullen foolishly agreed to pay me to have fun with John. As my dear friend, Eric Wahrenbrock, said at his

retirement: “I have put one over on you guys. All my life you have been paying me to have fun.”

So, I arrived, expecting to spend 1 or 2 yr in San Francisco, reveal all the mysteries of uptake, and then return to Kansas and either private practice or a faculty position at Kansas University. It did not work out that way.

John had a wonderful way of teaching research by doing. He made you answer questions; he posed questions; lots of questions. “How fast does the partial pressure of carbon dioxide increase in the lungs of an apneic human? Wouldn’t you like to figure that out, Ted?” “Of course, John. How do I do that?” “Well, go figure it out; go measure it.” John’s laboratory was the modern laboratory of its time, full of gadgets. John loved gadgets and could make them all work. He particularly loved gadgets that measured respiratory variables like carbon dioxide, and he knew I would make use of an infrared analyzer to solve the problem posed. Actually, the problem was not hard to solve, just have a preoxygenated anesthetized patient rebreathe from a small 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).<sup>2</sup> Aha! The first rapid increase 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-

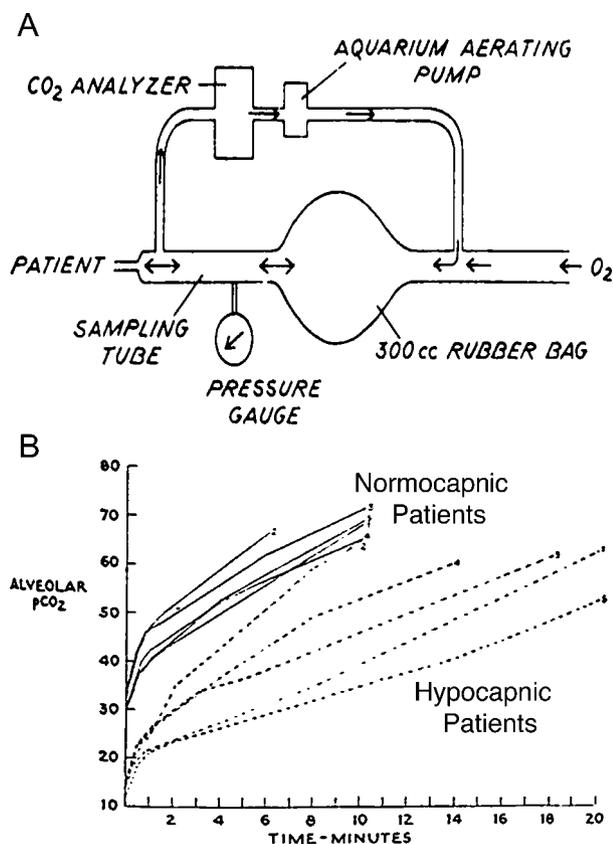


Fig. 2. The upper figure (A) illustrates the closed apparatus used to measure the rate of increase in alveolar carbon dioxide ( $\text{CO}_2$ ) in preoxygenated, anesthetized (thiopental) normocapnic or hypocapnic (previously hyperventilated) patients. Exchange of gases was ensured by intermittent compression of the rubber bag. Volume constancy was assured by adjustment of the inflow of oxygen ( $\text{O}_2$ ) (~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 equilibration with arterial blood gases to venous blood gases. It also probably resulted partly from initial ventilation/perfusion inequalities. The subsequent 3–5 mmHg/min increase in carbon dioxide reflected the rate of filling of the body with carbon dioxide—the buffering by the body. The figures are reprinted from figs. 1 and 2 from *ANESTHESIOLOGY* 1961; 22:419–25.<sup>2</sup>

tioned, to the fellow's surprise. John did not believe the report. "But John," the fellow protested, "You wrote the report." John wrote more than he could remember.

Oh, the wonder I fell into when I ended up in John's laboratory. I did not appreciate the importance of the discoveries discussed at these joyful Monday mornings. John's analyses of blood gases. Bob Mitchell's patient unearthing of why we breathe.<sup>3</sup> Quiet Bob, a fisherman by desire who during World War II had gone behind the lines for the Office of Strategic Services in Burma. And the cream of physiology came to John's laboratory. I had no idea who they were, but some of them changed my life. John was fascinated with the question of what governs breathing at altitude. A winter day

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 halopropane, 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 halopropane'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 halopropane 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 concentration was a partial pressure that would reflect the partial pressure in arterial blood, and what was in arterial blood would soon be equally found in the central nervous system that, we thought we knew, was the site of anesthetic action.

So, we had the dose. We needed the response. We were either too smart or too dumb to fall into a couple of traps. We could have gone high tech (for the time) and tried to connect the end-tidal anesthetic concentration with some change in the electroencephalogram. But that seemed messy (too variable among anesthetics) and hard to measure. So drop that. And vital signs also varied among anesthetics in inconsistent ways: blood pressure went up with some anesthetics (cyclopropane) and down with others (halothane). Drop that. What might be consistent across anesthetics? We drew on our clinical experience and came up with movement—no movement. Surgeons liked the latter and disliked the former. Movement—no movement applied to all inhaled anesthetics. The combination of end-tidal analysis and movement—no movement gave us MAC (the minimum alveolar concentration of inhaled anesthetic that produces immobility in 50% of subjects presented with a noxious stimulus), an incidental part of our extensive evaluation of halopropane,<sup>4</sup> an anesthetic that went nowhere.

