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Regional Anesthesia: Advancing the Practice of Medicine 31st Annual Gaston Labat Award Lecture

James C. Eisenach, MD

F.M. James, III Professor of Anesthesiology and Physiology & Pharmacology, Wake Forest University School of Medicine

Introduction

The Gaston Labat Award and its lecture were established in 1977 by the American Society of Regional Anesthesia (ASRA) to honor the memory of Gaston Labat, a pioneer in the field of regional anesthesia and a man who was instrumental in defining anesthesiology as the practice of medicine. I am extremely honored to receive this award and its recognition of my contributions to regional anesthesia. ASRA retains an apprenticeship culture in the greatest tradition of medicine, and I particularly thank Gerald Ostheimer, MD, a former Editor of this journal, who brought me into the ASRA family and mentored me on how to best serve the organization. I also want to take this opportunity to express my thanks and love to Patricia, the woman I married in the same year that this award was founded. She has and continues to lead me in a lovely path through life and in raising our wonderful children, Laurel and David.

Gaston Labat and anesthesiology as the practice of medicine

A brief biography of Dr. Labat's life and contributions to regional anesthesia have previously appeared in this journal (1), but it is traditional to begin the manuscript describing the award lecture with facets of Dr. Labat's life which apply to the topics discussed. Dr. Labat was born in 1876 in the Seychelles Islands off the East coast of Madagascar. To put the year of Labat's birth in perspective, 1876 was also the year of the death of General George Custer at the Battle of the Little Bighorn, the birth of Otto Diels who would go on to receive the Nobel Prize in chemistry, the publication by Mark Twain of *Tom Sawyer*, and the foundation of Johns Hopkins University and the National Lampoon at Harvard University. The American Presidential election of 1876 foreshadowed those of modern times, with a tight race, a contested vote with charges of voting irregularities in 3 states including Florida, and final selection of a President by an Electoral Commission formed by Congress that included 5 members of the Supreme Court.

Labat did not pursue medical training until he was nearly 40 years old, matriculating in Montpelier, then in Paris, where he made the acquaintance of Pauchet and served shortly thereafter as co-author on the 3rd edition of Pauchet's early text on regional anesthesia (2). He emigrated to the United States in 1920, spending one year at Mayo Clinic and the remainder

Address correspondence to Dr. Eisenach, Department of Anesthesiology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC, 27157. Telephone: 336-716-4182. FAX: 336-716-0288. Email: eisenach@wfubmc.edu.

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of his life in New York. He is best known in regional anesthesia for his classic textbook on the subject (3), which was accompanied by a foreword by William J. Mayo, M.D., and by his leadership in establishing the first ASRA in 1924. ASRA was instrumental in establishing Anesthesiology as the practice of medicine. As previously chronicled by Bacon (4), the path to a medical specialty in the United States involved first being designated a section of the American Medical Association (AMA). A requirement for such designation was sponsorship by two national specialties. Anesthesiology became a section of the AMA with sponsorship by the American Society of Anesthesiologists, which had been recently renamed from the New York Society, and by ASRA. Labat did not live to see this development in 1938, and the ASRA he founded was disbanded shortly thereafter. Nevertheless, it is thanks in large part to his efforts that regional anesthesia and anesthesiology in general became the practice of medicine and that ASRA was later reborn into the society which we recognize today.

Regional anesthesia as the practice of medicine: *primum non nocere*

A basic tenet of medicine is *primum non nocere*, “first do no harm”, and discussions of safety, complications, and contraindications represent a large part of the annual meeting of ASRA and of publications in this field. Medicine in general and regional anesthesia in particular suffer from a lack of good randomized, controlled trials (RCTs) to provide the evidence for safe interventions. Although some practices are so obviously an improvement on the alternative that no RCTs are necessary, such as the use of parachutes to prevent injury from free fall (5), without RCTs we must rely on weaker evidence including observational studies, case cohort studies, case series, or isolated case reports. The weakest form of evidence to guide clinical practice in medicine is that of the consensus statement, since this in most circumstances reflects opinion of a small subset of practitioners, usually academic experts, since this process unintentionally excludes the congregate experience of the wider clinical practice.

