T HE assertion that patients with a prior history of intra-operative awareness with recall (AWR) are at increased risk for future AWR has appeared in numerous textbooks, reviews, and practice advisories. But there has always been some ambiguity in the statement: although overall risk will be increased because some patients carry forward known risk factors such as increased body mass index and chronic benzodiazepine or ethanol use, there has been no rigorous investigation to establish whether prior AWR represents an independent risk factor when these other variables are controlled. The distinction is of both clinical and mechanistic significance, as the identification of AWR as an independent risk factor could imply that there is a subset of patients who have some degree of resistance to the effects of anesthetic drugs on consciousness and/or memory processes.

In this issue of Anesthesiology, Aranake et al.1 address the question in a secondary sub-study that combines data from three major randomized, controlled trials performed in the United States to evaluate effectiveness of the bispectral index (BIS; Aspect Medical Systems, Inc., Newton, MA) monitor in AWR prevention: the B-Unaware Trial,2 the BAG-RECALL Trial,3 and the Michigan Awareness Control Study.4 These three trials—which share a high degree of consistency in their assessment and reporting methodology—collectively enrolled 26,490 subjects. During enrollment in the trials, a cohort of 241 subjects (0.9%) self-reported a prior episode of AWR, and they are compared with a control group obtained through a sophisticated 5:1 matching algorithm. It is on the strength of this matching strategy—which appears to effectively balance the groups across a quite thorough list of known risk factors and other potential confounders—that the validity of the results rely. Aranake et al. report that subjects with a self-reported history of AWR are five times more likely to experience AWR than control subjects. The absolute number of AWR cases is low (4 of 241 compared with 4 of 1,205), so the 95% CI extends down to a relative risk of 1.3, but it is a clear result.

What mechanistic insights, if any, can be drawn from these observations? Central to any understanding must be the functional dissociation between consciousness and memory. The outcome measured by Aranake et al.—as by all clinical AWR studies—is the composite result of an exceedingly complex array of sequential and parallel neural processes underlying human cognitive function. Perhaps, because this outcome has consistently been described using some variant on the term “awareness”—a synonym for conscious perception—it is often overlooked that what is measured is not awareness at all. The phenomenon that is actually measured is episodic declarative memory—something that, unlike conscious perception, is absolutely dependent on processes occurring in the hippocampus and other medial temporal lobe structures.5 Awareness might be necessary for a patient to recall what happens to them during surgery, but it is not sufficient. And, as was so clearly demonstrated by the famous amnesiac Henry Molaison (February 26, 1926 to December 2, 2008), who had both hippocampi removed surgically in an attempt to treat a seizure disorder,6 it is entirely possible to have awareness of the world without forming and sustaining memory of the experience.

The results of the study by Aranake et al. demonstrate that there is a phenotypic subset of patients who might be more likely to have conscious perception during anesthesia—that is, they are more likely to have awareness. But the same...
Fig. 1. Relationships between intraoperative awareness, recall, and psychological morbidity. Venn diagrams depict two models describing the relationships between intraoperative awareness, recall, and psychological morbidity. In both panels, the large blue set Awareness Events represent all episodes in which patients experience conscious perception under anesthesia. The smaller red set Recall represents episodes that are remembered at a later time. The most important feature is that not all episodes of awareness are later recalled—those that are not are labeled Awareness Without Recall. In addition, some memories perceived as arising from the intraoperative period will in fact be false, and are labeled as False Recall (FR). Episodes of awareness that are recalled—the focus of Aranake et al.¹ and many other studies—are the intersection of the two sets, labeled Awareness With Recall (AWR). The distinction between the models lies in conditions required for psychologic morbidity. Events resulting in psychological morbidity are shown by the purple set labeled Psychological Morbidity. In the Common Model, shown at left, it is believed that morbidity will only arise if the awareness events are later recalled—hence the entire morbidity set is contained within AWR. We suggest an Alternate Model, at right, in which it is possible for psychological morbidity to occur as the result of an awareness event even if that event is not subsequently recalled. New methodologies will be required to address this difficult question.

Results could be obtained from a subset of patients who have unaltered conscious perception—and are no more likely to experience awareness—but who are more likely to establish and maintain a hippocampal-dependent memory trace of it. The methodology is agnostic—it is simply unable to discriminate whether increased AWR risk represents a problem of consciousness or a problem of memory.

Resolving these mechanistic questions is challenging—and it is especially difficult to conceive how they could be adequately addressed in the largely uncontrolled clinical setting in which AWR occurs. But the answers are at least partially knowable. In highly controlled experimental designs, rigorous neuropsychologic paradigms have been combined with functional neuroimaging and neurophysiology techniques to parse the dissociable effects of anesthetic drugs on consciousness, arousal, and memory, and to establish their neural correlates.²⁻⁹ But these studies have only been attempted on a general population. Were it possible—although we acknowledge the pragmatic hurdles—a study evaluating a cohort of patients with clinically demonstrated AWR risk could be of enormous value.

At some level, both conscious perception and memory are affected by anesthetic drugs, with unconsciousness and amnesia as major therapeutic endpoints. Therefore, even without knowing whether their outcome represents a phenotypic effect on consciousness or on memory, the authors’ suggestion that the underlying mechanism might involve genetically determined differences in responses to anesthetics is certainly plausible. There is excellent animal evidence for genetic differences in anesthetic sensitivity, including differences in potency between strains¹⁰ and resulting from targeted mutations in various subunits of γ-aminobutyric acid subtype-A receptors and other molecular substrates of anesthetic action¹¹ in mice. Evidence for such differences in humans is less robust, but clearly suggestive.¹²

There is one further explanation that must be considered. Declarative memory behavior can be modeled as a signal-detection problem, in which the determination of whether a memory (signal) exists or not represents a decision. This decision is governed by threshold criteria, which have the effect of establishing a response or reporting bias. Error is most likely when the true memory trace is weak and fragmented, and when confounding memories exist for items and events that are conceptually similar. Both of these conditions—fragmented intraoperative memories and conceptually similar experiences in the immediate perioperative period—impact the determination of AWR. Moreover, once a decision is made that a memory is “true,” subsequent recollections render the trace transiently plastic, enabling reinforcement and integration of new information—a process termed reconsolidation.¹³ If repeatedly recalled under the appropriate conditions, a memory that began as weak and vulnerable to forgetting can evolve to be perceived as strong and certain. The results of the study by Aranake et al. could reflect interindividual differences in reporting bias. This neither minimizes the significance of the event nor does it imply that the memories are false. It is, however, an explanation that does not require any altered response to anesthetics.

The functional dissociation between awareness and memory also poses a troubling question that is exceedingly difficult to answer: is awareness without recall harmful? If a patient experiences conscious perception during surgery, but...
is unable to establish and maintain a hippocampus-dependent memory trace of it, then that episode will be undetectable by standard AWR-detection methods. If psychologic morbidity does not occur with such an episode—and is instead dependent on the event being encoded into memory and accessible to conscious recollection—then AWR might be most constructively framed as a problem of memory rather than of consciousness. In contrast, if awareness without recall is able to lead to some form of psychologic morbidity as well (fig. 1), then an entirely new avenue of investigation will be required to characterize it and to develop strategies for prevention. The study by Aranake et al. does not address this question, but it does turn the conversation toward mechanism, which is the direction in which further investigations of these difficult but important questions of consciousness and memory must go.

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