

MEDICAL INTELLIGENCE ARTICLE

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Learning and Memory during General Anesthesia

An Update

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IN 1992, we published a review article in ANESTHESIOLOGY on learning and consciousness during general anesthesia.¹ Since then, there has been a steady flow of publications and two international conferences on the subject; one in 1992 in Atlanta, Georgia, and another in 1995 in Rotterdam, the Netherlands. In 1992, the issue of preservation of unconscious information-processing capability by the anesthetized patient was debated because of the mixed results of studies at that time. We and others^{2,3} thought that with improvement in the quality of work in this area, the issue of whether unconscious retention of intraoperative events is a reliable, replicable phenomenon might be resolved in a few years. Unfortunately, this has not happened. With conflicting reports and contradictory statements being published, we chose to update the reader on this and related subjects with particular emphasis on problems and difficulties in this area, and to provide some comments that we hope will be useful for future studies.

Here we address the following issues.

1. Explicit or conscious memory or "awareness";
2. Studies of anesthetized patients using implicit tests of memory;
3. Postoperative motor behavior after presentation of suggestions during anesthesia;
4. Studies of the efficacy of administration of therapeutic suggestions during anesthesia;

5. Studies of healthy volunteers;
6. Effects of anesthetics on animal learning and memory; and
7. Reports of cases of psychosomatic disorders after anesthesia and surgery.

In each area, we discuss in particular the studies that have been published since 1992, within the context of the earlier literature, followed by comments and critiques. We use the term *consciousness* as defining a state of awareness of the outside world and use the terms *consciousness*, *awareness*, and *wakefulness* interchangeably.

Distinctions between different types of learning and memory remain the subject of considerable debate. One such distinction, of particular interest to anesthesia, is between explicit and implicit learning. The essential difference is whether learning is manifested with or without concurrent awareness of remembering.^{4,5}

Explicit or Conscious Memory or "Awareness"

Incidence

The most recent study in which a structured interview was used in a large series of patients indicated that the incidence in nonobstetric and noncardiac surgical cases is 0.2%.⁶ The incidence is similar after total intravenous anesthesia.⁷ It is higher, however, when light anesthesia is used. The incidence in cardiac surgery ranges from 1.14-1.5%,^{8,9} with a balanced anesthetic technique consisting of benzodiazepines, low-dose fentanyl, and a volatile agent. A higher incidence has been reported for obstetric cases¹⁰ (0.4%) and major trauma cases¹¹ (11-43%), and this incidence varies according to the dose of anesthetic administered. Jones¹² estimates that only

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about 0.01% of patients report suffering from pain while being aware.

Consequences

Recently Cobcroft and Forsdick¹³ and Moerman *et al.*¹⁴ studied the consequences of recall of intraoperative events during anesthesia. Cobcroft and Forsdick described patients who responded to an article published by Forsdick about her own experience of awareness during anesthesia in a lay magazine widely distributed in Australia and New Zealand. Moerman *et al.* studied patients who were referred to them by anesthesiologists. Despite the different strategies of patient selection of the two groups, there was close agreement between the results. The two most frequent complaints were ability to hear events during surgery and sensations of weakness or paralysis, in addition to the recall of pain, if it was present. It seems that patients particularly recall conversations or remarks that are of a negative nature concerning themselves or their medical conditions. The most frequently reported postoperative effects were sleep disturbances, dreams and nightmares, flashbacks, and daytime anxiety.

For many patients, the experience of awareness may not leave prolonged after effects; however, some develop post-traumatic stress disorder, marked by repetitive nightmares (usually poorly disguised replays of an operative situation), anxiety and irritability, a preoccupation with death, and a concern with sanity, that make the patients reluctant to discuss their symptoms.¹⁵ It is not readily apparent why some patients develop a post-traumatic stress disorder and others do not.

The medicolegal consequences of awareness remain of interest. Domino[‡] recently analyzed claims from the American Society of Anesthesiologists Closed Claims Project. Claims for awareness during anesthesia were 2% of all claims. This incidence was similar to rates of claims for such familiar complications after anesthesia such as aspiration pneumonia and myocardial infarction. Female gender tripled the likelihood of an awareness claim, compared with other general anesthesia malpractice claims. Domino speculated that women may be more likely than men to sue for emotional injury.

‡ Domino KB: Closed malpractice claims for awareness during anesthesia. *ASA Newsletter* 1996; 60:14-17.

§ Bennett HL: Treating psychological sequelae of awareness. *American Society of Anesthesiologists Newsletter* 1994; 58:12-15.

Causes and Prevention

The precise concentration of anesthetic agent required to guarantee lack of recall is unknown. Minimal values of 0.8-1.0 minimum alveolar concentration of inhalation anesthetics currently appear acceptable. The effects of adding intravenous agents, such as benzodiazepines, propofol, and opioids, to inhalation anesthetics, as is sometimes done in clinical practice, remain to be studied. Inspection of the anesthetic records of awareness cases for relevant parameters such as heart rate, blood pressure, and anesthetic technique has not been helpful in retrospectively explaining why awareness or recall occurred.^{8,14} Moerman *et al.*¹⁴ also found that 65% of patients who experienced awareness and recall during general anesthesia did not inform their anesthesiologists about what happened. Asking the patient four simple questions—What was the last thing you remember before you went to sleep? What was the first thing you remember when you woke up? Can you remember anything in between these two periods? and Did you dream during your operation?—should be part of the anesthesiologists' postoperative interview and should allow the anesthesiologist to deal with this traumatic experience at an appropriate early time. Prompt referral to a qualified therapist and acknowledgment of what has happened yields the best chance for recovery. § Cobcroft and Forsdick¹³ concluded that, in most cases of awareness, understanding of the phenomenon and its management by medical personnel were poor or entirely lacking.

Conclusions

Conscious recall of intraoperative events is relatively rare and development of post-traumatic stress disorder is even more uncommon. However, when we consider that approximately 20 million general anesthetics are administered each year in the United States, a 0.2% incidence corresponds to 40,000 cases of awareness annually. It is probable that the incidence of this complication of anesthesia has reached a plateau and that further significant decreases depend on avoidance of "overly" light anesthetic techniques; gaining more knowledge about anesthetic requirements of patients; development of methods to detect consciousness during anesthesia¹; and disseminating information to anesthesiologists and their acceptance⁹ of the virtues of vigilance and rational use of muscle relaxants (*i.e.*, avoiding muscle paralysis unless it is needed for intubation or surgery and even then avoiding total paralysis if possible).

Future insights into the epidemiologic characteristics

and prevention of post-traumatic stress disorder associated with awareness, which may cause long-lasting devastating damage to patients' lives, are needed. Because of the low incidence, a multiple-center study is necessary, if such data are to be obtained.

An Awareness Monitor?

The concept of an awareness monitor that would track patients' arousal levels and warn of impending wakefulness is popular. Monitoring the mid-latency auditory-evoked responses¹² or the bispectral index of the electroencephalograph¹⁶ seems promising as an indicator of loss of consciousness and its unintended return during surgery. However, it remains for future work to identify some parameter that unambiguously defines when consciousness is lost. Although this may be feasible and a monitor could possibly be developed and adapted for clinical practice, two questions remain to be answered: Do we need such a monitor?, and Can we afford it? The answers are likely to be far from certain or unanimous. Proponents for the development of such a monitor will probably refer to anesthesiologists' inability to determine reliably whether a given anesthetized and paralyzed patient is conscious during surgery. They will point to medical malpractice claims resulting from consciousness and recall during general anesthesia, the high incidence of wakefulness without recall that has been reported in some studies,¹⁷⁻²⁰ and the possible psychic trauma that may result from the unconscious storage of a traumatic event.^{15,21} They may indicate that we currently have monitors for the actions of anesthetic drugs on the cardiovascular and respiratory systems and the neuromuscular junction but none for their actions on the brain, their primary target. Such a monitor also may help to ensure protection of the brain from injury under certain circumstances. Finally, such a monitor would be valuable in determining the role of consciousness in what is presumed to be implicit learning and memory (explained in the next section). This would have important clinical and theoretical implications. Could not the costs of a new monitor be justified by better outcome for the patients and shorter lengths of stay in the recovery room by improved intraoperative anesthetic management?

