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.4 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 conceptual 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 perceptual 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). 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-
tions of norepinephrine mimic natural stress.11 We
found no evidence for priming when words were pre-
sented during anesthesia but before surgery, but signifi-
cant 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 clin-
ically 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 detect-
able 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 rudimen-
tary memory activity. In what has become a classic experi-
ment, Bargh et al.12 asked participants to rear-
range word lists into sentences. When the lists included
words relating to the concept of old age (e.g., conserva-
tive, wrinkle), participants subsequently walked away
from the laboratory more slowly than participants ex-
posed to neutral words, even though they had not no-
ticed the repeated occurrence of references to old age.
Conversely, priming of the concept of professor im-
proved 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 quick-
ly.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’ aware-
cess, can affect behavior in many ways, making people
seem slower, thirstier, more prejudiced, or more intelli-
gent. 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 them-
seves, or about the anesthetic and may contribute to
postoperative anxiety, depression, and insomnia even in
patients with no explicit recollection of surgery.

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Continuous Peripheral Nerve Blocks

Less 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.5 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, respiratory 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 site 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...
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 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.

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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 private organizations began to help Japanese medicine advance to the levels experienced in the United States. This Editorial View accompanies the following article: Ikeda S: Government Account for Relief in Occupied Area: A Japanese physician’s journey to a new medical specialty. Anesthesiology 2005; 103:1089–94.

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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, 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.

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.

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