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Setting the "Furnace" during Anesthesia

FEW physiologic functions are so well guarded as the thermoneutral zone. It is kept within a narrow limit of ±0.2°C *via* most sophisticated sensing/effector mechanisms. This way, optimal working conditions for the cellular machinery are preserved. During anesthesia, the thermoneutral zone widens by a factor of 10.[1] Therefore, protective measures to prevent heat loss, such as vasoconstriction, may be impaired, permitting redistribution of body heat from core to periphery.

Countermeasures commonly used in clinical practice include external heating by convection, conduction, and radiation. In this issue of ANESTHESIOLOGY, Mizobe *et al.*[2] approach the problem of heat loss and temperature balance during anesthesia by infusing fructose solutions to stimulate endogenous heat production. This is an innovative approach to control core body temperature *via* nutrient driven endogenous mechanisms.

To be sure, manipulating endogenous heat production, particularly during the anesthetized state, calls for caution. There are few mechanisms that govern heat production when compensation for overheating is needed. The only mechanism by which we are able to decrease body heat is by sweating, which is known to be delayed during anesthesia.[1,3,4] Anesthesiologists are very much aware of the overheating problem during anesthesia because they sometimes are being confronted with the rare but threatening syndrome of malignant hyperthermia. This metabolic condition is a good example of how endogenous heat production can be deleterious.

Obligatory heat production, from basal metabolism and muscular exercise, is reduced by up to 25% by anesthesia.[5,6] Facultative heat gain from shivering and nonshivering thermogenesis are both reduced during anesthesia.[1,7] Mizobe *et al.* demonstrate that it is possible to improve temperature balance by infusion of fructose before and during anesthesia. Is this accomplished by an increased obligatory heat production or is it due to the facultative alternatives of shivering and nonshivering thermogenesis? In conformity with what Mizobe *et al.* demonstrated for fructose solutions, previous investigations have reached similar results after infusion of amino acid solutions.[8,9] In those studies of both awake and anesthetized adult humans, it was demonstrated that heat production caused by amino acid infusions occurred in muscle tissue.[6] However, responsible cellular mechanisms have not been clarified. A specific finding in previous studies that justifies caution with this approach was that heat production from 2.25 g amino acids per hour more than doubled heat production during anesthesia as compared with during the awake state.[8] Because recent reports have identified uncoupling proteins in skeletal muscle,[10] there are possibilities for an exaggerated mitochondrial heat production, such as malignant hyperthermia, from which the anesthetized individual has little chance to protect himself or herself because sweating, as stated above, is delayed as a result of the widened thermoneutral zone. In agreement with previous findings of enhanced heat production during anesthesia,[8] it was of great interest that heat production from the same amount of fructose was 20% higher during anesthesia as compared with during the awake state.[2] One wonders why. Nature has provided an interesting example. In a tetraplegic human, a defined amount of protein or amino acids result in a higher heat production than in a nontetraplegic individual.[11] Enhanced heat production from tetraplegics and from the unconscious anesthetized individual challenge the assumption that there might be descending inhibitory neuronal pathways permitting central nervous functions to balance metabolic rate and heat production.

So it now seems that stimulated endogenous heat production by either fructose or amino acid solutions reduces the degree of hypothermia during and after anesthesia. Although some concern has been raised with similar approaches that overheating could occur, this has not yet been reported. Another concern, raised in the late 1990s, was that the stimulated endogenous heat production during anesthesia enhances postoperative oxygen consumption.[9] This could have negative effects, particularly in cardiac patients with a compromised coronary circulation, but may be preferable to the shivering that may otherwise result. Indeed, previous reports on stimulated endogenous heat production during anesthesia have indicated that postoperative shivering disappears.[12] This may be beneficial, because postoperative shivering is relatively inefficient and may dramatically increase myocardial oxygen demands.[12] Shivering may also be associated with impaired quality of care, increased use of medications, and pain. It would be of interest to compare in future studies indices of oxygenation

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and myocardial oxygen demands in patients warmed with exogenous and endogenous methods.