Opponents of developing such a monitor would argue that consciousness and explicit recall of events during surgery are relatively rare. Because most cases occur from error by the anesthesiologist,¹ the most effective method of reducing their incidence is likely to relate to improved standards of care by anesthesiologists

rather than dependence on a monitor.²² A shorter stay in the operating room and in the recovery room through improved anesthetic management might not decrease costs.^{23,24} The costs incurred for research and development of the monitor, which eventually will be passed on to the consumer, may exceed its benefits, and its purchase will have a low priority compared with other necessary current and future health care expenditures.

Studies of Anesthetized Patients Using Implicit Tests of Memory

Explicit versus Implicit Memory

Explicit memory refers to intentional or conscious recollection of prior experiences as assessed by tests of recall or recognition. Implicit memory, by contrast, refers to changes in performance or behavior that are produced by prior experiences on tests that do not require any intentional or conscious recollection of those experiences.²⁵ The basic distinction between explicit or direct tests and implicit or indirect tests involves the nature of the instructions given to the person being tested. In a direct test, participants are asked to recall or recognize events that may have occurred during anesthesia. In an indirect test, the instructions make no reference to events during the operation. There is now evidence that performance on both direct and indirect tests may reflect both conscious and unconscious memory processes.^{26,27} In particular, indirect tests are prone to influence by explicit memory if participants become aware of the relationship between study and test items and exploit this knowledge.²⁸

Types of Memory Tests

There are various types of indirect or implicit memory tests. Some types may be more sensitive for detecting evidence of retention of events occurring during anesthesia. Table 1 lists the studies that used indirect tests of memory and identifies the anesthetic drugs used for maintenance of anesthesia, whether memory for information that was presented during anesthesia was found, and some brief comments. The task of recognition is usually construed as a measure of explicit memory, a view based on studies with patients with amnesia, whose performance on the task is usually impaired.⁵ An alternative view, based on studies of healthy persons, is that recognition depends on both explicit and implicit memories.^{27,56} According to Mandler,⁵⁶ two simultaneous processes are involved when a person must decide

Table 1. Studies with Indirect Tests of Memory

Memory Test	Parameter Measured	Anesthetic (maintenance)	Study	Results	Comments	
Category generation	No. of target examples of categories produced	N ₂ O:O ₂ , isoflurane, and sufentanil	Roorda-Hrdličková <i>et al.</i> ²⁹	+	Used familiar examples	
		N ₂ O:O ₂ and sufentanil or fentanyl	Jelicic <i>et al.</i> ³⁰	+	Used familiar examples	
		N ₂ O:O ₂ and isoflurane or N ₂ O:O ₂ with opioids	Block <i>et al.</i> ³¹	-	Used examples of difficult categories	
	Fame judgements	No. of fictitious names presented that were judged as famous	N ₂ O:O ₂ , isoflurane, and fentanyl	Brown <i>et al.</i> ³²	-	Authors suggested without adequate statistical evidence that the results were due to conditioned suppression of material learned during anesthesia
			N ₂ O:O ₂ , isoflurane, and fentanyl	Westmoreland <i>et al.</i> ³³	-	Used familiar examples
			N ₂ O:O ₂ , isoflurane, and sufentanil	Bonebakker <i>et al.</i> ³⁴	-	Used less frequent examples
			N ₂ O:O ₂ and isoflurane	Ghoneim <i>et al.</i> ³⁵	-	
Free association	No. of targets produced on presentation of cues	N ₂ O:O ₂ and alfentanil	Jelicic <i>et al.</i> ³⁶	+	Patients, in contrast to previous study, were not paralyzed during anesthesia	
		N ₂ O:O ₂ and enflurane	Jelicic <i>et al.</i> ³⁷	-	Authors attributed the negative results to premedication with midazolam	
		N ₂ O:O ₂ and alfentanil	De Roode <i>et al.</i> ³⁸	-		
	No. of targets produced on presentation of cues	Propofol and sufentanil	Donker <i>et al.</i> ³⁹	-		
		N ₂ O:O ₂ and halothane	Lewis <i>et al.</i> ⁴⁰	-		
		Isoflurane	Kihstrom <i>et al.</i> ⁴¹	+		
		N ₂ O:O ₂ and sufentanil	Cork <i>et al.</i> ⁴²	-	Material was presented during surgery and in the immediate postoperative period	
Story-related association on presentation of a cue	Fentanyl and propofol or methohexital	Bethune <i>et al.</i> ⁴³	+			
	Fentanyl and flunitrazepam; fentanyl and isoflurane; and fentanyl and propofol	Schwender <i>et al.</i> ⁴⁴	+			
Forced-choice recognition*	No. of items recognized	N ₂ O:O ₂ , fentanyl, and isoflurane	Van der Laan <i>et al.</i> ⁹⁹	+	Subjects in the group that showed priming for a presented intraoperative story, also heard a story preoperatively; subjects who failed to show priming did not hear a story preoperatively	
		N ₂ O:O ₂ and halothane or enflurane or thiopental	Dubovsky and Trustman ⁴⁵	-		
	No. of items recognized	N ₂ O:O ₂ and halothane	Millar and Watkinson ⁴⁶	+		
		N ₂ O:O ₂ and halothane or enflurane or isoflurane or opioids	Eich <i>et al.</i> ⁴⁷	-		
		N ₂ O:O ₂ and halothane or enflurane	Evans and Richardson ⁴⁸	+		
		N ₂ O:O ₂ and isoflurane or N ₂ O:O ₂ and opioids	Block <i>et al.</i> ³¹	+		
		N ₂ O:O ₂ , sufentanil and isoflurane	Casey-Rondi <i>et al.</i> ⁴⁹	+		
N ₂ O:O ₂ , isoflurane, and sufentanil or propofol and alfentanil	Bonebakker <i>et al.</i> ⁵⁵	+				

(continues)

Table 1 (continued). Studies with Indirect Tests of Memory

Memory Test	Parameter Measured	Anesthetic (maintenance)	Study	Results	Comments
General knowledge	No. of questions answered correctly	N ₂ O:O ₂ and halothane	Goldmann ⁵⁰	+	
		isoflurane	Dwyer <i>et al.</i> ⁵¹	-	
		N ₂ O:O ₂ and alfentanil	Jelicic <i>et al.</i> ³⁶	-	
		N ₂ O:O ₂ and enflurane	Jelicic <i>et al.</i> ³⁷	-	Patients, in contrast to previous study, were not paralyzed during anesthesia
Homophones	Spelling of homophones	Propofol and sufentanil	Donker <i>et al.</i> ³⁹	-	
		N ₂ O:O ₂ and halothane or enflurane or isoflurane or opioids	Eich <i>et al.</i> ⁴⁷	-	
		N ₂ O:O ₂ , isoflurane, and fentanyl	Brown <i>et al.</i> ³²	-	Authors speculated that the results were due to conditioned suppression of material learned during anesthesia
Preference	No. of items preferred that have been presented before	N ₂ O:O ₂ , isoflurane, and fentanyl	Westmoreland <i>et al.</i> ³³	-	
		N ₂ O:O ₂ , isoflurane, and fentanyl	Winograd <i>et al.</i> ⁵²	-	
		N ₂ O:O ₂ and isoflurane or N ₂ O:O ₂ with opioids	Block <i>et al.</i> ³¹	+	Used melodies Used nonsense words
		N ₂ O:O ₂ and halothane	Bonke <i>et al.</i> ⁵³	-	Used a coloring task in children
		N ₂ O:O ₂ , sufentanil, and isoflurane	Caseley-Rondi <i>et al.</i> ⁴⁹	-	Used melodies
		N ₂ O:O ₂ and halothane	Kalf <i>et al.</i> ⁵⁴	-	Used a coloring task in children, replicating Bonke <i>et al.</i> study, ⁵³ although benzodiazepine premedication was omitted, implicit memory remained undetected
Word completion	Completion of word stems to targets	N ₂ O:O ₂ and isoflurane or N ₂ O:O ₂ with opioids	Block <i>et al.</i> ³¹	+	
		N ₂ O:O ₂ , isoflurane, and sufentanil or propofol and alfentanil	Bonebakker <i>et al.</i> ⁵⁵	+	

+ = positive results; - = negative results.