ASRA, especially under the leadership of Teresa Horlocker, M.D., has been very active in requesting broad clinical input at national meetings in order to generate consensus statements to guide aspects of clinical practice as they relate to safety in regional anesthesia. These include meetings and consensus statements on local anesthetic toxicity, neuraxial anesthesia and the anticoagulated patient, and infectious complication of neuraxial blockade. All of these are freely available at the ASRA Web site (www.asra.com). The 2008 ASRA annual meeting included discussions on the development of a consensus statement regarding the use of intralipid to treat cardiovascular toxicity from local anesthetics, based on the pioneering work of Guy Weinberg in this area (6). I do not mean to disparage these efforts, since they are providing valuable guidance on the principle of *primum non nocere*, but merely indicate that these are the earliest and least reliable of the degrees of evidence for safe practice.

Substances which may be safe and therapeutic when administered systemically may be either dangerous or ineffective or both when administered perineurally or neuraxially. Regional anesthesia has a checkered history in this regard, with research reports of well meaning but cavalier injection on peripheral nerves or neuraxially of drugs which happen to be available for systemic administration, but for which nothing is known regarding their neurotoxic potential. In response to this concern, *Anesthesiology* and *Anesthesia & Analgesia* changed their Guide to Authors in 2007 to include a statement that Institutional Review Board approval of a study of perineural or neuraxial administration of a drug does not guarantee ethical practice, since these boards may lack the expertise or understanding regarding these potential risks. In the harmonized Guide to Authors of these two journals, we indicate that such studies will be considered for publication only if **A**) they are approved for that route of administration by regulatory agencies (the Food and Drug Administration in the United States), **B**) the study is being performed under the oversight of the regulatory agency, or **C**) there is a large and accepted

clinical practice with the drug by that route. Several other journals in our specialty are considering adoption of this wording.

Regional anesthesia as a technical field

Medicine is defined as the art or science of treating disease and restoring or preserving health by means of drugs, surgical operations, and other manipulations. Historically, the practice of medicine was distinguished from that of surgery and obstetrics, and remnants of this distinction remain today (e.g., the naming of medical schools such as the Columbia University College of Physicians and Surgeons). A focus on technical interventions remains more common in the surgical specialties than in those of medicine, and regional anesthesia is much closer to pure surgery than medicine in this regard.

Peripheral nerve blocks were performed by Gaston Labat and his successors for many years with a simple reliance on a knowledge of anatomy and obtaining positive responses of fluid (cerebrospinal fluid in the case of spinal anesthesia, arterial blood in the case of a through-the-artery approach to axillary blockade) or paresthesias from deforming or piercing the nerve with the needle. I likened this approach in my lecture to the children's game of Battleship, wherein one uses logic but also semi-blind probing to identify the desired target. There is no doubt that this classic approach to regional anesthesia involved a thorough understanding of anatomy, manual dexterity, and close communication with the patient, but I personally consider this approach to represent more a technical feat than a strong example of the art of medicine. These methods were mastered by a relatively few individuals and performance of regional anesthesia by these methods was difficult, time consuming, or failed in many cases because of relatively common and far ranging anatomic variations.

There has been a rebirth and democratization of regional anesthesia over the last 25 years resulting from the application of technology, first by electrical stimulation and later by ultrasound, to guide the performance of peripheral nerve blocks. One can question whether the positive demonstration of anatomy with these techniques has increased the speed with which blocks can be performed and their reliability and safety. But one cannot question that these methods have facilitated the teaching of regional anesthesia and have made it less mysterious to both doctor and patient. These are good things. On the other hand, these new methods are simply aids in the accomplishment of the technical task of inserting a needle or catheter in the correct position. Of course this must be done before regional anesthesia can occur, and it is appropriate that a considerable portion of the annual meeting of ASRA be dedicated to demonstration of these technical aspects, especially in small group learning sessions. But this procedure itself should not be confused with the practice of medicine.

Anesthesiology is the practice of perioperative, critical care, and pain medicine

Anesthesiology recently reorganized its table of contents into the 3 aspects of medicine which define our specialty: perioperative medicine, critical care medicine, and pain medicine. We spend relatively little time in regional anesthesia and in ASRA discussing how we treat disease and restore health within these 3 fields of medicine. To get a sense for current research in this regard, I searched clinicaltrials.gov, one of the central repositories for registration of major clinical trials and where all NIH supported clinical research is registered. While searching only for studies which were funded by the NIH, I noted in perioperative medicine a trial by Brian Ilfeld, M.D., on continuous femoral nerve block following total knee replacement (Clinicaltrials.gov identifier NCT00135889) and another by Daniel Sessler, M.D. on regional anesthesia and breast cancer recurrence (Clinicaltrials.gov identifier NCT00418457). In pain medicine, I noted a trial by Rollin M. Gallagher, M.D., M.P.H. on regional anesthesia in combat

