

Does Memory Priming during Anesthesia Matter?

THE article in this issue of ANESTHESIOLOGY by Iselin-Chaves *et al.*¹ consolidates recent evidence that memory “priming” persists during adequate anesthesia. We are now in a position to move on from wondering whether memory priming happens during anesthesia to asking how much happens, under what conditions does it happen, and what is its impact on patients’ well-being. Research in psychology shows that even this very basic form of learning can have profound effects on behavior.

Early studies of learning during anesthesia produced equivocal results with interpretation hampered by inconsistent methodology.² An important recent development is the combining of careful memory testing with monitoring of intraoperative awareness or anesthetic depth. Iselin-Chaves *et al.* presented the repetitions of each stimulus word consecutively while recording the Bispectral Index (BIS), allowing estimation of the anesthetic depth at which each word was presented. They found implicit memory for words presented with BIS between 41 and 60. *Implicit memory* refers to memories that we are unaware of, that we cannot consciously recall or recognize, but that reveal themselves through changes in behavior. Implicit memory is often preserved after brain damage or experimental manipulations that abolish conscious recall.

The type of learning demonstrated by Iselin-Chaves *et al.* is actually very limited. If human memory is conceptualized as a network of nodes representing different pieces of information, the simplest form of learning is temporary activation of a single node, known as *perceptual priming* because it facilitates subsequent perception of stimuli against background noise or, as here, from fragments such as word stems. Spread of activation to related nodes (e.g., tractor → farm) is known as *conceptual priming* because it facilitates perception of, or responding with, conceptually related information. Conceptual priming is prevented by adequate anesthesia.³

In contrast, perceptual priming seems to be preserved during anesthesia.³ Lubke *et al.*⁴ showed enhanced word stem completion performance for words presented during trauma surgery with isoflurane, with BIS between 40 and 60. The study by Iselin-Chaves *et al.* extends these

findings to elective surgery with isoflurane. We found⁵ and then replicated⁶ word stem completion priming during elective surgery with relatively deep propofol anesthesia (median BIS = 42 and 40^{5,6}). Perceptual priming thus seems to be a general feature of anesthesia, not a peculiarity of a particular anesthetic technique.

The findings are still mixed, however. Kerssens *et al.*⁷ tested patients undergoing elective surgery and used a word stem completion task but found no evidence for priming during BIS-guided propofol or isoflurane anesthesia. They suggested that maintaining a constant anesthetic depth prevents priming. In the study of Iselin-Chaves *et al.*, moments of light anesthesia just before or after presentation of a particular word may have facilitated priming, but this explanation does not apply to our own demonstration of priming.⁶ We found priming even in a retrospectively selected subgroup of patients for whom BIS happened to remain below 60 throughout word presentation. The evidence for priming during anesthesia is not simply an artifact of inadequate depth control.

It is generally true, though, that memory activation is more likely with lighter anesthesia. It is more likely to occur with opiate-based techniques than with volatile anesthetics that produce deeper hypnosis,⁸ and it does not occur when BIS is less than 40.^{1,4} The exact relation between priming and depth is not clear. Lubke *et al.*⁴ found a significant although not very strong linear relation between memory and anesthetic depth at which words were presented. However, the measure of memory used in this analysis included explicit as well as implicit components. Using a measure specifically of implicit memory, Iselin-Chaves *et al.* found as much memory for words presented during anesthetic depths of BIS 41–60 as for words presented to volunteers receiving no anesthesia (and no surgery). Their inclusion of a group of awake participants is interesting because it raises the question of whether priming during anesthesia is a mere shadow of priming activity in the conscious brain or whether perceptual priming is insensitive to all but the most extreme manipulations of brain function. Their finding suggests that a sudden decrease in perceptual priming occurs when anesthetic depth decreases below BIS of 40, but until then, it is unaffected by the transition from consciousness to unconsciousness.

Another factor affecting memory priming is the presence of surgical stimulation. The sudden increase in concentrations of circulating catecholamines caused by surgery may enhance any residual memory function *via* the amygdala.^{5,9} Fear conditioning occurs in the amygdala,¹⁰ as does enhancement of memory consolidation during emotional events or when experimental applica-

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tions of norepinephrine mimic natural stress.¹¹ We found no evidence for priming when words were presented during anesthesia but before surgery, but significant priming at equivalent anesthetic depth during surgery.⁵ Most stimulus presentation in the study of Iselin-Chaves *et al.* was completed before surgery began, making their priming effect more impressive than it might seem at first glance.