* Although forced-choice recognition is usually classified as an explicit memory test, there is some basis for considering it an implicit test for material presented during anesthesia.

whether he or she recognizes an item. First, the "familiarity" of the item is retrieved; second, a search process determines whether the item was presented previously. The first process may fall within the domain of implicit memory. The success of some researchers with forced-choice recognition tasks in anesthetized patients (table 1) may support this contention, assuming that patients are guessing and are guided by feelings of familiarity. Therefore we included this task in the table.

An unforced recognition task, which allows participants not to respond if they are unsure, may be less sensitive to implicit memory than a recognition task in which participants are forced to respond to every test item, even if they believe they are only guessing, because guesses may reflect implicit memory.⁷⁵ Several groups of investigators found evidence for memory during anesthesia using forced-choice recognition tasks.^{3,46,48,49,55}

Other tasks have been used with mixed results. An exception is the word-completion task, for which the results have been positive. However, this task has been used only by two groups of investigators.^{31,55}

Other variables in the studies that may influence their outcome include the anesthetic technique, the salience of the experimental stimuli, the number of stimulus presentations, the time interval between presentation and the test, and sample size.

Comments and Critiques

We could argue that any learning during general anesthesia is implicit, because the patient is rendered unconscious by the general anesthetic drugs. Skeptics may, however, counter that there is no reliable way to determine adequacy of anesthesia, particularly in the paralyzed patient. The interaction between the administered anesthetic doses and varying levels of surgical stimulation may lead to episodes of awareness. In addition, as we discuss later, explicit recall is abolished before loss of responsiveness, so it is possible for a patient to be responsive and conscious during surgery and yet not remember this after recovery. Therefore appropriate performance on indirect tests of memory after anesthesia may not necessarily imply the presence of unconscious learning and implicit memory during anesthesia.^{26,58} Conceivably, an implicit test might show memory while an explicit test does not show memory because the former test is more sensitive than the latter, rather than because it engages a memory system different than the explicit one.

Therefore it would be of interest to use procedures that may provide uncontaminated estimates of con-

scious and unconscious processes. Caseley-Rondi *et al.*⁴⁹ recommend two such approaches, "relatively sensitivity" and "qualitative differences," that they assert might provide more rigorous evidence of unconscious learning during anesthesia.

The "relative sensitivity" approach uses explicit and implicit tests that are as comparable as possible in all respects except whether they overtly request recollection of previously presented information. Under these circumstances, if participants show more memory on the implicit test than the explicit test, unconscious learning can be inferred. If the explicit and implicit tests differ in other respects, according to Caseley-Rondi *et al.*,⁴⁹ these other differences might be responsible for any differences in performance and would complicate an interpretation in terms of unconscious learning. Unconscious learning during anesthesia has not yet been definitively demonstrated in a manner satisfying Caseley-Rondi *et al.*'s requirement, because the two studies using the most similar explicit and implicit tests—forced-choice recognition and preference judgments, respectively—did not demonstrate differential performance on these tests.^{31,49}

The "qualitative differences" approach⁴⁹ uses a test in which conscious and unconscious learning should produce qualitatively different (*i.e.*, opposite) effects on performance. For example, using a procedure developed by Jacoby *et al.*,⁵⁹ participants might be presented with nonfamous names such as John Schultz during anesthesia. After operation, they would be presented with these names, mixed together with other nonfamous names and famous names, and asked to indicate whether each name is famous or not. They would be told before the test that all the names presented during anesthesia were not famous. Conscious retention of presentation of the name John Schultz during anesthesia should, therefore, lead to classifying it as nonfamous, whereas unconscious retention might lead to classifying it as famous.

Application of the relative sensitivity and qualitative differences approaches may lead to more definitive demonstrations of unconscious learning during anesthesia. However, such methods may not appeal to all investigators. Tests that do not fit within these approaches may have other virtues; for example, they may prove more sensitive to learning during anesthesia or be more realistic or meaningful. It remains appropriate for investigators to use other types of tests to study learning during anesthesia, and, perhaps, to assume tentatively that learning detected by these tests is unconscious,

provided that this assumption is consistent with patients' self-reports and anesthesia seems to be adequate; that is, patients cannot recollect hearing anything during anesthesia and they have no concept that a relationship exists between material that was presented during anesthesia and their performance on an incidental, seemingly "nonmemory" test. If patients have no concept of such a relationship, they cannot be aware that the presented material influences their performance on the test.

Influence of Anesthetic Regimens on Outcomes of Studies. Because some benzodiazepines impair implicit memory,⁶⁰⁻⁶² it is prudent to avoid their use in studies of implicit memory during anesthesia. Block *et al.*³¹ found that the anesthetic technique—nitrous oxide with opioids or with isoflurane—did not affect performance on the implicit memory tests that were used. However, an influence of anesthesia method could have been missed because of the small sample size. Kihlstrom *et al.*⁴¹ found evidence for implicit memory during anesthesia with isoflurane but no implicit memory in a second study⁴² in which they used nitrous oxide and sufentanil. Schwender *et al.*⁴⁴ found that in patients with implicit memory after operation, the midlatency auditory-evoked potentials during anesthesia continued to show a pattern similar to the awake state, but in contrast, in the patients without implicit memory, the waveforms were severely attenuated or abolished. Most of the patients in the first group were anesthetized with flunitrazepam and fentanyl and most of the patients in the second group were anesthetized with isoflurane and fentanyl or propofol and fentanyl. This may suggest that implicit memory is possible mainly under light anesthesia. The results of Jelicic *et al.*,³⁷ in which they failed to replicate their earlier demonstration of learning³⁶ when they used nitrous oxide and enflurane instead of nitrous oxide and opioids, are consistent with this suggestion. The contradictory results of Kihlstrom *et al.*^{41,42} may represent failure of replication of an earlier study rather than a difference caused by the two anesthetic methods.

Jelicic and Bonke,⁶³ in an attempt to explain the effects of different anesthetic techniques on implicit learning during anesthesia (table 1), hypothesized that single words can be activated in postoperative implicit memory during both nitrous oxide anesthesia and anesthesia with potent volatile agents. However, learning of more complex information may be only possible in patients during nitrous oxide anesthesia, alone or supplemented with opioids. Whatever the explanation, it seems that, in the absence of a monitor for the depth

of anesthesia, investigators should standardize the anesthetic methods used as closely as possible with respect to drugs and their dosages.

