

EDITORIALS



General Anesthesia — Minding the Mind during Surgery

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William Morton's demonstration of the use of ether in 1846 was powerful in part because the patient had no memory of the procedure; nowadays, patients expect to have amnesia with general anesthesia. But conscious awareness — the ability to remember and explicitly recall events that transpire during surgery — still occurs on occasion, sometimes with devastating psychological consequences. The easy explanation is that awareness is due to underdosing of the anesthetic agent. This explanation provides a sense of control and a ready fix (administer more anesthesia) but conveniently overlooks a secret: the state of consciousness is typically not monitored directly during general anesthesia. There simply is no accepted way to do it.

In this issue of the *Journal*, Avidan et al.¹ have addressed this in a large, prospective, multicenter study involving patients at high risk for intraoperative awareness owing to preexisting illness or the nature of the surgery. Subjects were randomly assigned to the management of anesthesia by means of the monitoring of end-tidal anesthetic-agent concentration (ETAC) or with the use of an electroencephalogram (EEG)-derived, commercially available depth-of-anesthesia monitor. The former, which is the standard method, measures exhaled volatile agent as a correlate of brain concentration; the latter reduces raw EEG data to a unitless bispectral index (BIS) that ranges from 100 (awake) to 0 (isoelectric EEG). Alerts were triggered when the ETAC or BIS values were outside the ranges that were considered to be adequate for surgical anesthesia (0.7 to 1.3 age-adjusted minimum alveolar concentration in the case of ETAC and 40 to 60 in the case of the BIS). Depth-of-anesthesia monitors are controversial, largely because they per-

form poorly under some conditions, and data on their ability to prevent awareness are conflicting.^{2,3} The results of the study by Avidan et al. add important new information to the debate. Despite arguably optimal management, definite or possible awareness occurred in 0.47% of the patients, and as compared with ETAC monitoring, the depth-of-anesthesia monitor conferred no benefit. Moreover, 41% of the cases of awareness occurred when the ETAC or BIS values were in the target ranges. Thus, although a combined ETAC and BIS protocol was not tested, intraoperative awareness was not entirely preventable with either monitoring method.

These findings are disappointing but not surprising. The key variables — consciousness, memory, and general anesthesia — are obscure, and tools to assess them intraoperatively are rudimentary. The nature of consciousness is a metaphysical problem that has challenged philosophers for centuries and neuroscientists for decades.⁴ Memory, a prerequisite for explicit recall, is similarly complicated,⁵ and agents that are used to produce general anesthesia have varied receptor profiles, actions on neural networks, and ways of producing amnesia.^{6,7} As such, general anesthesia is not a single phenotype, and there is little wonder that the neurobiology of the state is poorly understood. Yet amid this complexity, brain functioning is judged clinically much as it was 165 years ago, with the use of bodily signs and responses (e.g., blood pressure, heart rate, and movement) that are, at best, loosely related to higher brain function. The astonishing thing is not that awareness occurs but that it occurs so infrequently.

Having found no benefit from processed EEG monitoring, the investigators imply that an ETAC-

based protocol, complete with alarms and a checklist, is the way forward.¹ This inference is premature. Without an unmonitored control group, there is no proof that ETAC is superior to doing nothing special. Simply drawing attention to the possibility of awareness, as was done in both groups with a sign on the anesthesia machine, might be equivalent. Nor is ETAC feasible when only intravenous medications are used for anesthesia, which is now common practice. ETAC targets may also be unwise. Even low doses of volatile agents can produce hypotension, potentially exposing the sickest patients to unnecessary cardiovascular and cerebrovascular risk. In addition, ETAC puts the focus on the dose that is administered, not on the response of the brain. Applying similar logic to the cardiovascular system would mean administering predetermined doses of anesthetic agents without measuring blood pressure. Finally, basing ETAC ranges on age disregards the fact that chronologic age is a poor proxy for cognitive function, particularly among seniors, who constitute a large percentage of surgical patients and often have subclinical cerebral pathologic conditions or preexisting cognitive impairment.⁸ Thus, an ETAC protocol may inadvertently result in overdosing of the brain in cognitively vulnerable persons. This is worrisome because deep sedation is associated with a higher incidence of postoperative delirium, other adverse cognitive outcomes, and increased mortality in elderly surgical and critically ill patients.^{9,10} Association does not prove causation, but in some cases, too much anesthesia or sedation may be as undesirable as too little.

Monitors are meant to supplement, not supplant, clinical decision making, and depth-of-anesthesia monitors that reduce complex neurobiology to simple numbers are no exception. It is unreasonable to expect any such monitor to unfailingly detect conscious awareness — a specific and still

mysterious property of the brain and mind — and neither patients nor physicians should think otherwise. Notwithstanding this and other weaknesses of current devices, a window into the anesthetized brain, albeit a foggy one, may still be useful, in conjunction with information from other monitors, in operating rooms, endoscopy suites, and critical care units as a generic, all-purpose index of the brain's response to powerfully sedating drugs. Whether these devices add value in this way remains to be seen, but when minding the mind during sedation and general anesthesia, a little insight into how the brain is reacting is apt to be better than none, especially if it challenges historical ways of gauging anesthetic depth and catalyzes the search for something better.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Hamartoma Syndromes, Exome Sequencing, and a Protean Puzzle

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Gross malformations have been well known for centuries, even millennia. However, it was not until 1904 that Albrecht coined the concept of

hamartoma. In 1934, the concept entered the field of developmental pathology generally in reference to tissue malformations. Hamartomata