Therefore, some memory function persists during clinically adequate anesthesia. Patients do not learn new information or even new associations between already familiar information. All that happens is slight activation of existing representations of words in memory detectable on a carefully designed memory test. Given that patients are unlikely in everyday life to be asked to complete memory tests, is this any cause for concern? Research in psychology suggests it may be, showing profound effects on behavior of even this very rudimentary memory activity. In what has become a classic experiment, Bargh *et al.*¹² asked participants to rearrange word lists into sentences. When the lists included words relating to the concept of old age (*e.g.*, conservative, wrinkle), participants subsequently walked away from the laboratory more slowly than participants exposed to neutral words, even though they had not noticed the repeated occurrence of references to old age. Conversely, priming of the concept of professor improved performance on a test of general knowledge.¹³ Physiology is not immune to these priming effects: Hull *et al.*¹⁴ found that subliminal exposure to an "angry" prime increased blood pressure relative to exposure to a "relax" prime.

You can only prime behaviors that are likely to happen anyway. Surreptitious exposure to words related to speed led to better performance on a timed test of intelligence than exposure to neutral words, but only when participants already had the goal of working quickly.¹⁵ People poured themselves a larger drink, and drank more of it, after subliminal presentations of smiling faces compared with angry faces, but only if they were already thirsty.¹⁶ Subliminal priming of the concept "blacks" led white participants to form a more negative impression of someone described verbally, but only if they already had high levels of prejudice.¹⁷

These laboratory studies show that priming of con-

cepts in memory, occurring without participants' awareness, can affect behavior in many ways, making people seem slower, thirstier, more prejudiced, or more intelligent. Iselin-Chaves *et al.* have shown that priming can still happen when patients are anesthetized. Comments made in the operating room about a patient's prognosis, appearance, or state of consciousness could exacerbate their existing anxieties about the operation, about themselves, or about the anesthetic and may contribute to postoperative anxiety, depression, and insomnia even in patients with no explicit recollection of surgery.

Jackie Andrade, Ph.D., Department of Physiology, University of Sheffield, Sheffield, United Kingdom. j.andrade@sheffield.ac.uk

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Continuous Peripheral Nerve Blocks

Fewer Excuses

FOR a technique to become widely adopted, it must address an important need or solve a persistent problem better than available alternative choices. The method must also be efficacious and reproducible and have a favorable side effect and safety profile. Many of these attributes can take years to ascertain despite a long period of use and a sound literature base. In this issue of *ANESTHESIOLOGY*, Capdevila *et al.*¹ report on a large prospective multicenter trial examining continuous peripheral nerve blocks after orthopedic surgery with a focus on neurologic and infectious adverse events. Using a nonrandomized design, they followed up 1,416 patients in the postanesthesia care unit and every day for up to 5 days, examining efficacy and complications related to the use of continuous catheters. The results are compelling because they demonstrate excellent analgesic results while providing benchmark data on neurologic outcome, bacterial colonization, and incidence of infection. Perhaps most important, their data provide the best evidence to date that continuous peripheral nerve blocks can be implemented over a broad spectrum of institutions, by different individuals, with uniformly excellent success and a low incidence of complications—effectively challenging many of the excuses for avoiding this technique.

Addressing pain is a cornerstone of our profession. Failure to treat severe pain can have profound negative effects, resulting in increased cardiac stress,² poor surgical outcome,³ decreased ambulation,⁴ and higher healthcare costs. Despite this, achieving prolonged analgesia after painful orthopedic surgery is a persistent challenge. The intense pain after osteotomy and tissue dissection is especially difficult to treat. Despite multimodal approaches, which include intravenous opioids, patients still rate pain as intense after these procedures.⁵ Opioid-related side effects still remain an obstacle associated with postoperative nausea and vomiting, sedation, sleep disturbances, respira-

tory depression, and increased morbidity and costs.⁶ Central neuraxial techniques such as spinal and epidural blockade are fundamental for lower extremity orthopedic procedures and have been well validated. However, with the increased use of low-molecular-weight heparin and heparin analogs, causing concern about epidural hematoma formation, there is an increasing desire to provide continuous delivery of local anesthetics in a more compliant anatomical compartment.