Giles was the first author of the first MAC article on dogs,<sup>4</sup> and Larry was the first author of the first MAC article on humans (fig. 3).<sup>5</sup> 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 evidence of any mental function being exercised, and consequently, no voluntary motions occur, but muscular contractions, in addition to those concerned in respiration, may

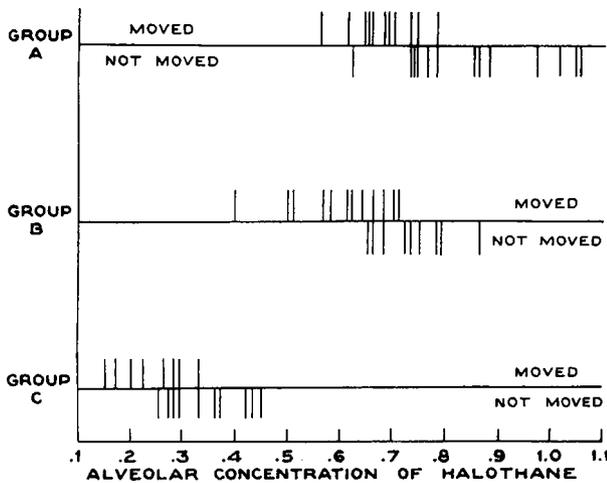


Fig. 3. This figure is reprinted from (fig. 1 in ANESTHESIOLOGY 1964; 25:302–6<sup>5</sup>) the first report for humans of the determination of MAC (the minimum alveolar concentration of an inhaled anesthetic that abolishes movement in response to a noxious stimulus in 50% of subjects). In the current case, the MAC determined was that of halothane in 17- to 78-yr-old humans.<sup>5</sup> We induced anesthesia with halothane, intubated the trachea after spraying the larynx with 1–2 ml of 5% cocaine, and then brought the end-tidal concentration of halothane (ultraviolet analysis) to some predetermined concentration, which was held constant for at least 10 min before surgical incision. The patient was observed for movement or nonmovement. Each vertical line indicated the results for an individual patient: an upward line indicated a patient who moved and a downward line indicated a patient who did not move. The position of the line indicated the concentration. The concentrations were selected to cover the range of movement or nonmovement for each experimental group. Group A received only halothane–oxygen. Group B received 10–15 mg of morphine subcutaneously plus halothane–oxygen. Group C received halothane–oxygen plus 70–75% nitrous oxide.

sometimes take place.”<sup>6(pp1,2)</sup> 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. Larry paled. “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:<sup>7–9</sup> 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.<sup>10</sup> 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.

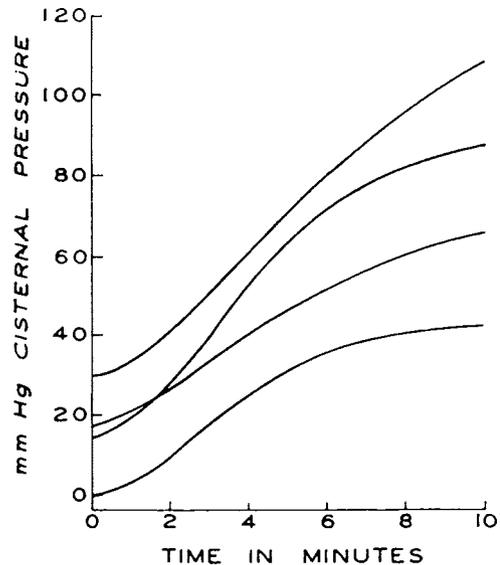


Fig. 4. In dogs anesthetized with halothane–oxygen, we placed a needle into the cisterna magna, removed 5–10 ml of cerebrospinal fluid, and injected an equal volume of air.<sup>12</sup> At time 0, we administered 75% nitrous oxide and monitored the associated increase in cisternal fluid pressure. Pressure increased to a relatively steady level over the next 10 min. This figure was reprinted from fig. 1 of the original report (ANESTHESIOLOGY 1965; 26:67–72).<sup>12</sup>

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.<sup>11</sup> 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),<sup>12</sup> “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,<sup>13</sup> and John Nunn had predicted this effect of nitrous oxide in 1959 in an obscure letter to the editor.<sup>14</sup> 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 EC<sub>50</sub>. 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 in science.” “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.<sup>15</sup> 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.<sup>1</sup> The capacitors and resistors were great; they could predict the effects of tissue groups on uptake—just as Hal Price had done with thiopental.<sup>16</sup> 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.<sup>17</sup> 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 circulation in young volunteers. We were young and fearless, and foolish, sometimes imposing anesthetic concentrations that severely depressed the circulation. Did this depression have untoward effects on mentation? We measured IQ in these volunteers, finding that it did not decrease, rather it tended to increase after anesthesia.<sup>18</sup> For a short time, we entertained the notion of setting up a business to augment the public's IQ. But our colleagues in psychology cautioned us that repeated administration of IQ tests always increased scores, even though each test differed in specifics from the preceding test. A learning effect. Sure enough, in volunteers given the tests without anesthesia, IQ inched up. Alas, anesthesia neither increased nor decreased mentation.

