David S. Warner, M.D., Editor

Adventures in Anesthetic Mechanisms

Joseph F. Antognini, M.D., M.B.A.*

Exaggerated Anesthetic Requirements in the Preferentially Anesthetized Brain. By J. F. Antognini and K. Schwartz. ANESTHESIOLOGY 1993; 79:1244–9. Abstract reprinted with permission.

Background: The brain is assumed to be the site of anesthetic action, but anesthetics have effects elsewhere, such as the spinal cord. A preferentially anesthetized goat brain model was used to determine the importance of anesthetic action in the brain.

Methods: Six goats were anesthetized with isoflurane; after tracheal intubation and insertion of a femoral arterial catheter, bilateral neck dissections were performed to isolate the external carotid arteries and external jugular veins. The occipital arteries were ligated to prevent vertebral blood from entering the carotid system. (Goats do not have direct, significant vertebral artery contributions to the brain, and they lack internal jugular veins.) Control isoflurane minimum alveolar concentration (MAC) was determined using a dew-claw clamp as the painful stimulus. Following this, cranial venous blood was drained into a bubble oxygenator in which an isoflurane vaporizer was placed in line with the gas flow. Oxygenator arterial isoflurane concentration was estimated from the isoflurane partial pressure in the oxygenator exhaust. Isoflurane administration *via* the lungs was discontinued and the isoflurane partial pressure in the blood delivered *via* the carotid artery was increased by an amount required to bracket the partial pressures permitting and preventing movement in response to dew-claw stimulation. The native circulation was reestablished and MAC determined again.

Results: Cerebral isoflurane requirements were 1.2 ± 0.3% (mean ± SD) before bypass, increased to 2.9 ± 0.7% during bypass when the brain was preferentially anesthetized, and decreased to 1.3 ± 0.1% after bypass.

Conclusions: The results support the importance of subcortical structures, such as the spinal cord, in the generation of purposeful movement in response to a painful stimulus under general anesthesia.

I BEGAN my research career without any formal research training. Even back in the early 1990s this approach to research was unusual, and it is certainly even more so today. But, as I look back, I realize that, just like so many other times in my life, I was in the right place at the right time. My study on the importance of the spinal cord to anesthetic-induced immobility[1] germinated from idle thoughts on mechanisms of anesthesia.

* Professor, Division of Peri-operative Services, University of California, Davis Medical Center, Davis, California.

Received from the Department of Anesthesiology and Pain Medicine, University of California, Davis, Davis, California. Submitted for publication November 10, 2011. Accepted for publication December 1, 2011. Support was provided solely from institutional and/or departmental sources.

Address correspondence to: Dr. Antognini: Division of Peri-operative Services, University of California, Davis Medical Center, 2315 Stockton Boulevard, Sacramento, California 95817. joseph.antognini@ucdmc.ucdavis.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

Copyright © 2012, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2012; 116:701–4

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/116/3/701/256883/0000542-201203000-00031.pdf by guest on 17 May 2022

After residency I decided to enter into private practice, which I did at a small community hospital in the Sacramento, California, area. But, within just 2 yr, I was bored and I needed more intellectual stimulation. I thought more seriously about coming back to the University of California, Davis. While still in private practice, I started to get involved with a few small projects, including some case reports[2,3] and a case series,[4] just enough to get my feet wet. But I did not have many thoughts about any basic science projects, as I lacked the background and the training to generate any meaningful ideas.

I recall sitting at my desk at home (I was still in private practice) pondering something that Ted Eger, M.D. (Professor Emeritus, University of California, San Francisco, San Francisco, California), had written: basically that anesthetics produced their effects by action in the brain.[5] I thought to myself, "How does he know? Is there a way to test this question?" Around the same time, two of my former teachers, Dave White, M.D. (Professor Emeritus, University of California, Davis, Davis, California), and John Reitan, M.D. (Professor Emeritus, University of California, Davis, Davis, California), had published a paper on selective delivery of anesthetics and drugs to the hindlimb of a dog.[6] I wondered whether such a technique could be used to selectively deliver an anesthetic to the brain of an animal (in this case, a dog).