Historically, one of the most effective ways of addressing this has been the use of continuous peripheral nerve blocks. Since first being described by Ansboro in 1946,⁷ continuous peripheral nerve catheters have been an integral part of acute and chronic pain management. Over more than half a century, numerous clinicians have developed techniques and equipment to facilitate catheter placement with an increasingly higher rate of success. Randomized clinical trials have refined the optimal infusion strategies and demonstrated uniformly excellent results defined by improved patient well-being and minimal adverse effects.^{8,9} Despite this body of evidence, wide-scale implementation has been slow. Detractors of the technique often cite the inconsistencies in success rates. It is argued that wide-scale application requires infrastructure and specialized skills, factors not currently present in many institutions. Equally important is the concern for safety when a technique is implemented beyond the reported experience in one facility or a small clinical trial protocol. Infection, local anesthetic overdose, and neural injury are concerns commonly voiced as a rationale for not performing continuous nerve blocks.

Previous randomized controlled trials have demonstrated sustained effective postoperative analgesia and opioid sparing when comparing continuous peripheral nerve blocks to single-injection techniques,¹⁰ epidural anesthesia,¹¹ and opioids.¹² In the current study, the authors move beyond their previous collective works and demonstrate impressive pain control for a wide range of painful orthopedic surgical procedures, including shoulder, elbow, hip, and knee arthroplasty, performed in 1,422 patients. Although this study did not include a comparison group, in the postoperative period, the median visual analog pain scores at rest and during movement were impressive—less than 25 mm out of a possible 100 mm. Equally remarkable was the fact that 75% of patients were able to avoid morphine on the first postoperative day, and 84% were able to avoid morphine 1 day after surgery. Obtaining these results in so many patients undergoing painful orthopedic procedures is truly noteworthy and persuasive.

Equally impressive is the fact that failure of pain relief

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only occurred in 3% of patients. Catheter failure is a reason often cited for avoiding continuous peripheral nerve blocks, but was not supported here. Similarly, despite the fact that the investigators documented increasing pain scores at 24 h and a high (18%) incidence of technical problems with catheter management, these issues were readily surmountable. Rapid resolution of the surgical block at 24 h likely represents the transition to a less intense analgesic block with dilute local anesthetic and emphasizes the potential need for additional analgesics and strategies during this timeframe. Advances in equipment design and catheter localization may increase precision and decrease technical problems, further enhancing these results.

The potential to cause damage from a percutaneously placed needle has been a consistent concern in regional anesthesia literature. A host of studies have documented a low incidence of complications after continuous catheters.¹³⁻¹⁶ Most neurologic complications are usually not long lasting, and their etiology is frequently difficult to discern from that associated with the surgery itself. In many respects, this topic has dominated debate and has been a flawed argument or excuse used by anesthesiologist and surgeons alike for avoiding the technique. This is further reinforced in this study, where there were only 0.84% serious adverse events, and only 0.21% of patients had persistent neurologic lesions attributed to the continuous peripheral nerve blocks. In either case, all events resolved without sequelae. The fundamental question is, Are the risks, effort, and maintenance involved in placing these catheters worth the outcome benefits? As we see in this study by Capdevila *et al.*,¹ the resounding answer is yes.

Infection and colonization from an indwelling foreign body (catheter) is another potential but serious complication that has not received the required level of attention. The relatively few accounts of this complication in the literature suggest that the incidence is low, but only a few studies have set adequate criteria and have been large enough to detect this.¹⁴ By diligently collecting data from multiple institutions, Capdevila *et al.*¹ have helped to demonstrate that catheters routinely become colonized (29%) but only 3% have even local inflammatory signs (focal pain, redness, and induration). These signs are associated with a higher rate of colonization (44%), but only one patient in the entire series developed an infection. A psoas muscle abscess and cellulites were detected in woman with diabetes who had a femoral catheter after a total knee replacement. The patient recovered with antibiotic treatment. This finding is important because the true merits of continuous catheters are not briefly extending a single injection block, but rather providing days of safe efficacy to optimize the perioperative experience.

