ANESTHESIOLOGY

Serendipity: Being in the Right Place at the Right Time

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I was introduced to anesthesiology as a third-year medical student at the University of Michigan (Ann Arbor, Michigan) in 1960, after which I chose the University of California, San Francisco (San Francisco, California) as the department in which to undertake residency training (fig. 1). I knew little of this department other than that it offered a third year of training (3 yr must be better than 2), and my wife, Arlene, and I (neither of whom had been west of the Mississippi) preferred San Francisco to Philadelphia or New York City.

Imagine my good fortune to have chosen University of California, San Francisco, wherein Edmond "Ted" Eger II, M.D., and John Severinghaus, M.D., were investigating all things related to inhaled anesthetic pharmacokinetics and pharmacodynamics (fig. 2). Ted Eger, at the time an assistant professor of anesthesia, had just published a paper with Giles Merkel, M.D., describing the minimum alveolar concentration (MAC) of halopropane needed to suppress a response to noxious stimulation in dogs.[1]

Several months after starting my training in 1962, I found myself being "grilled" by Ted, my faculty supervisor for the day, about my knowledge of gas laws (Boyle, Charles, Gay–Lussac, Dalton). Apparently I passed this test, for Ted subsequently invited me to participate in the first study to determine MAC in humans.[2] This study was performed in 68 surgical patients undergoing inhalation induction with halothane plus oxygen, oxygen with 70% nitrous oxide, or oxygen with opioid premedication. The end-tidal concentration of halothane that appeared to produce a light surgical plane of anesthesia was held constant for 10 to 15 min before surgical incision.

Neither intravenous induction agents nor muscle relaxants were used before incision. Each patient's response to the skin incision (movement *vs.* the absence of movement) was noted. The MAC of halothane in humans (0.74%) was determined as the transition point between responses of movement and nonmovement (fig. 3). Our study also demonstrated that 70% nitrous oxide and opioid premedication reduced the halothane alveolar concentration required to eliminate movement by 61% and 7%, respectively. The discovery of MAC in humans was revolutionary for clinical and research purposes in that it allowed the pharmacologic effects of inhaled anesthetics to be compared against each other at a similar anesthetic depth.

Ted and I then decided to determine MAC in each of four additional patients by a different method to validate our initial measurements. Rather than observing a response to a single skin incision occurring after a fixed concentration of halothane, we examined each of these four patients' responses to cutaneous electrical stimulation by increasing or decreasing the end-tidal halothane concentration. This process, which continued until the minimum concentration needed to eliminate movement was found, required several hours to accomplish! Remember that the early 1960s preceded the era of human study committees, and these patients had only been told that we would try to determine the precise amount of anesthetic needed for their surgery. These four latter patients' MAC determinations confirmed the data derived from the responses of the original 68 patients in whom a single surgical incision had occurred.[2]

In three of the four patients studied during the extended presurgical period, no untoward events occurred. The fourth patient, however, was very different.[3] The patient

Effect of Nitrous Oxide and of Narcotic Premedication on the Alveolar Concentration Required for Anesthesia. By Saidman LJ, Eger EI II. ANESTHESIOLOGY 1964; 25:302–6.

Hyperthermia during Anesthesia. By Saidman LJ, Havard ES, Eger EI II. JAMA 1964; 190:1029–32.

Abstract

The minimum alveolar concentration (MAC) of an inhaled anesthetic preventing movement in response to a surgical incision as a measure of equipotency was "invented" in 1964 at the University of California, San Francisco. The principal advantage of MAC is that it allows the pharmacologic effects of inhaled anesthetics to be compared against each other at a similar anesthetic depth. Thus, if the hemodynamic effect (hypotension, decreased cardiac output) of anesthetic "A" is greater than that of anesthetic "B," the anesthesiologist may elect to use "A" in patients with myocardial dysfunction. A rare side effect of a volatile anesthetic is that in some patients, malignant hyperthermia may occur with or without succinylcholine use. This phenomenon was detected in a patient in whom halothane MAC was being measured. The availability of the Severinghaus blood gas device allowed for the first ever measurement of the metabolic and respiratory acidemia that accompanies malignant hyperthermia.