trauma improves pain disability outcomes (Clinicaltrials.gov identifier NCT00431847). In critical care medicine, I found nothing. These are important clinical trials to determine the role of regional anesthesia to affect rehabilitation after surgery, reduction in cancer burden, and reduction chronic pain after war injury. But the number of such studies is extremely modest and the time we spend discussing them at the ASRA annual meeting is equally modest. This reflects in part the general dearth of federally funded research in our specialty (7), and hopefully ASRA will facilitate such work by support of important research through its own Carl Koller Award and its support of the Foundation for Anesthesia Education and Research.

Advancing medicine: peripheral nerve block

Regional anesthesiologists are experts at selectively regulating peripheral nerve function by elegantly applying drugs in proximity to major nerves. We have restricted our practice nearly exclusively to the injection of local anesthetics to produce anesthesia and analgesia. Recent studies from the laboratory suggest that we should as a field expand our thinking in this regard and foster and present research related to novel approaches to perineural therapy.

One problem relating to perineural injection of local anesthetics is the toxicity associated with their absorption, or more likely, accidental injection into the circulation. This risk of toxicity is inherent in the local anesthetics themselves, and is reduced but not eliminated by technical maneuvers such as fractionation of doses, slow injection, and visualization of injection site with ultrasound. Recent research on the transient receptor potential vanilloid-1 (TRPV-1) channel, the so called capsaicin receptor, suggests that another approach might be taken to reduce the risk inherent in local anesthetic molecules themselves.

The TRPV-1 channel, first cloned by a research group including an anesthesiologist (8), is present primarily on C-fibers and, when stimulated by acidosis, heat, or the active ingredient in hot chili peppers, produces the sensation of hot, burning pain. Whereas one would imagine that TRPV-1 channels would only be expressed at peripheral endings of pain fibers, they happen also to be expressed on axons of peripheral nerves that are exposed to drug during peripheral nerve block. When capsaicin binds to the TRPV-1 channel it opens and allows sodium and other cations to enter, resulting in depolarization and, in the case of C-fibers, the sensation of pain (Figure 1). This is normally a transient phenomenon, but if capsaicin remains bound to the channel it alters its configuration, increasing the pore size (9).

Of what relevance is this biophysical curiosity of sustained activation of the TRPV-1 channel to regional anesthesia? This increased pore size may represent a gate to therapy with new local anesthetics (or other neural therapeutics) or use of much lower doses of existing local anesthetics. Local anesthetics block axonal conduction primarily by blocking sodium channels, and to do so they must first enter the nerve, where they bind to the channel on the cytoplasmic side. For this reason, permanently charged analogues of local anesthetics such as QX-314 have either a very slow onset of action or fail to act *in vivo* to produce anesthesia, since they cannot traverse the lipid rich membrane of axons. Recently, Binshtok and colleagues (10) showed that addition of capsaicin allows these normally ineffective local anesthetic analogues to produce sodium blockade *in vitro* and peripheral nerve block *in vivo*, presumably because capsaicin-induced opening of the TRPV-1 channel pore allows direct entry of these molecules into the cytoplasm of the axon (Figure 1).

Several questions remain regarding the intriguing concept of using the TRPV-1 channel pore to gain entry to the nerve. For example, others have suggested that these permanently charged local anesthetic analogues do indeed produce anesthesia *in vivo*, and that the addition of capsaicin is not necessary (11). Clinical trials will ultimately determine whether perineural injection of capsaicin or other activators of TRPV-1 channels is safe and effective to increase permeability of drugs to enter the peripheral nerve. Should they prove to be so, their

combination with local anesthetics could enhance the safety of peripheral nerve block, since accidental intravenous injection would dilute the capsaicin enough to prevent it from opening pores in the central nervous system or the cardiac conduction system. Without a gate to the inside of these cells, the local anesthetic analogues might be harmless. But just as importantly, we in regional anesthesia should be at the front of this research and examining new therapeutics this might afford for treating disease by targeting therapy to peripheral nerves.