Types of Information Presented and Tested. Many implicit memory tasks can be categorized as perceptual or conceptual.⁶⁴ Perceptual memory tests can be exemplified by the word completion task. The beneficial effect of study on test performance has been labeled *perceptual priming* because the cue in these tests specifies the perceptual form of the studied stimulus word. In contrast, an implicit test may provide information that is conceptually related to the studied information but with no apparent perceptual similarity between the study and test stimuli. Examples of such tasks include answering general knowledge questions or generating category exemplars. The increased likelihood that participants say or write the target word if it was presented at study has been labeled *conceptual priming*. An unambiguous classification of priming tasks according to whether they depend on perceptual or conceptual priming remains elusive, however. Carlesimo,⁶⁵ for example, presented evidence that both perceptual and conceptual processes may contribute to priming in word-completion tests. It has been suggested⁶⁶ that anesthetized patients may perform better on perceptual rather than conceptual tasks, but there is insufficient evidence to confirm this suggestion.

Another distinction pertinent to implicit memory concerns locating and activating information that already exists in memory (e.g., a representation in memory of a word that is already part of a person's vocabulary) *versus* forming a new representation in memory (e.g., learning a new word and storing in memory some kind of cognitive structure that represents that word).⁶⁷ There are two important differences between implicit memory for "old" (already existing) and new representations.⁶⁸ First, the creation of new representations in memory may require the participant to engage in some mental activities that are not necessary for locating and activating old representations. Second, implicit memory for new information is difficult to observe in severely amnesic patients. Kihlstrom and Schacter⁶⁸ have, therefore, hypothesized that implicit memory for events during anesthesia might be confined to the activation of preexisting knowledge. However, the study of Block *et al.*³¹ using nonsense words and Jelicic *et al.*³⁶ using fictitious nonfamous names suggest that new representations or associations may be formed in memory during anesthesia.

Familiarity of Stimuli. The issue of familiarity of

the material used in the memory tests is also of interest. So, too, is the material's associative frequency or dominance (*i.e.*, the probability with which a stimulus evokes a response). For example, if participants are asked to name examples of the category "metal," some examples with high associative frequency or dominance are given frequently (such as iron), whereas other examples with low associative frequency or dominance are given infrequently (such as tungsten). Jelacic *et al.*³⁰ and Roorda-Hrdlicková *et al.*²⁹ tested patients with a category-generation task using familiar categories and familiar target words. They obtained evidence for learning during anesthesia. However, Bonebakker *et al.*³⁴ from the same research group found no such evidence when they used less familiar target words. Bonebakker *et al.*⁵⁵ found that, using the word-completion task, patients showed more evidence of priming for words with high associative frequency or dominance compared with words with lesser ratings. Results from studies with persons with and without amnesia show that less familiar words result in larger priming effects.^{69,70} This may not be the case in anesthetized patients. Bonebakker *et al.*⁵⁵ suggested that familiarity with the information to which patients are exposed during anesthesia is important for successful priming.

Number of Stimulus Presentations. In conscious persons, repetition and duration of exposure to the stimulus seem to enhance conceptual, but not perceptual, priming.^{71,72} Recently, Bonebakker *et al.*⁵⁵ found that memory during anesthesia was apparent after one, but not after 30 presentations of a word list. An explanation that has been offered for these results⁵⁵ is that patients may unconsciously associate the presented material with an aversive period during surgery. Brown *et al.*³² found that performance on indirect memory tests was worse for words that were presented three times during anesthesia than for words that were not presented at all. The investigators suggested that memory may be suppressed by the aversive experience of surgery. However, this somewhat implausible speculation stands in contrast to several studies that showed memory effects after multiple presentations.^{31,36,41} Brown *et al.*'s³² statistical analyses of their results were also questionable. Because the effect was only marginal in the primary analysis, follow-up analyses were not warranted. The analyses were also based on pooling the results of two entirely separate types of tests.

Time of Postoperative Testing. Priming effects (*i.e.*, hearing the words on the list increases participants' ability to identify with the correct solutions when

they respond to the test) were found in anesthetized patients when they were tested very early after operation (3–5 h after surgery)³⁰ or as late as 5 days after surgery.⁴⁴ The optimal time of testing after operation could be influenced by several factors. Patients should be tested when they have recovered sufficiently from the detrimental effects of anesthetics on cognitive function that could impair their performance, but before priming effects have dissipated. Durations of the priming effects may vary according to the task used.⁶⁷ Andrade⁷³ suggests that testing should be conducted in the hospital to minimize changes in context between stimulus presentation and the memory test, although it remains to be demonstrated that context effects significantly influence performance on indirect tests of memory. Extraneous stimuli may also interfere with the specific stimuli administered during anesthesia, if the testing is delayed. Merikle and Daneman⁷⁴ recently conducted a meta-analysis of studies investigating memory for events during anesthesia. Memory decreased systematically as the interval between the end of surgery and the administration of the memory test increased, and there seemed to be no memory when testing was delayed more than 36 h after surgery.

In contrast, consolidation of implicit memory, active during sleep, depends strongly on rapid eye movement sleep.⁷⁵ Sleep pattern after surgery is severely disturbed with early depression of rapid eye movement and slow wave sleep and with rebound of rapid eye movement sleep on the second and third nights.⁷⁶ Conceivably, this might favor testing on the third postoperative day.

Sample Size. In studies providing evidence of learning during anesthesia, the effects usually have been small.^{31,41,46} This is consistent with the possibility that only a minority of persons can learn during anesthesia, perhaps due to a relatively light level of anesthesia.⁷⁷ Positive findings seem more likely to be replicated in studies with substantial samples of patients, which provide adequate power to detect relatively small effects. Studies with small samples, such as 20–30 patients, may lead to conflicting results.

Postoperative Performance after Behavioral Suggestions Presented during Anesthesia

Bennett *et al.*⁷⁸ introduced this method in 1985. Initially, three groups of investigators reported positive results,^{31,78,79} despite criticisms of absence of baseline assessment of the target behavior, presence of too light

a level of anesthesia during presentation of the suggestions, and deficiencies in the statistical analyses. Later reports were negative both in anesthetized patients and in healthy volunteers treated with subanesthetic concentrations of inhalation anesthetics.^{51,80-83}

The Influence of Therapeutic Suggestions Administered during Anesthesia

In addition to providing evidence of learning during anesthesia, the possibility of improving the postoperative course of patients by presentation during anesthesia of therapeutic suggestions predicting a rapid and comfortable postoperative recovery is an attractive clinical goal. Table 2 lists the studies that have been done in this area.

Hospital Stay

Evans and Richardson⁴⁸ reported that patients who received therapeutic suggestions during anesthesia for hysterectomy had shorter postoperative stays than did a nonsuggestion control group. In contrast, Liu *et al.*⁹³ could not find positive effects. Millar⁷⁷ conducted a meta-analysis of the results of Evans and Richardson and Liu *et al.* He concluded that Evans and Richardson's results may have been caused by chance bias in allocation of patients to the control group as a result of a relatively small sample size (fig. 1). Jelicic *et al.*⁹⁵ exposed patients to both affirmative ("you will be comfortable") and nonaffirmative ("you will have no pain") suggestions, affirmative or nonaffirmative suggestions separately, or some irrelevant text. They obtained somewhat contradictory and confusing findings: Patients who received both affirmative and nonaffirmative suggestions spent less time in the hospital than did patients in the other three groups. The authors acknowledged the possibility that the outcome might have been due to chance.

Postoperative Pain and Analgesic Use

Korunka *et al.*⁹⁴ found that suggestions or music prolonged the period before patients asked for their first postoperative analgesic, compared with a control tape of operating room sounds, but only the music tape reduced total analgesic consumption. Caseley-Rondi *et al.*⁴⁹ also reported reduction in analgesic requirements in patients who were played therapeutic suggestions during anesthesia. However, differences between the experimental and control groups were only marginally

significant in analyses controlling for the greater age of the patients and longer duration of anesthesia (and presumably larger doses of intraoperative opioids) in the experimental group. Furthermore, the significance level in the analysis of morphine use after operation was not adjusted for the number of measures of postoperative recovery that were assessed, increasing the probability of a type 1 error. Van der Laan *et al.*⁹⁹ also found that therapeutic suggestions had no effect on postoperative analgesic requirements.