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The first paper (Saidman and Eger) was presented at the PostGraduate Assembly in Anesthesiology in New York, New York, in 1963. The second paper (Saidman, Havard, and Eger) was presented at the Anesthesia Section of the American Medical Association Meeting in San Francisco, California, in 1963.

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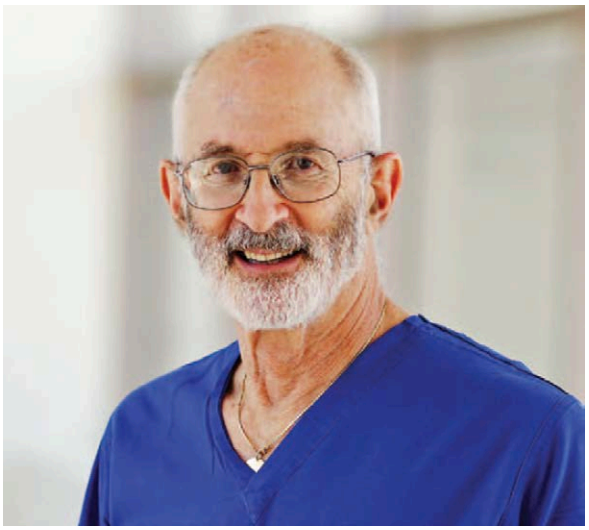

Fig. 1. Dr. Lawrence Saidman was Chairman of Anesthesia at the University of California, San Diego (San Diego, California) from 1973 to 1985; Editor-in-Chief of ANESTHESIOLOGY from 1986 to 1996; and President of the American Board of Anesthesiology from 1994 to 1995. Image courtesy of Stanford University (Stanford, California) and the International Anesthesia Research Society (San Francisco, California).

was a 47-yr-old man undergoing repair of a large ventral hernia. During the extended presurgical period described, he had been anesthetized with halothane–oxygen after premedication with 0.8 mg intramuscular atropine. After the MAC determination, surgery was started, and anesthesia was maintained with halothane, oxygen, and 65% nitrous oxide, along with a continuous infusion of succinylcholine for deep abdominal relaxation. Monitoring included a noninvasive blood pressure cuff, an esophageal temperature probe, and a continuous electrocardiogram.

One hour into surgery, the patient became diaphoretic, and his temperature had increased to 100°F. In order to maintain adequate muscle relaxation, it was necessary to increase the rate of the succinylcholine infusion. Alarmingly, the patient's temperature rapidly increased to 108.5°F, after which his blood pressure abruptly decreased from 100/70 mmHg to 40/0 mmHg. Fortuitously, we had access to John Severinghaus's apparatus (now called a blood gas machine),[4] and arterial blood gas analysis showed profound metabolic and respiratory acidosis (pH 6.8; P_{CO_2} 179 mmHg; base deficit 14.7). The surgeon was alerted to these events, and during the next 4 hr, the patient was packed in ice and given intravenous bicarbonate, vasopressors, prednisolone, and 3,000 ml cold lactated Ringer's solution. Gradually, his temperature decreased, his acidosis mostly resolved, and we were able to extubate his trachea. His subsequent recovery was uneventful.

I presented this case report to the Anesthesia Section of the American Medical Association meeting in San Francisco in 1963. At the end of my presentation, the moderator queried the audience if anyone had cared for a patient exhibiting similar events. To my surprise, several attendees described a similar combination of hyperthermia and hemodynamic instability occurring in patients to whom halothane and succinylcholine were given. However, they were unable to measure the metabolic derangement that is the hallmark of the condition.

We published this case report that presented the first-ever acid–base data associated with hyperthermia in a

Fig. 2. Personnel working in the Severinghaus Lab in 1962 to 1963. From left to right: Richard Shargel, Cedric Bainton, Lawrence Saidman, Robert Mitchell, Freeman Bradley, Ted Eger, Ed Munson, Dorothy Herbert, John Severinghaus, and Pat Bradley.