Although basic mechanisms responsible for stimulated endogenous heat production during anesthesia are not well delineated, it seems to be an effective method to improve temperature balance during anesthesia and surgery. We know that improved control of perioperative temperature has definite practical benefit to important outcomes such as hospital duration of stay.[12] We already have effective means to do so using exogenous heating. Before this method using endogenous heating could be widely adopted, important questions remain, such as the capacity to precisely set the "furnace" during anesthesia and indeed a better understanding of the of central mechanisms responsible for this effect. Other issues of importance when comparing the two methods that will be important to address include cost effectiveness and provider compliance with regimens. Nonetheless, given the importance of perioperative temperature control, this is a promising method that deserves further evaluation.

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Do General Anesthetics Add Up?

ANESTHESIOLOGISTS practice the skilful use of pharmacologic synergism, or supra-additive drug interactions, to enhance desirable anesthetic actions while minimizing agent-specific undesired effects through reduced individual drug doses. Often this art is supported by experimental and clinical evidence (*e.g.*, synergism between midazolam and propofol in hypnosis,[1,2] used to advantage in coinduction of anesthesia), but the cellular and molecular mechanisms underlying these important drug interactions are usually poorly understood, if at all. Our incomplete understanding of the molecular mechanisms of the defining drugs of our specialty certainly contributes to this knowledge gap. However, advances in the molecular pharmacology of general anesthetics and drug interactions are facilitating investigations into the mechanisms of anesthetic action. These developments are evident in the complementary reports in this issue of ANESTHESIOLOGY that compare the interactions of the prototypical intravenous and volatile anesthetics propofol and sevoflurane both at the behavioral level in human volunteers[3] and at the level of an anesthetic-sensitive neurotransmitter receptor.[4]

Current models of general anesthesia suggest that different molecular targets in various regions of the nervous system are involved in the multiple components of anesthetic action and that these targets can vary among specific anesthetics.[5,6] Immobilization is a property of anesthetic action that is used as a standard measure of anesthetic potency (as minimum alveolar concentration), whereas lower anesthetic concentrations are required for other anesthetic end points (*e.g.*, amnesia and unconsciousness). Although there is no universal target that explains all of the actions of every general anesthetic, or even of a single anesthetic, neurotransmitter-gated ion channels, particularly certain receptors for γ-aminobutyric acid and glutamate, are modulated by most anesthetics and are probably important molecular targets *in vivo*.

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The studies by Harris *et al.*[3] and Sebel *et al.*[4] represent two extremes of the pharmacologic research spectrum: behavioral responses *in vivo* and receptor responses *in vitro*. Although such a comparison is informative (much more than either study alone), much happens between the receptor and the behavioral response, and how anesthetics affect these intermediate processes is poorly understood. So a comparison of the nature of anesthetic interactions on two clinically relevant behavioral end points (loss of consciousness and immobility) thought to involve different sites of action in the central nervous system (forebrain and spinal cord[7,8]) and on an important molecular target (γ-aminobutyric acid receptor type A [$GABA_A$] receptor) that is positively modulated by both propofol and sevoflurane[4] should provide important clues to mechanisms of anesthesia. Such studies are of mechanistic value because an additive drug interaction supports a common mechanism or site of action for each drug, whereas a synergistic interaction suggests separate interacting sites.[9] By examining a single point on the predicted lines of additivity for loss of consciousness or immobility ($EC_{50}/2$ for propofol and sevoflurane), Harris *et al.* found additivity for both anesthetic end points *in vivo*. Sebel *et al.* used response surface modeling (which covers a range of concentrations) of anesthetic enhancement of $GABA_A$ receptor affinity for γ-aminobutyric acid to demonstrate an additive interaction *in vitro* as well.