Nausea and Vomiting

Williams *et al.*⁹⁶ reported that presentation of positive intraoperative suggestions reduced patients' recalled incidence of vomiting in the first 24 h after surgery by 37% compared with a control group. Patients who received therapeutic suggestions also required smaller doses of metoclopramide. Oddby-Muhrbeck *et al.*⁹⁸ more recently failed to find positive effects on postoperative nausea and vomiting, although therapeutic suggestions did reduce patients' recall of these distressing postoperative symptoms. Differences between these two studies with respect to dependent variables, contents of the therapeutic suggestions tapes, postoperative antiemetic medications, and types of surgery could have contributed to the different conclusions that were reached.

Smoking

Hughes *et al.*⁹⁷ presented smokers during surgery with a tape encouraging them to give up smoking or a control tape. Compared with patients who received the control tape, more of those who received the suggestions tape had stopped or reduced their smoking according to self-reports 1 month after operation. However, Myles *et al.*¹⁰⁰ failed to confirm this finding. The strength of the findings of Hughes *et al.*⁹⁷ as evidence of implicit learning during anesthesia is limited, because of several factors. Although no patients recalled the message, their memory was not tested until 1 month after operation; however, some might have recalled it had their memory been probed earlier. The assessment of postoperative smoking was not based on objective records of cigarette smoking or on self-reports obtained at frequent intervals, but only on a single, delayed self-report covering a 1-month period. The validity of such a self-report, especially for patients who reported decreased smoking rather than complete abstinence, is uncertain.

Table 2. Therapeutic Suggestions Studies

Study	Outcome Measure(s)	Anesthetic (maintenance)	Surgery	Results	Comments
Wolfe and Miller ⁸⁴	Postoperative pain, nausea and vomiting, and many others	Not stated	Wide variety	No measurements done	Uncontrolled study
Hutchings ⁸⁵	Postoperative pain, nausea and vomiting, and many others	Not stated	Wide variety	No measurements done	Uncontrolled study
Pearson ⁸⁶	Duration of hospitalization	Not stated	Several types	Shortened	Experimental and control groups not matched Small sample size
Abramson <i>et al.</i> ⁸⁷	Postoperative analgesic requirements and duration of hospitalization	Not stated	Abdominal and orthopedic procedures	No effect	
Bonke <i>et al.</i> ⁸⁸	Duration of hospitalization, postoperative pain, nausea and vomiting, subjective well being, and nurses' evaluations	N ₂ O:O ₂ and fentanyl; sometimes with dyhydrobenzperidol	Biliary tract	Shortened the duration of hospitalization in older patients	
Woo <i>et al.</i> ⁸⁹	Duration of hospitalization, postoperative analgesic requirements, days until p.o. fluids and solid food, and wound drainage	N ₂ O:O ₂ and enflurane	Abdominal hysterectomy	No effect	Small sample size
Boeke <i>et al.</i> ⁹⁰	Duration of hospitalization, postoperative pain, nausea and vomiting, subjective well being, and nurses' evaluations	N ₂ O:O ₂ and fentanyl; sometimes enflurane added	Cholecystectomy	No effect	
Evans and Richardson ⁴⁸	Duration of hospitalization, pyrexia, pain intensity and distress, nausea and vomiting, urinary difficulties, difficulties with bowels, flatulence, mobilization rating, and nurses' assessment of recovery	N ₂ O:O ₂ and halothane or enflurane	Abdominal hysterectomy	Shorter hospital stay, shorter period of pyrexia, and better rating by nurses	
McLintock <i>et al.</i> ⁹¹	Postoperative analgesic requirements, pain scores, and nausea and vomiting	N ₂ O:O ₂ and enflurane	Abdominal hysterectomy	Reduced analgesic requirements in the early postoperative period	Analgesia was provided through a PCA system
Block <i>et al.</i> ⁹²	Duration of hospitalization, postoperative analgesic requirements, nausea and vomiting, gastrointestinal and urinary symptoms, and ratings of pain, anxiety, and recovery	N ₂ O:O ₂ and isoflurane or N ₂ O:O ₂ and opioids	Several types	No effect	Analgesia was provided through a PCA system to 52% of patients
Liu <i>et al.</i> ⁹³	Duration of hospitalization, postoperative analgesic requirements, nausea, flatulence, pyrexia, ease of mobility, mood state and anxiety level, and nurses' assessments	N ₂ O:O ₂ and enflurane	Abdominal hysterectomy	No effect	

(continues)

Table 2 (continued). Therapeutic Suggestions Studies

Study	Outcome Measure(s)	Anesthetic (maintenance)	Surgery	Results	Comments
Korunka <i>et al.</i> ⁹⁴	Duration of hospitalization, postoperative analgesic requirements, and pain ratings	N ₂ O:O ₂ , fentanyl, and isoflurane or halothane	Hysterectomy: abdominal or vaginal	Relative to presentation of operating room sounds, presentation of therapeutic suggestions reduced time elapsed until the first postoperative analgesic dose and some ratings of pain, whereas presentation of music reduced not only these two measures but total analgesic consumption as well	It is difficult to explain why mixed suggestions produced the best results
Jelicic <i>et al.</i> ⁹⁵	Duration of hospitalization and subjective well being	N ₂ O:O ₂ and sufentanil or fentanyl	Cholecystectomy	Patients who received both affirmative and nonaffirmative suggestions spent less time in hospital than patients who received affirmative or nonaffirmative suggestions separately, or some irrelevant text	
Caseley-Rondi <i>et al.</i> ⁴⁹	Duration of hospitalization, postoperative analgesic requirements, patients and nurses' ratings, and assessments of anxiety, mood, and nausea	N ₂ O:O ₂ , sufentanil, and isoflurane	Abdominal hysterectomy	Reduced analgesic requirements for the first 2 postoperative days	Analgesia was provided through a PCA system
Williams <i>et al.</i> ⁹⁶	Nausea and vomiting	N ₂ O:O ₂ and isoflurane	Major gynecologic surgery	Incidence and severity reduced	
Hughes <i>et al.</i> ⁹⁷	Smoking	Not specified	Several types	Stopped or reduced	
Oddby-Muhrbeck <i>et al.</i> ⁹⁸	Nausea and vomiting	N ₂ O:O ₂ , fentanyl, and isoflurane	Breast surgery	No effect	The experimental group had a lower frequency of recall of their nausea and vomiting compared with the control group
van der Laan <i>et al.</i> ⁹⁹	Postoperative analgesic requirements	N ₂ O:O ₂ , fentanyl, and isoflurane	Hysterectomy, myomectomy, or gynecologic laparotomy	No effect	Analgesia was provided through a PCA system
Myles <i>et al.</i> ¹⁰⁰	Smoking	Isoflurane, enflurane, and others	Elective or semi-elective surgery	No effect	

PCA = patient-controlled analgesia.