Gerry Gronert, M.D. (Professor Emeritus, University of California, Davis, Davis, California), who had just recently been recruited to the University of California, Davis and who had also trained me, had been trying to get me to come back to the University of California, Davis anesthesiology department. He had been helping me with editing my case reports. During this time I also started thinking about a potential project related to my question of anatomic sites of anesthetic action. I decided that I needed to address some more preliminary issues. For example, if I intended to use a bypass machine/oxygenator, I needed to know whether bypass might alter anesthetic requirements (*e.g.*, minimum alveolar concentration, or MAC). Hall *et al.* had just published data showing that cardiopulmonary bypass using bubble oxygenators decreased MAC.[7] I thought that this might be related to microbubbles and hypothesized that bypass using a membrane oxygenator would not alter MAC. I went about planning the experiment and discussed it at a departmental research meeting. I was still in private practice, but Gronert supported my project. As I look back, I quite frankly cannot believe that Gronert let me do this project and that he provided the needed resources; he saw something in me that others did not. Indeed, after I gave my presentation, Gronert solicited comments from the faculty attending the research meeting. It wasn't until many years later that I came across some of these comments. One person wrote: "Currently, this study is poorly designed" and "I would encourage Joe to join us, but his current expectations are unreasonable." Looking back, these were fair and accurate comments, especially considering that I had no research training, formal or otherwise.

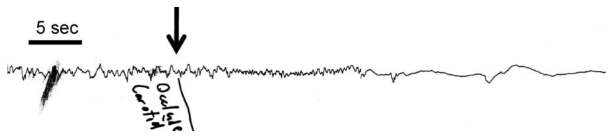

Fig. 1. An electroencephalogram tracing from an experiment on January 28, 1993. The goat was anesthetized with isoflurane (1.4% end-tidal). One carotid artery and both occipital arteries had been ligated; blood flow to the brain was supplied by the remaining carotid artery. At the *arrow* the patent carotid artery was occluded; the electroencephalogram became silent within a few seconds, indicating functional isolation of cerebral blood flow.

Notwithstanding the comments noted above, my first project was successful, and we showed that bypass did not substantially alter MAC.[8] At this point, I was now full time on the faculty and was planning my study for bypass of the cranial circulation. But, there was a problem. As I read about the anatomy of the canine cerebral circulation, I learned that dogs have a rich and extensive collateral circulation. In fact, if the carotid arteries and vertebral arteries are ligated most dogs, after a 1–3 week recovery, will walk around as if nothing is amiss.[9] Clearly I needed another animal model. I walked into Gronert's office to discuss this dilemma and he casually mentioned that Albrecht and his colleagues had used a goat model to isolate the cerebral circulation. I quickly read about Albrecht's model[10] and realized that the goat would probably work for my project. I needed to gain experience working with goats and also to use cardiopulmonary bypass in this species. Thus, I completed two studies: one that investigated the cardiopulmonary effects of volatile anesthetics[11] and the other that examined the effects of profound hypothermia on MAC, which required cardiopulmonary bypass.[12]

I felt that I was set, except for one thing: learning the neck anatomy of the goat. The vertebral arteries in goats form only a small, insignificant basilar artery that does not contribute to the cerebral circulation, but the occipital artery is an anastomosis between the carotid artery and the vertebral arteries. Hence, blood could flow from the vertebral arteries through the occipital arteries and then into the carotid artery. Albrecht's model required that the occipital arteries be ligated. I dissected the necks of several goats to figure out the anatomy, but I felt that I also needed physiologic confirmation that I could isolate the occipital arteries. In preliminary studies I accomplished this goal by placing ligatures around various arteries and branches and sequentially ligating each while monitoring the electroencephalogram. According to Albrecht and others, the goat would maintain adequate cerebral circulation when both carotid arteries were ligated below the occipital artery takeoff and when only one of the occipital arteries was ligated; if both carotid arteries and both occipital arteries are ligated the electroencephalogram should go flat, which was indeed what happened in my preliminary work (fig. 1).

My next step was to actually perform bypass and determine whether the proposed model was workable. One of the first problems that I faced was that I had extremely low carbon dioxide partial pressures in the arterial blood in the bypass. I thought to myself that the project was doomed. But, on mentioning this

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/116/3/701/256883/0000542-201203000-00031.pdf by guest on 17 May 2022

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

problem to Gronert, he nonchalantly asked if I was using pure oxygen for the oxygenator gas, and if so, I should switch to carbogen. I felt rather silly that I had not thought of this obvious cause, but at that point, I was used to making silly mistakes. What was one more? I plodded onward.