Another potential for perineural administration of drugs to treat disease builds on recent knowledge regarding the role of peripheral inflammatory processes in neuropathic pain. Mechanical nerve injury, either from trauma or by tumor enlargement, results in cell death and Wallerian degeneration, often followed by regeneration. These processes result in activation and release of pro-inflammatory compounds from cells which reside in the peripheral nerve, including Schwann cells and immune cells, and from circulating immune cells that are recruited by chemokines. The pro-inflammatory compounds, including prostaglandins and cytokines, as well as co-secreted neurotrophins, enter the peripheral nerve and result in sensitization by upregulating ion channels and by inducing further spinal cord release of cytokines (Figure 2) (12).

Animal studies and some anecdotal clinical experience suggests that neuropathic pain associated with peripheral nerve injury and presumed inflammation can be effectively treated by perineural administration of drugs which modulate the immune response. For example, some patients with neuropathic pain associated with cancer receive prolonged analgesia from perineural administration of the α_2 -adrenoceptor agonist, clonidine (Personal Communication, Patricia P. Lavand'homme, M.D., Universite Catholique de Louvain, Brussels, Belgium). The slow onset and prolonged (weeks) duration of analgesia observed in these patients suggest a modulatory effect of clonidine on genetic expression or immune regulation rather than a transient pharmacologic effect on the nerves themselves. This observation resulted in a series of investigations in the laboratory that demonstrated that α_2 -adrenoceptors are localized to macrophages and T cells in states of neuritis (13,14). Temporary activation of these receptors downregulates their pro-inflammatory products while upregulating their anti-inflammatory products, and these effects are accompanied by a reduction in hypersensitivity (15).

Advancing medicine: targeting the spinal cord

Following the demonstration 25 years ago of opioid receptors in the spinal cord and analgesia from spinally applied opioids in animals (16), regional anesthesiologists have embraced the use of opioids by the spinal and epidural route in the treatment of acute and chronic pain. These initial positive findings with opioids led rapidly to an explosion of description in animals of receptors, ion channels, and intracellular signaling systems that could be manipulated by intrathecal administration of compounds to produce selective analgesia without other sensory or motor weakness. Clinical application of this new knowledge has been modest, with a α_2 -adrenoceptor agonist (clonidine) and a calcium channel antagonist (ziconotide) approved for epidural or spinal use in the United States. This lagging application of new knowledge into practice reflects the cost and time required to perform the requisite neurotoxicity studies to ethically proceed with study in humans and in the realities of the small marketplace for this specialized route of delivery.

One of the more topical approaches to spinal analgesia and the process of central sensitization, which is presumed to underlie chronic pain is targeting glial modulation of spinal cord neuronal function. Peripheral injury and inflammation result in activation of microglia, the main resident immune cells of the spinal cord. Activated microglia synthesize and release prostaglandins, pro-inflammatory cytokines, and chemokines, all of which result in central sensitization (17). This glial activation, which occurs after incisional surgery in animals (just as it does in models

of chronic neuropathic pain), can be targeted to reduce hypersensitivity and pain (17). Following preclinical toxicity studies (18), we recently introduced ketorolac as an experimental spinal analgesic to probe the role of prostaglandin production by spinal cord microglia in human pain states (19). Preliminary data suggest that ketorolac is active against postoperative pain and hypersensitivity, and we have begun a study of the effect of spinal ketorolac on mechanical hypersensitivity after total hip replacement (Clinicaltrials.gov identifier NCT00621530).

It is conceivable that regional anesthesiologists will advance medical practice by using light therapy in the spinal cord to treat pain or other diseases. Experimental neuroscience has recently embraced the use of microbial rhodopsins in the study of circuits in the nervous system. Specific cells in the nervous system can be transfected with viral vectors encoding either excitatory or inhibitory rhodopsins, ion channels that either excite or inhibit the cell when exposed to light of a specified wavelength. By transfecting only one class of neurons, for example only those which synthesize acetylcholine, one can determine their role in complex circuitry in the brain by examining the effects of inhibiting or activating them with fiberoptic light (20). This research technology could have direct applications to the treatment of chronic pain, akin to the current use of electricity in spinal cord stimulation. As such, one could imagine transfecting pain transmitting cells in the spinal cord, those which express the receptor for substance P, with an inhibitory rhodopsin. Implanting a small fiberoptic bundle and illuminating the spinal cord would then inhibit these cells, leaving other sensory modalities intact (Figure 3). Regional anesthesiologists should also be at the forefront of research to determine whether such novel therapy is feasible.