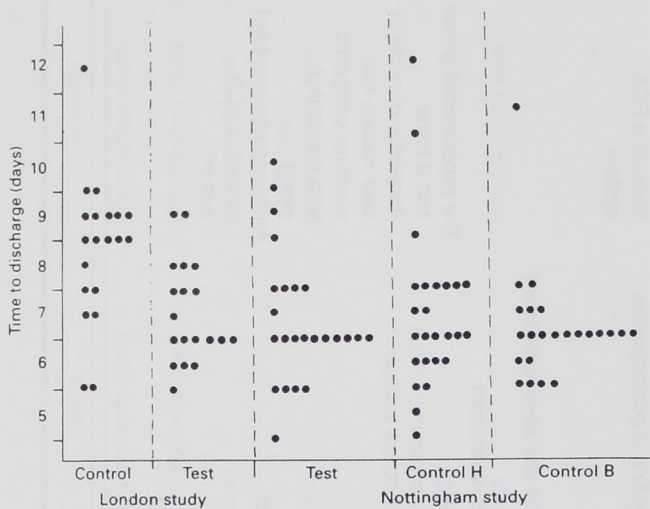


Fig. 1. Distribution of patient data points (days to discharge) in the two groups of Evans and Richardson (1988) in London and three groups of Liu *et al.* (1992) in Nottingham. Test groups were presented with therapeutic suggestions during anesthesia. The suffixes "B" and "H" indicate that those control groups received a blank or "history" tape, respectively, in the Nottingham study. With the presentation of data in scatter plots, it is evident that, although four of the groups were similar in their mean and typical durations of stay in the hospital, the London control group was distinctive, with most patients staying longer in the hospital. (Reproduced with permission from Millar.⁷⁷)

Hypnotic Ability

The interaction of patients' hypnotic ability with the outcome of presentation of therapeutic suggestions has been addressed by two groups of investigators, Caseley-Rondi *et al.*⁴⁹ and Korunka *et al.*⁹⁴ Hypnotic ability was not significantly associated with therapeutic outcome. The two groups also raised the issue of what mediates the therapeutic effect of suggestions. They suggest that it is possible that the soothing tones of a voice rather than semantic processing of connected discourse may be important. Soothing tones, by reducing stress, might aid recovery. The beneficial effect of music in the Korunka *et al.* study⁹⁴ may be consistent with such an explanation and suggests that evidence for postoperative benefit does not necessarily imply that memory is involved.

Critiques and Conclusions

Statistical Concerns. Andrade and Munglani¹⁰¹ criticized many studies reporting beneficial effects of presentation of therapeutic suggestions during anesthesia on the grounds that some of these effects might have been due to chance, because the studies assessed multiple measures of recovery without controlling statisti-

cally for the number of variables analyzed. When many variables are analyzed and a statistical method such as Bonferroni's method is used to control for the number of variables, an effect must be rather large to be deemed statistically significant. Because beneficial effects of presentation of therapeutic suggestions may not be large, judicious selection while planning a study of a smaller set of dependent variables may be preferable.

Methodologic Concerns. Millar⁷⁷ made useful suggestions for improving the methods used. The first suggestion concerns the sample size. Considerably larger sample sizes than the usual samples of 20 or fewer are required, considering the likely possibility that only a few patients in a given sample may be in a state to register auditory information during anesthesia and the sensitivity of the assay. The second suggestion concerns the mode of presentation of the results. Millar suggests that rather than presenting the data exclusively in the summary form of means and standard deviations, better insights into treatment effects may be gained by presenting full data sets in graphic form (fig. 1).

Measures of postoperative well-being and recovery are affected by complex sets of factors that may not be controlled by the experimenter and that may lead to bias when assessing their interactions with presentations of therapeutic suggestions.

Hospital Stay. It appears that the length of hospital stay is not influenced by presentation of therapeutic suggestions to anesthetized patients,⁷⁷ and there does not seem to be a good reason anymore to focus on this measure of postoperative recovery. This measure is likely to be affected by factors that are usually beyond the experimenters' control.

Postoperative Pain and Analgesic Use. Although patient-controlled analgesia provides a better measure of patients' requirements of opioids than drugs prescribed on an as-needed basis by physicians and delivered by nurses, some pitfalls may confound this measure. One issue is that the dose and timing of administration of preoperative and intraoperative opioids may reduce postoperative patient-controlled analgesic consumption.^{102,103} Another issue is sample size. A simulation study suggested that detecting a 25% decrease of analgesic use between control and intervention groups (the effect size that has been reported in studies of therapeutic suggestions with positive results) requires a sample size of 116 patients.¹⁰⁴ This suggests that none of the studies of therapeutic suggestions had large enough sample sizes.

Nausea and Vomiting. The cause of nausea and

vomiting is also multifactorial; that is, it is influenced by type of surgery; anesthetic agents and techniques; patient sex, age, and weight; duration of anesthesia; experience of the anesthesiologist; and history of postoperative nausea and vomiting, motion sickness, middle ear disease, pain, and so on.^{105,106} Authors should report these factors and specify whether they were equally represented in patients receiving therapeutic suggestions and controls. This has not been the case.

Conclusions. It is, therefore, apparent that therapeutic suggestions tasks are particularly liable to both type I and type II errors. This is probably the reason for inconsistent results in this area. In addition, even if some patients register the auditory information that is presented, it may not influence their behavior. A recent meta-analysis of studies in this area by Merikle and Daneman⁷⁴ found little or no effect of therapeutic suggestions on postoperative recovery.

Studies of Healthy Volunteers

One of the main aims for work in this area is to determine the concentrations of anesthetics that prevent learning and memory. "Light" anesthesia is commonly used to avoid toxicity or delayed recovery, or because of intolerance of some patients to higher concentrations. Yet the precise concentrations that guarantee absence of recall are unknown. In addition, largely unknown has been whether different anesthetics equally affect different types of memory. These objectives can be achieved by studying complete dose-response functions of acquisition and retention, studying minimum alveolar concentration-equivalent concentrations of different inhalation anesthetics, equipotent plasma concentrations of intravenous anesthetics, and assessments of the degrees of memory impairments in different types of memory tasks. Other related aims are to investigate the effects of sex and aging and the interactions of anesthetics with one another and with arousing stimulations. All these factors are important for clinical application to patients. It should be remembered, however, that the arousing effect of surgery and emotionally charged information may increase the anesthetic concentrations required to prevent consciousness and memory. Table 3 summarizes the literature.

Critiques and Conclusions

Concentration-Effect Relations. The concentrations of anesthetics that block explicit memory are less

than those that prevent voluntary responses to verbal commands.^{17-20,51} Thus anesthetic concentrations that prevent voluntary responses also prevent conscious memory. At minimum alveolar concentration-awake and Cp₅₀-awake (the plasma concentration required to prevent responsiveness to command in 50% of patients), both explicit and implicit memory are abolished. These results are inconsistent with reports of implicit memory during general anesthesia.

Although Block *et al.*¹⁰⁷⁻¹⁰⁹ found that 30% nitrous oxide impaired performance on direct tests of memory but not some indirect tests of memory, Chortkoff *et al.*⁸² found that implicit learning was suppressed at concentrations of isoflurane nearly identical to those that suppressed explicit learning. The inconsistency extends even to explicit memory. Contrary to several reports,^{107-109,121-124} Dwyer *et al.*⁵¹ found no impairment with a 30% nitrous oxide concentration. Newton *et al.*¹¹⁰ found that recall and recognition of neutral words were lost at 0.2 minimum alveolar concentration of isoflurane inhalation. In contrast, Chortkoff *et al.*⁸² found that this concentration was only the median effective dose for explicit learning, and the 95% effective dose was 0.4 minimum alveolar concentration. Zacny *et al.*¹¹⁶ found that immediate and delayed recall were still possible during and after inhalation of 0.6% isoflurane. It is probable that the inconsistencies of these results are caused by methodologic flaws, some of which we describe.

Electroencephalographic Changes. Neither Munglani *et al.*,¹¹⁴ Andrade *et al.*,¹¹⁵ nor Dwyer *et al.*¹¹² provided convincing evidence of correlations between auditory evoked response (AER) or other electroencephalographic parameters and responsiveness to commands or memory of information presented during anesthetic administration. Future work might identify some parameter that unambiguously defines the point of loss of consciousness.