Numerous examples of synergistic drug interactions exist in anesthesiology, including interactions between two drugs (*e.g.*, propofol and midazolam[1,2]) or of a single drug delivered to two sites (*e.g.*, spinal and supraspinal morphine[10]). Such synergistic interactions imply distinct sites of action, such as different anatomical sites, cell populations, or signaling pathways/receptor sites within the same cells. Conversely, additive interactions imply convergent actions on the same protein site, molecular pathway, or cellular site. There is convincing electrophysiologic and genetic evidence that propofol and sevoflurane act on $GABA_A$ receptors. Together with the finding that they interact in an additive manner, the indication is that both anesthetics interact at a single site ($GABA_A$ receptors) to produce anesthesia. However, a single amino acid substitution in the $GABA_A$ receptor β_3 subunit second transmembrane domain results in nearly complete resistance to propofol but only modest resistance to volatile anesthetics,[11,12] whereas an analogous mutation in the α_1 subunit reduces sensitivity to volatile anesthetics without affecting sensitivity to intravenous agents.[13] In light of these observations, how could propofol and sevoflurane be acting at the same site, as suggested by their additive effects on immobility and loss of consciousness? The most parsimonious explanation of these findings is that propofol and sevoflurane act at different sites/subunits on $GABA_A$ receptors to produce a similar effect on gating. In the case of $GABA_A$ receptors *in vitro*, this seems to involve separate binding sites on the same receptor converging to produce enhanced agonist affinity. However, the *in vivo* evidence does not allow us to rule out interactions through separate receptors that converge at a common downstream site to yield an additive interaction. Indeed, such a multisite mechanism seems necessary to explain the observation that spinal $GABA_A$ receptors are not involved in immobilization by isoflurane.[14] Therefore, although synergistic interactions indicate distinct sites of action (and thus are more informative mechanistically), additive interactions do not necessarily indicate an identical site of action, at least at the molecular level.

A simple explanation of the results presented by Harris *et al.* and Sebel *et al.* would be that both propofol and sevoflurane produce loss of consciousness and immobility through potentiation of $GABA_A$ receptor function. However, 150 yr of investigation have taught us that anesthetic mechanisms are far from simple. Accumulating evidence obtained using a variety of experimental approaches indicates that volatile anesthetics are unlikely to produce immobility solely through potentiation of $GABA_A$ receptors.[5,6,14] Rather, general anesthetics probably act at multiple sites (anatomical and molecular) to produce the defining anesthetic end points. Therefore, switching from one anesthetic to two does not significantly impact the overall anesthetic effect mediated by the convergent actions of various affected receptors and anatomical sites. Despite the parallel observations of additive interactions between propofol and sevoflurane both *in vivo* and on a subtype of $GABA_A$ receptor *in vitro*, the reductionist view of a common molecular mechanism does not add up. Nevertheless, the important clinical implication is that propofol and sevoflurane can be combined without concern for overdosing or underdosing as a result of potential synergistic or antagonistic interactions.

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Ansel Marion Caine, M.D.

A Timeless Lesson in Professionalism?

WHY study the life and career of Ansel Marion Caine (1882–1961)? There are those in the history community who have de-emphasized biography as a tool in historical study because it brings together the twin sins of "hero worship" and elitism. However, this argument is fallacious, because in writing a biography, the author studies carefully the person, his or her life, and the times in which he or she lived. It is a picture of an individual set in the background of events of the person's life that makes compelling reading. Drs. Broussard, Vachon, and Winthrop have done just that with Dr. Caine.[1] They are to be especially commended for seeking not just the secondary source material, *i.e.*, what has been written about the subject, but seeking family members and primary documents such as correspondence, telegrams, and photographs and doing interviews with those who remember Dr. Caine. This article is an excellent example of how the history of medicine needs and ought to be written by physicians.

Methodology aside, why does an anesthesiologist who has been dead for 45 yr make for such compelling reading? In essence, the question becomes, is there anything that can be learned from the life of a physician who practiced a half century ago? What compelling thoughts or actions did Dr. Caine have to which the modern reader can relate? Why does the leading journal in the specialty devote pages to this New Orleans, Louisiana, anesthesiologist when there are clinical studies ready to be published that may have a more direct impact on clinical care? How does Ansel Caine "stack up" when compared with 21st century ideals of medical professionalism?

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First and foremost, the word portrait painted by Dr. Broussard and his colleagues of Ansel Caine brings to life a figure who, until now, has not been recorded as being on the forefront of the development of anesthesiology. But he was. As the article points out, he cared deeply for and about the patient, the most important person in any anesthetic. Dr. Caine was willing to leave his practice and see to a patient in Miami, Florida. Jumping on a plane and flying from New Orleans to southern Florida seems of little significance to the 21st century reader. But in 1930, air travel was new, novel, and risky. A scant 3 yr before, Charles Lindbergh had been the first to fly solo across the Atlantic Ocean. A plane coming into a city was often a time for spectators to gather to see this novel flying machine. In another episode, Dr. Caine anesthetized Tomas Gabriel Duque, the President of Panama. Dr. Caine faced a patient most likely in thyroid storm, weak, frail, and at extremely high risk. A bad outcome could have ended in his death, but Ansel Caine was willing to put his own life in jeopardy to see to the life of another.