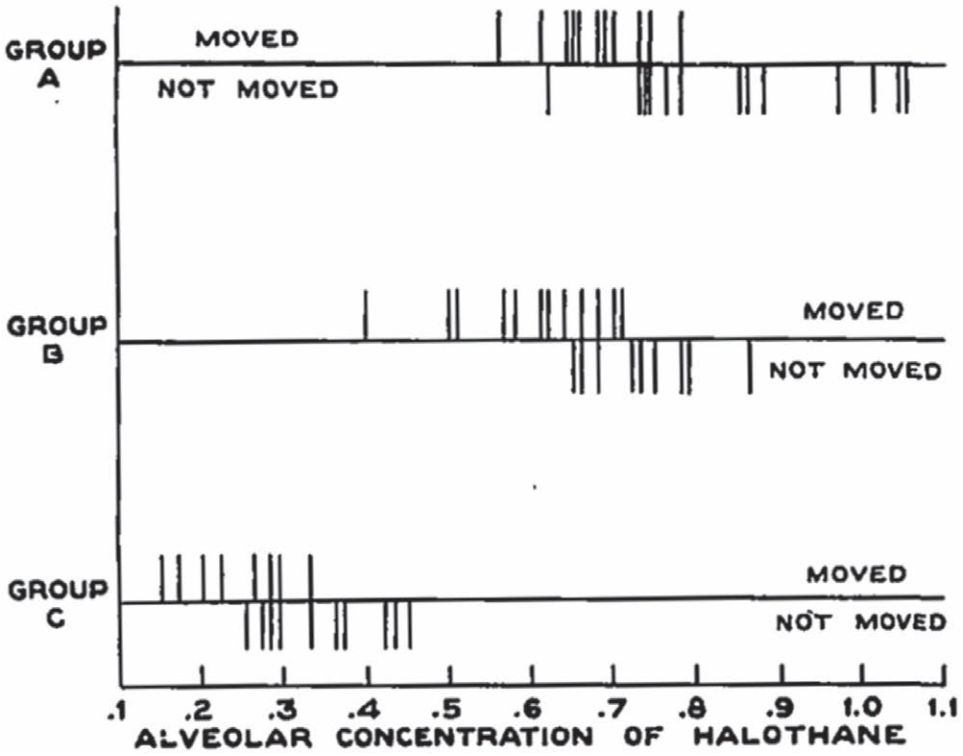

Fig. 3. Responses to skin incision in surgical patients in the first human minimum alveolar concentration study. Reprinted from Saidman and Eger[2] with permission.

patient anesthetized with halothane.[3] Denborough *et al.* had published a paper in 1962 describing deaths in a family who had received general anesthesia.[5] While these deaths may well have been related to malignant hyperthermia, no acid–base data had been readily available at the time.

The association between profound hyperthermia and severe acidosis had remained undescribed until our paper was published. I include "serendipity" in the title of this article because of the unusual set of circumstances that led to two separate papers, each of which included information from the same patient.[2,3] The serendipitous circumstances included the lengthy presurgical interval of halothane MAC measurement during which succinylcholine was not used, and body temperature remained normal[2,3]; the previously unknown association between halothane and malignant hyperthermia[3]; and the fortuitous availability of the Severinghaus blood gas machine—an early version of which now rests in the Smithsonian Institution (Washington, D.C.).

The second part of the MAC study during which four patients were anesthetized for several hours before surgery might not have been possible today due to the need for approval from an institutional human research committee. In addition, even if the study had been approved by a review board during that era, the cause of the hyperthermia would not have been properly diagnosed due to the lack of clinical experience with malignant hyperthermia. By contrast, PubMed citations of papers dealing with malignant hyperthermia now number in the thousands.

Our experience with this patient is a classic example of first observing a clinical phenomenon, then funding basic research to discover the mechanism underlying the problem, and finally applying this knowledge to clinical practice to prevent the problem from occurring. Personally, this experience left me in awe of how close our patient came to dying from a previously unknown phenomenon. He was rescued due to a device that had only recently become clinically available. This case also illustrates how what we do every day renders our patients susceptible to the vagaries of chance events. Most importantly, it affirmed the essential role of anesthesiologists in responding to these rare and unpredictable events.