In addition, their specific criteria can also be used to standardize definitions for future trials. By using such a large multicenter design, broader examination of the

data can also be performed. This has allowed them to use regression analysis to look at independent risk factors for neurologic and infectious adverse events.

Perhaps the most important aspect of the study by Capdevila *et al.*¹ is not the comprehensive information and follow-up from use of a large number of continuous catheters, but rather their experimental design. They were able to orchestrate a multicenter trial to examine relevant issues that are difficult to assess at a single institution. This created enhanced statistical power to begin examining events that may be rare but important, and it helps to eliminate the criticism that the findings were skewed because of the institution. This spirit of collaboration should not be overlooked. Regional anesthesiologists tend to be enthusiastic and devoted with a firm belief in their techniques. This level of enthusiasm is often viewed with skepticism by those who do not harbor the same passion. The coordination of thought leaders in any field to collaborate is always difficult because of their creativity and independence. For peripheral nerve blocks and catheters, this study is a first.

Ultimately, the greatest strength of the study by Capdevila *et al.*¹ is also its greatest downside. Detractors will still criticize the current study not because of its success but because of the high training and talent level of its participants. Wide-scale reproducibility or "the risk of failure" is still perceived by many as an obstacle to greater implementation. The potential need for an alternative technique and the inherent "failure rate" should not be dissuasive given the growing body of evidence of safety and efficacy in the face of ubiquitous poor pain control offered by systemic analgesic therapy. Based on this and the results of the current study, adopting an alternative perspective seems warranted. Capdevila *et al.*¹ demonstrate in a large population of patients that outstanding analgesia with a favorable side effect profile is obtainable.

Capdevila *et al.*¹ have set a new standard by demonstrating safety and efficacy of continuous peripheral nerve block in a large population of patients. The same standard of a multi-institutional collaboration can be applied in subpopulations such as pediatrics, geriatrics, and those receiving low-dose anticoagulants. These efforts, along with improvements in continuing education, novel teaching designs, and refinements in catheter insertion and precision, may serve to increase use of continuous peripheral nerve blockade and improve patient outcome after surgery.

Stephen M. Klein, M.D., Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina. klein006@mc.duke.edu

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The Academic Highway between the United States and Japan

THIS issue of *ANESTHESIOLOGY* contains a unique and impressive account of a young Japanese physician, Dr. Michinosuke Amano, who in 1950 journeyed to the United States to learn modern clinical anesthesia, supported by the Government Account for Relief in Occupied Area program.¹ He returned to his mother country and planted the first seeds of modern academic and clinical anesthesia in Japan. This article is similar to two others documenting the significant American contribution to Chinese and German anesthesia. These articles focused on the role played by specific pioneer anesthesiologists, rather than a comprehensive review of the state of anesthesia at the time. However, through these articles, the reader begins to understand the state of clinical anesthesia and of medicine in general in these countries. These are narratives of humanity and the medical sciences beyond the borders of the United States, rather than a biography of important anesthesiologists in each country.

At the end of the Second World War, America stood at the forefront of medical advancement in the world. Governmental and private organizations began to help Japanese medicine advance to the levels experienced in the

United States. The Government Account for Relief in Occupied Area program was one scholarship opportunity for Japanese physicians, and others were funded through the China Medical Board, the Rockefeller Foundation, and the Fulbright Foundation. Gracious in victory, America helped the defeated Japanese who were struggling in hunger and poverty after the war.

The most significant American contribution, among many, to Japanese medicine was provided by the Unitarian Service Committee, sending American physicians to Japan to help initiate reforms of medical care. Dr. Meyer Saklad (Director of Anesthesia, Rhode Island Hospital) was a participant in the Joint Meeting of the Japanese and American Educators. Although misnamed, the meeting was organized under the direction of the General Head Quarters of the Allied Forces in 1950.² This was a revolutionary event for Japanese medicine, not only for anesthesiology, but for all disciplines within the health-care system. One of the most important contributions made by Dr. Saklad was that he emphasized the importance of the basic sciences as they related to the delivery of clinical anesthesia. Through his lectures, Japanese physicians learned that clinical anesthesia must have its base in pharmacology and physiology. This approach surprised many people who had regarded anesthesia as a "small art," subservient to the powerful surgeons. Dr. Saklad's visit to Japan gave impetus to the beginnings of research activity in anesthesiology.