Dr. Caine did not have the facilities of the modern anesthesia department, a formalized curriculum in anesthesiology, or any of the amenities we associate with academia. But he taught all those willing to learn anesthesia. Moreover, when Charity Hospital in New Orleans recruited a chief anesthetist, which would today be regarded as the chair of the department, Dr. Caine supported the new person, Dr. John Adriani (1907–1988), personally and financially. The idea presented by Jerome Model, M.D., D.Sc. (Professor Emeritus, Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida), during his 2004 Rovenstine Lecture, of giving a small percentage of each anesthesiologist's annual salary to help support academics, seems to be a continuation of a tradition started by those who helped to create the medical specialty of anesthesiology as this article so clearly documents.

In the true sense of being a physician, Dr. Caine published his observations. In the current medical literature, the "how I do it" article has been transformed into the clinical study, replete with sophisticated statistics and randomization methodologies, but in Dr. Caine's era, this did not exist. However, it was important that successful patient management strategies be published. His work with oxygen was innovative for the time, and there were concerns about how much oxygen patients could inspire without damage to their lungs. In addition to publishing his clinical observations and experience, Dr. Caine also worked to improve the equipment with which he administered anesthesia. In an age when there was no standardization of connectors and tubing and no temperature-compensated vaporizers, and while working as a full-time clinician, he managed to devise and patent a method to warm ether and overcome the loss of heat due to vaporization.

Ansel Caine also understood the need to be involved with the professional organizations in the specialty. His willingness to travel to Rochester, Minnesota, to see what Dr. John Lundy (1894–1973) had to offer in the inaugural Anesthetists Travel Club meeting demonstrates this commitment. His further work with the club, including hosting the meeting, shows that he had innovative anesthesia techniques to offer the group. The fact that Dr. Caine sought certification by the then fledgling American Board of Anesthesiology, after more than 25 years as a specialist, demonstrated his commitment to advancement of the field. He was a founding member of the American Society of Anesthetists (which became the American Society of Anesthesiologists in 1945) board of directors and was integral to the creation of the Louisiana Society as an American Society of Anesthesiologists component in the late 1940s.

Why should one study Ansel Caine? His career is in many ways a road map for anesthesiologists in the 21st century studying professionalism. In 2002, the *Annals of Internal Medicine* published an article entitled "Medical Professionalism in the New Millennium"[2] as a guide to the study and teaching of professionalism. The article cites three fundamental principles and 10 commitments. Ansel Caine's story clearly demonstrates one of the principles, the *Principle of primacy of patient welfare*. He also exhibits several of the commitments starting with the *Commitment to professional competence*— both by his desire to be American Board of Anesthesiology certified and by his ongoing teaching of the art of anesthesiology to other physicians. By recruiting and supporting new anesthesiologists in New Orleans, he demonstrated his *Commitment to improving access to care*; likewise, his publications and invention show a *Commitment to scientific knowledge*. His work within the professional organizations could be classified as a *Commitment to professional responsibilities*.

However, Ansel Caine was unaware of how his story would be used a half century later. To him, patient care was paramount, even if the circumstances could endanger the life of the physician. Be it air travel, infectious disease, or a dictator's bullet, caring for the patient was what Dr. Caine held in highest esteem. To deliver the best care possible, he continued to study his methods, report results, and create new and hopefully better ways by which patients could be helped. Dr. Caine's mind, his pen, and his time elevated the specialty of anesthesia, often at some personal risk. What if the credentials committee of the American Board of Anesthesiology had refused his petition, and he had to take the examinations? No doubt Caine would have, because it was the right thing to do—to demonstrate to his patients that he was a recognized specialist and to elevate the practice of this particular part of medicine he so enjoyed. Until now, memories of Dr. Ansel Marion Caine may have been few, as his contemporaries and students are slowly fading from the anesthesia scene. But today, decades after his death, Dr. Caine's biography outlined in this issue of ANESTHESIOLOGY clearly resonates with a clear demonstration of the highest forms of professionalism. It is for this reason we should study his career and continue work in the history of anesthesiology to better understand the foundations on which the current practice of anesthesiology rests.

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