Methodologic Issues. There are two components of value in the design of experiments investigating the effects of drugs on cognition. The first is comparison of the behavior of the patient before and after administration of the drug, allowing unambiguous attribution of behavioral changes to the influence of the drug in question. The second design component is the use of a nondrug (placebo) control in which the same or other persons receive identical treatment except for administration of the drug. Pre-post comparisons alone are imperfect because practice on experimental tasks (fig. 2), environmental influences, fatigue, and other factors (fig.

Table 3. Studies of Healthy Volunteers

Study	No. of Subjects	Anesthetic Agents	Tasks	Design	Results
Block <i>et al.</i> ^{107,108}	32	30% N ₂ O	Recall and recognition of word lists and first names, category-example task, free associations, word completion and preference, and recognition of nonsense words	Double-blind and randomized	Recall and recognition were impaired. Impairments were milder in forced choice recognition than in yes/no recognition. Performance in category-example task and word completion showed resistance to memory impairment
Block <i>et al.</i> ¹⁰⁹	32	30% N ₂ O	Classical conditioning of skin conductance responses	Double-blind	Although N ₂ O seemed to prevent conditioning during its inhalation, learning took place because conditioned responses could be elicited after cessation of inhalation
Newton <i>et al.</i> ^{110,111}	8	0, 0.1, 0.2, and 0.4 MAC of isoflurane	Recall and recognition of word lists, responses to commands, and auditory evoked response AER	Double-blind, randomized, and crossover	Recall and recognition were lost at 0.2 MAC. Half of the subjects recalled a "shock" word at the same concentration. Responses to command were lost at 0.4 MAC. It was difficult to demonstrate changes in the AER that were specifically related to changes in memory.
Dwyer <i>et al.</i> ^{51,112}	17	0.15, 0.3, and 0.45 MAC isoflurane and 0.3, 0.45, and 0.6 MAC N ₂ O	Responses to commands, learning of obscure general knowledge, responses to behavioral suggestions, and EEG	Open, randomized, and crossover; the different concentrations of each drug were given consecutively in a fixed order in one session	Explicit and implicit memory were prevented by 0.45 MAC isoflurane. N ₂ O did not completely prevent either type of memory. EEG showed very limited relationships to response to command and learning.
Chortkoff <i>et al.</i> ⁸²	10	0.15, 0.28, and 0.4 MAC isoflurane	Category-example task and responses to behavioral suggestions	Open; the different concentrations were given consecutively in a fixed order in one session	0.4 MAC abolished both explicit and implicit memory.
Chortkoff <i>et al.</i> ¹¹³	24	40% N ₂ O combined with 0.06, 0.22, and 0.38% isoflurane	Category-example task, learning of obscure general knowledge, responses to commands, and responses to behavioral suggestions	Open; the different concentrations were given consecutively in a fixed order in one session	There was a small degree of antagonism between the two anesthetics. There was no evidence of learning during inhalation of the high concentration.

(continues)

Table 3 (continued). Studies of Healthy Volunteers

Study	No. of Subjects	Anesthetic Agents	Tasks	Design	Results
Munglani <i>et al.</i> ¹¹⁴ and Andrade <i>et al.</i> ¹¹⁵	7	0, 0.2, 0.4, and 0.8% isoflurane.	Category-example task and measurement of the "coherent frequency" of the AER	Open; the different concentrations were given consecutively in a fixed order in one session	Increasing concentrations of isoflurane decreased coherent frequencies and performance on the tests. There was no evidence of implicit learning with 0.8% concentration. Dose of anesthetic was a better predictor of cognitive function than coherent frequency. Both drugs impaired immediate and delayed recall in a concentration-related fashion. There were no differences between the two drugs. MAC-awake for desflurane was 2.6% and the Cp50-awake for propofol was 2.69 μ g/ml.
Zacny <i>et al.</i> ¹¹⁶	9	0, 0.3, and 0.6% isoflurane and 0, 20%, and 40% N ₂ O	Immediate and delayed free recall	Double-blind, randomized, and crossover.	
Chortkoff <i>et al.</i> ¹¹⁷	22	Desflurane and propofol concentrations were increased in stepwise fashion until the subjects stopped following commands	Response to commands	Open; order of administration of the two drugs was randomized over two sessions	
Chortkoff <i>et al.</i> ¹¹⁸	23	Desflurane and propofol at a concentration 1.5-2 times each individual MAC-awake or its equivalent for propofol	Presentation of emotionally charged information, learning of obscure general knowledge, and responses to behavioral suggestions	Subjects and interviewers were blinded to the information which was presented; materials and treatments were randomized and balanced	The drugs prevented explicit and implicit learning.
Zacny <i>et al.</i> ¹¹⁹	10	0, 30% N ₂ O, and 0.2 and 0.4% isoflurane, alone, and in combination with 30% N ₂ O	Immediate and delayed free recall	Single-blind, randomized, and crossover; different sessions for each treatment	Drug combinations produced profound impairments. Isoflurane appeared to produce more impairment than N ₂ O.
Gonsowski <i>et al.</i> ¹²⁰	12	0.6 MAC desflurane or isoflurane, followed by 1.7 MAC, then 0.6 MAC again	Category-example task, learning of obscure general knowledge, and responses to behavioral suggestions	Open and crossover	0.6 MAC prevented explicit and implicit learning.

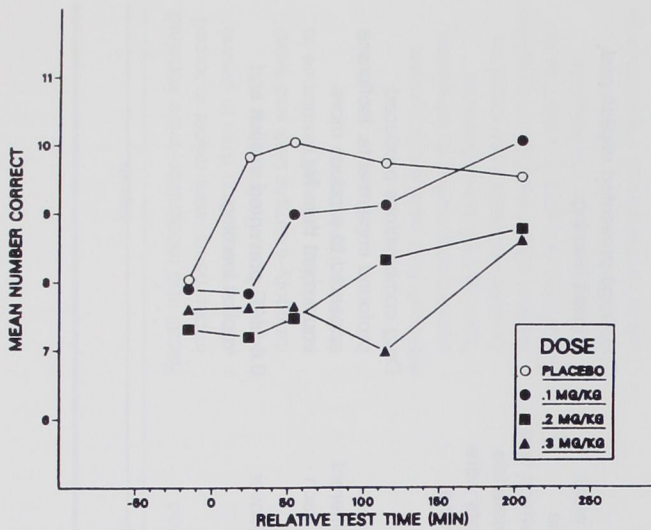


Fig. 2. The mean number of digits recalled at intervals before and after diazepam and placebo treatments. Zero was the time of drug administration. Different random 15-digit numbers were presented each time. The score represents the mean of three trials. A delayed practice effect caused by varying doses of diazepam is apparent. (Reproduced with permission from Ghoneim *et al.*¹⁵¹)

3) can change behavior over time and affect the comparison of performance before and after drug administration. Comparison of separate treatment and control groups alone does not provide evidence that the groups were equivalent before treatment, so the possibilities that observed differences could have been present regardless of treatment or true differences could have been masked by different baseline levels between groups cannot be excluded. Although some studies with subanesthetic concentrations conducted since our previous review have shown some methodologic improvements relative to earlier work, many have omitted one or the other of these design components.

Some investigators, rather than testing different concentrations of an anesthetic in separate sessions or with separate participants, have used a series of increasing and then decreasing concentrations of the drug within a single session. Practice effects, fatigue effects, cumulative effects of the anesthetic agent, tolerance development, proactive or retroactive interference, and other potential confounders are inherent risks of this type of design. Some investigators administered the indirect test(s) of memory only during the inhalation of the highest concentration of the anesthetic (e.g., Chortkoff *et al.*⁸² and Munglani *et al.*¹¹⁴). In the absence of testing in a control group, during inhalation of lower concen-

trations of the anesthetic, or both, it is difficult to determine whether the absence of learning was due to the effect of the drug, insensitivity of the task, or both. Other concerns are use of different lists of words with no evidence that they were comparable in their normative characteristics or had been equated in pilot studies; absence of counterbalancing of lists over treatments, which may confound differences among lists with differences among treatments; and use of tasks that have not been adequately validated.