Up until the end of the Second World War, anesthesia in Japan was essentially conduction anesthesia: spinal anesthesia, supplemented with opioid and scopolamine, for everything, including laparotomy, thoracotomy, and even craniotomy! General anesthesia for children was

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performed with ether by the open drop method. The reason for this lack of sophistication in anesthesia before World War II can be traced back to at least 1922, when the Japanese Surgical Society debated whether positive-pressure respiration was necessary for open chest surgery. After serious discussion, which lasted a couple of years, the belief that positive-pressure respiration in open chest surgery was not necessary was accepted in 1938. Dr. Fujita,³ who is a historian of Japanese anesthesia, examined this conviction and believes it to be a retarding factor in the development of Japanese anesthesia. Furthermore, Dr. Fujita described the case of Dr. Nagae, who was a teacher at the Japanese army medical school. Dr. Nagae was sent to the Mayo Clinic in 1936 to study experimental surgery under Dr. Mann and to observe Dr. Lundy's anesthetic techniques, which included local, spinal, and epidural anesthesia, as well as intravenous and general anesthesia. His report contained the details on the use of carbon dioxide absorbance in general anesthesia and endotracheal anesthesia and also included a description of the size and shape of endotracheal tubes. Unfortunately, his report never received attention from either the Army Medical Office or from public hospitals within Japan. Dr. Fujita's comment on this story was that modern Japanese anesthesia would have significantly advanced before the Second World War if his report had been seriously evaluated at that time.³

The first academic anesthesiology department was established at Tokyo University in 1952 and was followed by several university hospitals shortly thereafter. When it became an established presence in medical schools, anesthesiology started to grow as an independent specialty. Promising medical students who were highly motivated entered these anesthesia departments training to become specialists. In the early 1970s, Japanese anesthesiology branched out into critical care and pain medicine. At the same time, research activity became increasingly prominent in major academic departments, a result of the training of young Japanese anesthesiologists at American institutions. In the United States, these trainees learned basic science, clinical skills, and an educational system in anesthesiology that had been practiced for decades.

In the late 1970s, young Japanese anesthesiologists still desired to travel to America to further their training; however, it had become difficult to do clinical anesthesia in America because of licensure requirements. Alternatively, many Japanese anesthesiologists journeyed to American academic departments to engage in research. Some of them had previous research experience and publications before going to America, and they further advanced their skills by hard work with their American mentors. Thus, it is not an exaggeration to say that most of the current academic departments in Japan have

strong connections to American departments through either clinical or laboratory work. Although American training has greatly magnified the quality of research in Japanese academic departments, it has remained mostly within the area of the basic sciences, and there is a lack of clinical investigation on a large scale because surgical cases are scattered over the different hospitals, with each having a relatively small number of cases to study. It is interesting to note that the rapid expansion of research activity in Japan almost paralleled economic development. Currently, Japan seems to represent one of the largest contributors to anesthesiology research outside the United States.

No one could imagine the current state of Japanese anesthesiology soon after the end of the Second World War. In the intervening 60 yr, academic university departments have grown to 124, while the number of Board Certified Anesthesiologists increased to 5,548 from 44 in 1963. However, the increasing demand of surgical cases and the resultant increased clinical load in both the operating room and the intensive care unit has forced anesthesiologists to increase the time spent in clinical setting endeavors. This shortage of personnel and time allotted for research may decrease the number of anesthesiologists who can work in the laboratory.

In summary, American influences on Japanese anesthesia have been very significant, allowing for rapid progress mainly due to American anesthesiologists who were willing to accept and encouraged Japanese anesthesiologists in both the clinical and basic science arenas for the past 60 yr. Japan's research-minded anesthesiologists, despite a critical shortage of manpower, took advantage of increased research funds to create a successful research enterprise. However, the future of Japanese anesthesiology is unclear because of the somewhat anticipated drastic changes in health care associated with an aging population that will peak in the coming 30 yr. Nevertheless, it is hoped that Japanese academic anesthesiology will continue to prosper and grow and that the academic highway between America and Japan will be shortened and strengthened for the betterment of patient care in both countries.

Hiroshi Takeshita, M.D., Ph.D.,* Douglas R. Bacon, M.D., M.A.†

* Ube Frontier University, Ube, Japan. † Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, Minnesota. bacon.douglas@mayo.edu

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