I still vividly remember the first time I actually selectively delivered an anesthetic (halothane) to the cerebral circulation. I had determined MAC with whole body delivery and obtained an expected result, around 1%. I then placed the goat on cerebral bypass, discontinued halothane to the torso, but continued halothane to the head at 1%. After waiting a short period, perhaps around 10–15 min, I applied the noxious clamp. The animal moved violently, and I nearly lost the various cannulae. There was only one thing I could think to do to prevent the animal from moving: stopping the bypass. I did so, and within 5–10 s, the animal ceased moving. I restarted bypass after 20–30 s and increased the halothane concentration in the bypass. Although a scientist is loathe to draw conclusions with n = 1, I was certain that subsequent experiments would yield similar results (which they did).

Once I had sorted out some of these initial problems, the project went well. My coauthor, Kevin Schwartz, M.D. (former Resident, University of California, Davis, Davis, California), was a resident at the time, and he along with some of the lab technicians (Renae Wurstschmidt, B.S. [former Staff Research Associate, University of California, Davis, Davis, California], Brock Lewis, B.S. [former Staff Research Associate, University of California, Davis], and Kameron Chun, B.S. [Staff Research Associate, University of California, Davis]) and fellow faculty (Gronert, Nguyen Kien, Ph.D. [former Professor, University of California, Davis, Davis, California]) contributed to the project's success.

Like anyone else engaged in creative work, my colleagues and I had humorous things occur. Twice a goat escaped during the transport from the cage to the laboratory. The first time it happened was in the early morning and I eventually started driving around campus in my truck to find the animal. I then saw a fireman chasing a goat (the campus firehouse was close to my lab). I remember thinking, "Ah, that must be my goat." I managed to literally tackle the goat in full view of morning commuters arriving on campus. It was an interesting start to their day, but not all that unusual on a campus with strong agricultural and veterinary traditions.

Working with goats has taken a physical toll. In addition to the "aches and pains" of working with these large animals, I recently learned that I have antibody titers to *Coxiella Burnetii*, the bacteria responsible for Q fever (we have had at least one goat with this infection, although we did not know it at the time). In an odd way I consider these antibodies a badge of courage and a link between me and my experimental subjects.

Although Ira Rampil, M.D. (Professor, SUNY Stony Brook, Stony Brook, New York), published his work on spinal effects of isoflurane before our paper,[13] none other than Claude Bernard (1813–1878), 150 yr earlier and using a frog model, had concluded that the spinal cord was important to anesthetic-induced immobility.[14] We subsequently used a frog model and had similar findings.[15] In addition, Yang *et al.* used a goat model with a different selective delivery technique to show that the spinal cord was important to immobility.[16] Likewise, my colleague Steve Jinks, Ph.D. (Associate Professor, University of California, Davis, Davis, California), has used lamprey and found similar results.[17] Thus, I am gratified that multiple scientists have used several species (rats, goats, frogs, lamprey) and different techniques and have come to the same conclusions. Although many others had examined anesthetic effects on components of the spinal cord (*e.g.*, dorsal horn neurons) these collective data provided relevance within the context of a clinical endpoint (immobility).

Immobility is an important clinical goal and an equally important experimental endpoint. As John Snow (1813–1858) noted, anesthesia keeps patients still who otherwise would not be. Movement in response to a noxious stimulus is a basic defense mechanism present in most organisms, from bacteria to large animals. Indeed, vertebrate animals share common neuronal pathways, receptor systems, and neurotransmitter systems that subserve movement. Anesthetics likely cause immobility by a common mechanism across many species.

Today when people ask me about getting involved in research, I tell them that they need to do it the right way so as to maximize their chances for success: find a good mentor and get training. But the most critical element is to have novel and interesting ideas that you pursue with passion. When you are thinking about your ideas from the moment you awake in the morning to the moment you are asleep at night, then you will know that you have found your passion. The training and mentor are there to guide that passion and energy.