Advancing medicine: regional autonomic regulation

Regional anesthesia has provided little advance in the medical care of critically ill patients, aside from providing pain relief. In preparing for this lecture I asked my intensive care unit colleagues what was the leading cause of major morbidity and mortality in their units, and they uniformly and rapidly responded with, “Sepsis and uncontrolled inflammation, leading to multi-system organ failure”. It is conceivable that regional anesthesiologists could have a major impact on this central problem in the intensive care unit by investigating the role of regional autonomic nervous system activity.

We are comfortable with the concept that some of our central and peripheral nerve blocks result in regional reduction in sympathetic nervous system activity, and we occasionally utilize this as a primary therapeutic measure, for example in the treatment of complex regional pain syndrome. But we rarely manipulate or alter parasympathetic nervous system activity, especially as relates to the vagus nerve. There has been an explosion of research in the last several years regarding the role of vagal nerve activity in inflammation, sepsis, and shock. This was catalyzed by the observation that vagal stimulation reduces inflammation (21), an effect due to acetylcholine acting on nicotinic acetylcholine receptors on peripheral immune cells to reduce pro-inflammatory product secretion. Thus, there is an ongoing communication between peripheral inflammation and the central nervous system, with the central route of communication represented by the vagus nerve. Vagal afferent terminals in the periphery express receptors for and respond to products of peripheral inflammation, and signal to sub-cortical and cortical regions when inflammation is present. The resultant reflexes include stimulation of vagal efferents, which release acetylcholine in a regionally selective manner to reduce peripheral inflammation (22).

How might regional anesthesiologists build upon this new knowledge regarding the role of vagus nerve activity in sepsis and uncontrolled inflammation? We have not in the past attempted to deposit drugs on branches of the vagus, in part because of the complexity of this anatomy in the neck and upper thorax and in part because of our inability in the past to localize

such small nerves. With increasing resolution of ultrasound methods and development of new and even better methods to visualize nerves, we should in the near future have the ability to target branches of the vagus nerve for drug injection. This would allow us to manipulate local acetylcholine release in inflammatory states, potentially without the side effects of systemically administered drugs that increase or decrease cholinergic receptor signaling. We have much to offer this important research avenue in the care of the critically ill patient.

In summary, Gaston Labat was instrumental in importing and popularizing regional anesthesia in the United States. He also demonstrated that anesthesiology is the practice of medicine and advanced the national recognition of this by the AMA. In my opinion, Dr. Labat would be disappointed on the emphasis in regional anesthesia and ASRA on technical aspects of needle and catheter insertion and consensus opinions on how to avoid complications, and our neglect of fundamental and applied research and collaboration to advance the practice of medicine through the use of our unique talents and techniques. I have outlined a few areas in which we could become more engaged, and hope to see an increasing emphasis on our role in advancing the practice of medicine as ASRA matures and continues to grow.

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Figure 1.

Mechanisms by which transient receptor potential vanilloid 1 (TRPV1) channel on axons can enhance peripheral nerve block. Brief exposure of TRPV1 channels to an agonist, such as capsaicin, results in pore opening and depolarization of the axon by entry of Na^+ and other cations. Prolonged exposure of TRPV1 channels to an agonist results in a widening of the pore, allowing larger molecules, such as the permanently charged lidocaine analogue, QX-314, to enter the axon, where it can bind to the sodium channel and produce neural blockade.

Figure 2.

Inflammatory response to peripheral nerve injury which can be modulated by locally applied drugs. Nerve injury results in injury to Schwann cells (S) which release cytokines to cause recruitment and activation of macrophages (M). Activated Schwann cells and macrophages release pro-inflammatory cytokines, such as tumor necrosis factor α (TNF α) and interleukin 1 β (IL-1 β) and growth factors, such as nerve growth factor (NGF) which either signal through receptors on nerve axons or are transported centrally to the dorsal root ganglion, where they result in peripheral and central sensitization.

Figure 3.

Use of rhodopsin for spinal cord illumination for analgesia. **A)** Halorhodopsin, a microbial channel, is permeable to chloride (Cl^-) when illuminated with light of certain wavelengths. **B)** Transfection of cells with halorhodopsin in the spinal cord which express the receptor for substance P (neurokinin-1 receptors – NK-1) would specifically target cells which receive nociceptive input from C fibers. **C)** Spinal cord illumination would result in hyperpolarization and hence inhibition of only the NK-1 expressing pain transmission neurons, resulting in analgesia.