With each of our measurements of the effects of inhaled anesthetics on vital functions, we used MAC as our yardstick

so that we could compare the effects of one anesthetic with another.<sup>19</sup> Other investigators pursued similar determinations of inhaled anesthetic effects on vital functions such as the circulation to the brain, heart, and kidney or the effects of these anesthetics on muscle relaxation or the electroencephalogram, always with MAC as the yardstick.<sup>20</sup>

The devices used to measure end-tidal concentrations became more sophisticated. The Beckman Coulter (Fullerton, CA) LB-1, the device we used to measure end-tidal anesthetic concentrations in our determination of MAC, had severe limitations. It was alinear (a calibration curve had to be made for each gas and concentration range). The presence of other anesthetics (*e.g.*, nitrous oxide) or carbon dioxide could alter the readings and thus their accuracy.<sup>21</sup> Water getting into the analyzer would cause collapse of the reading and could damage the potassium-rubidium crystal that made up the detector cell window. A ghastly device relative to today's miracles, but a wonder to Saidman and me; they were our babies, and if one broke down, we had but to go to the ultimate gadgeteer, John, and he would fix it. John, God of gadgets.<sup>22</sup>

What others and we did, filled our journals. Anesthesia changed from an art based on little information to a science where much was known about what the body did to anesthetics (pharmacokinetics) and what anesthetics did to the body (pharmacodynamics). What others and we did indicated the importance of end-tidal analysis both for research and clinical care. The result was another example of translational research. The demand for clinical measurement of gases increased, and the analysis of end-tidal gases became a standard, resulting in the development of ever-better analytical tools. First, the multiplexed mass spectrometer (analogous to a centralized, high-powered computer) pioneered by John,<sup>23</sup> and then the presently favored individual infrared analyzer (analogous to a personal computer or a Macintosh computer). Today, despite the fact that inhaled anesthetics constitute the oldest form of anesthesia, they continue to be popular because of the control over the anesthetic state that this form of anesthesia provides, a precise control not possible presently with other approaches to anesthesia.

The work we did with inhaled anesthetics led to a consideration of what constituted the ideal anesthetic. What were we after? There was no single answer. We wanted a lot of things, and early on, Wendell Stevens and I tried to summarize these.<sup>24</sup> Again, after you, please. Of course, the ideal would produce anesthesia and not convulsions (but note that we have had more than one useful anesthetic that, incidentally, occasionally produced convulsions).<sup>25,26</sup> The ideal anesthetic would have a potency that would allow administration of lots of oxygen. It would be halogenated because it needed to be nonflammable. It would resist hepatic metabolism or degradation by carbon dioxide absorbents, especially to noxious substances. Its solubility in blood and tissues would foster rapid elimination. It would not have untoward 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.<sup>27</sup> And, as in the Goldilocks story, it must not be too small or too big because too small or big diminishes potency and increases the tendency to convulsions.<sup>27,28</sup>

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.<sup>29</sup> The anesthesia community had already gotten two widely used clinical anesthetics (enflurane and isoflurane) from the work of this genius in synthetic chemistry.<sup>30</sup> 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.<sup>31</sup> 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.<sup>32</sup> And subanesthetic concentrations down to roughly a half MAC also suppressed learning, even implicit learning.<sup>33</sup> 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.<sup>34</sup> 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.<sup>35</sup> 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.<sup>36,37</sup> 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

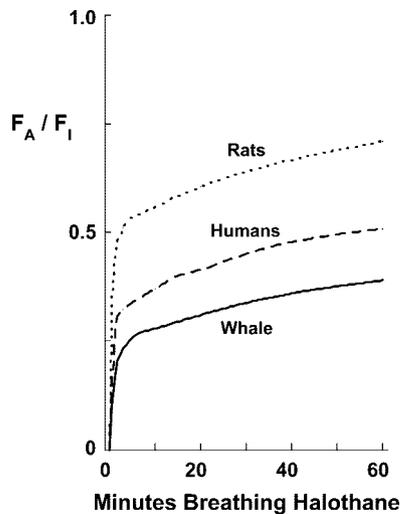


Fig. 5. We measured the rate of increase of the alveolar ( $F_A$ , end tidal) concentrations of halothane and four other gases toward the concentration inhaled ( $F_I$ ) in five rats, four humans (ourselves), and one 7-ton California Gray whale named Gigi.<sup>38</sup> Trace concentrations of the gases were used (e.g., 0.014% halothane.) The study tested and confirmed the notion that the rate of increase would be faster in smaller animals because ventilation and perfusion per kg would be greater. Gigi was released into the Pacific Ocean shortly after completion of the study and has not been seen since. Adapted from ANESTHESIOLOGY 1974; 40:19–23.<sup>38</sup>

ever/could ever repeat this experiment.) So, we did the experiment and no one has ever repeated it (fig. 5).<sup>38</sup>

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.

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