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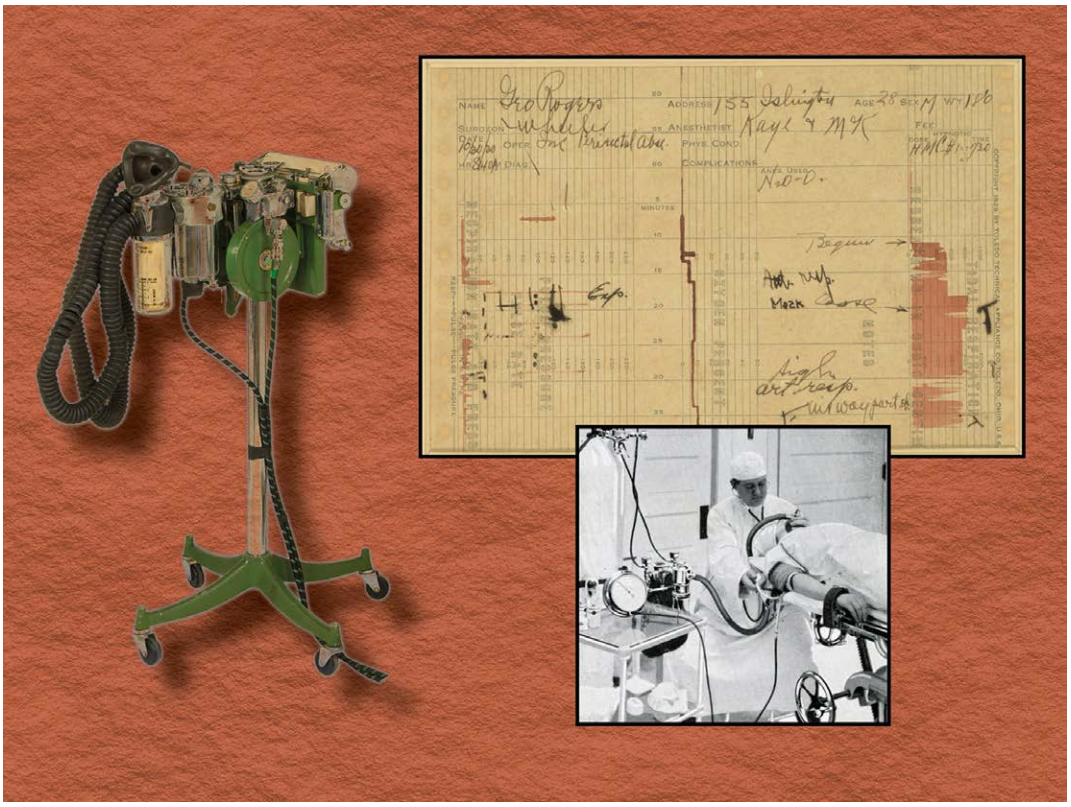
Let the Record Show: McKesson's Automated Nargraf



A high school principal who became a physician, inventor, and entrepreneur, Elmer McKesson, M.D. (1881 to 1935, *lower right*), championed technology to optimize physiology under anesthesia. Enchanted by nitrous oxide anesthesia as an intern, he designed his first gas apparatus and founded his successful McKesson Appliance Company a few years later. He also served as the first President of the International Anesthesia Research Society. Truly ahead of his time, McKesson invented the first semiautomated anesthesia record when intraoperative blood pressure measurement was only beginning to gain favor. His revolutionary Nargraf Model J (1930, *left*) fed a preprinted paper record through a machine that charted blood pressure, tidal volume, oxygen concentration, and inspiratory gas pressure (*red ink, upper right*). The anesthetist would document the patient's heart rate and respiratory rate by hand (*black ink, upper right*). While fully automated records would not be in vogue until the twenty-first century, McKesson's Nargraf was a harbinger of things to come. (Image of record from the Geoffrey Kaye Museum of Anaesthetic History, VGKM5042. Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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