References

1. Antognini JF, Schwartz K: Exaggerated anesthetic requirements in the preferentially anesthetized brain. ANESTHESIOLOGY 1993; 79:1244–9
2. Antognini JF, Hanowell LH: Intraoperative hypoxemia complicating sequential resection of bilateral pulmonary metastases. ANESTHESIOLOGY 1991; 74:1137–9
3. Antognini JF, Andrews S: Anaesthesia for caesarean section in a patient with acute fatty liver of pregnancy. Can J Anaesth 1991; 38:904–7
4. Antognini JF: Anaesthesia for Charcot-Marie-Tooth disease: A review of 86 cases. Can J Anaesth 1992; 39:398–400
5. Quasha AL, Eger EI 2nd, Tinker JH: Determination and applications of MAC. ANESTHESIOLOGY 1980; 53:315–34
6. White DA, Reitan JA, Kien ND, Thorup SJ: Decrease in vascular resistance in the isolated canine hindlimb after graded doses of alfentanil, fentanyl, and sufentanil. Anesth Analg 1990; 71:29–34
7. Hall RI, Sullivan JA: Does cardiopulmonary bypass alter enflurane requirements for anesthesia? ANESTHESIOLOGY 1990; 73:249–55
8. Antognini JF, Kien ND: Cardiopulmonary bypass does not alter canine enflurane requirements. ANESTHESIOLOGY 1992; 76:953–7
9. Whisnant JP, Millikan CH, Wakim KG, Sayre GP: Collateral circulation to the brain of the dog following bilateral ligation

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/116/3/701/256883/0000542-201203000-00031.pdf by guest on 17 May 2022

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

of the carotid and vertebral arteries. Am J Physiology 1956; 186:275–7

10. Albrecht RF, Miletich DJ, Rosenberg R, Zahed B: Cerebral blood flow and metabolic changes from induction to onset of anesthesia with halothane or pentobarbital. ANESTHESIOLOGY 1977; 47:252–6
11. Antognini JF, Eisele PH: Anesthetic potency and cardiopulmonary effects of enflurane, halothane, and isoflurane in goats. Lab Anim Sci 1993; 43:607–10
12. Antognini JF: Hypothermia eliminates isoflurane requirements at 20 degrees C. ANESTHESIOLOGY 1993; 78:1152–6
13. Rampil IJ, Mason P, Singh H: Anesthetic potency (MAC) is independent of forebrain structures in the rat. ANESTHESIOLOGY 1993; 78:707–12
14. Bernard C: Anesthetics, Lectures on Anesthetics and on Asphyxia. Paris, J-B Balliere & Son 1875; pp 70–84
15. Barter LS, Mark LO, Smith AC, Antognini JF: Isoflurane potency in the northern leopard frog *Rana pipiens* is similar to that in mammalian species and is unaffected by decerebration. Vet Res Commun 2007; 31:757–63
16. Yang J, Chai YF, Gong CY, Li GH, Luo N, Luo NF, Liu J: Further proof that the spinal cord, and not the brain, mediates the immobility produced by inhaled anesthetics. ANESTHESIOLOGY 2009; 110:591–5
17. Jinks SL, Atherley RJ, Dominguez CL, Sigvardt KA, Antognini JF: Isoflurane disrupts central pattern generator activity and coordination in the lamprey isolated spinal cord. ANESTHESIOLOGY 2005; 103:567–75

ANESTHESIOLOGY REFLECTIONS

25 Years of Curating for the Wood Library-Museum

In 1986 one of my then colleagues at Yale, a past editor-in-chief of ANESTHESIOLOGY, Dr. Nicholas Greene, had joined his fellow Wood Library-Museum (WLM) Trustee, Rod Calverley, in asking me to do at a national level what they had seen me do at Yale: set up a *bona fide* museum gallery. Consequently, 25 years ago this month, in March of 1987, I arrived at the WLM's Busse Highway address in Park Ridge, Illinois, on a scouting mission to transform the museum side of the WLM. Sadly our "national gallery" had dwindled down to a single display cabinet (*right*) in the photocopy room of the headquarters building of the American Society of Anesthesiologists. As "Acting Curator," I soon began exploring the basement of the two-story building. I was heartbroken to find myself wading through scores of vintage anesthesia machines that had been haphazardly crushed together inside a tiny room next to the furnace. Clearly my first task would be to inventory the large apparatus. . . . (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.

Copyright © by the American Society of Anesthesiologists. Unauthorized reproduction of this article is prohibited.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/116/3/701/256883/0000542-201203000-00031.pdf by guest on 17 May 2022