Brain Imaging. Studies of the effects of anesthetics on memory may eventually take advantage of the remarkable advances in noninvasive functional brain-imaging research. Correlates of anatomic systems involved in perception, memory, and other mental functions in the brains of living persons are being studied using positron emission tomography combined with magnetic resonance imaging. These technologies can sample anywhere within the brain, measuring changes in blood flow that occur in conjunction with neuronal activity. Measurements are made while participants perform specified behavioral tasks. By imaging blood flow multiple times during performance of different tasks, the experimenter can relate specific functional attributes with activity in local cortical areas. Learning with and without awareness may involve different anatomic

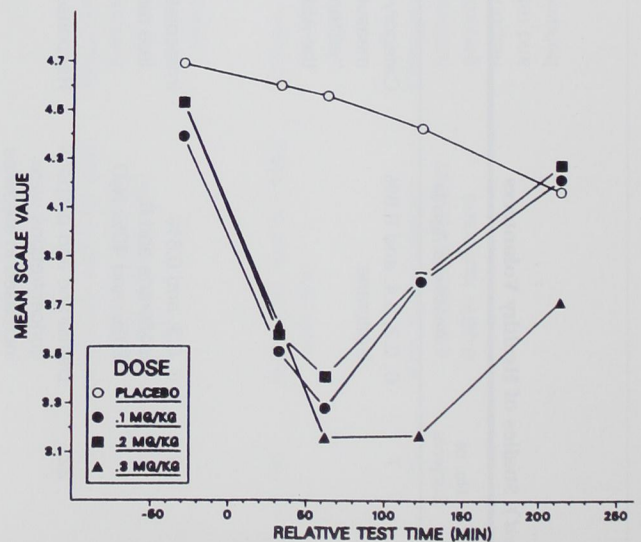


Fig. 3. Composite mood evaluation scores on visual analog scales before and after administration of diazepam and placebo. The vertical axis represents the mean value of seven scales. A decreasing score is associated with increasing sedation. The figure illustrates changes in subjective mood evaluations over time with or without active drug treatment. (Reproduced with permission from Ghoneim *et al.*¹⁵²)

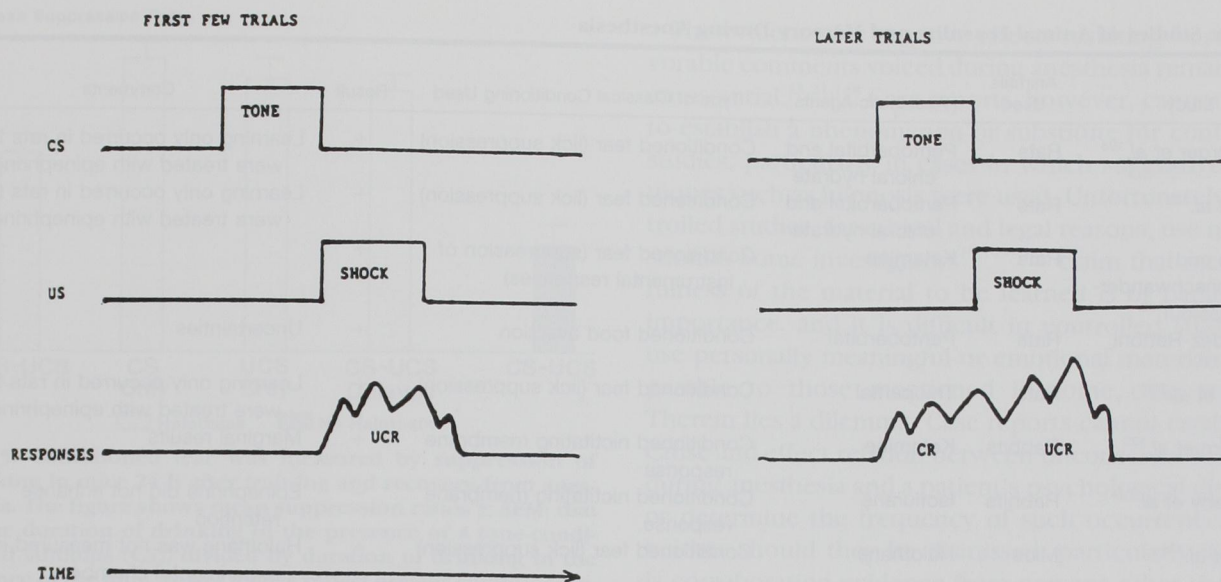


Fig. 4. The events of a classical or Pavlovian conditioning trial before a conditioned response (CR) is established and after. The upward deflection of the trace indicates stimulus or response onset. The downward deflection indicates offset. A tone (the CS or conditioned stimulus) is paired with shock (the US or unconditioned stimulus). The latter elicits the unconditioned response (UCR). Responses may be salivation, eyelid closure, increased skin conductance, and so on. During later conditioning trials, repeated pairings of the tone and shock elicits a response to the tone (the CR) and to the shock.

systems. Working memory, explicit memory, and implicit memory involve activity that is highly distributed in multiple cortical, subcortical, and cerebellar areas. Priming is associated with decrements in activity in auditory or visual association cortex, depending on the modality of testing. Other types of implicit memory use different anatomic systems.¹²⁵

Electroencephalography records electric activity of the brain from the scalp and hence does not accurately localize the source of neuronal activity. It records the signals associated with neuronal activity over a much shorter time period than positron emission tomography and magnetic resonance imaging. A combination of brain imaging and electric recording may complement each other and define the anatomy of the circuits and the time course of events in these circuits that are involved in a particular behavior.¹²⁶ Studies of healthy volunteers in the awake state and during anesthesia using well-defined cognitive tasks may provide answers to questions difficult to obtain in other ways.

Effects of Anesthetics on Animal Learning and Memory

Studies in anesthetized patients having surgery who were subjected to multitudes of extraneous influences,

which constitute most of the current literature, may not produce conclusive and convincing results for implicit memory during anesthesia. Animals offer the opportunity to gather information that is not obtainable in any other way and allow tighter control of the experimental procedures.

Methods of Studying Learning and Memory and the Effects of Anesthetics

Classical conditioning and operant conditioning probably are responsible for most of an animal's learned responses.¹²⁷ Compared with humans, animals often require elaborate training programs and possess a more restricted repertoire of behavior. It is difficult to dissociate implicit and explicit memory systems in animals and determine whether a particular task taps into one of these systems or the other. The classical or Pavlovian conditioning paradigm includes several different procedures that can be used to study various aspects of the conditioned response. All of these procedures have in common the association of a neutral conditioned stimulus, such as a tone or white noise, with an unconditioned stimulus, such as an electric shock or air puff. Initially, the conditioned stimulus does not elicit a response but the unconditioned stimulus elicits an unconditioned response. With repeated pairings, however, the conditioned stimulus alone also elicits a response —

Table 4. Studies of Animal Learning and Memory During Anesthesia

Study	Animals Used	Anesthetic Agents	Type of Classical Conditioning Used	Result	Comments
Weinberger <i>et al.</i> ¹²⁸	Rats	Pentobarbital and chloral hydrate	Conditioned fear (lick suppression)	+	Learning only occurred in rats that were treated with epinephrine
Gold <i>et al.</i> ¹²⁹	Rats	Pentobarbital and chloral hydrate	Conditioned fear (lick suppression)	+	Learning only occurred in rats that were treated with epinephrine
Edeline and Neuenschwander-EIMassioui ¹³⁰	Rats	Ketamine	Conditioned fear (suppression of instrumental responses)	+	
Bermudez-Rattoni <i>et al.</i> ¹³¹	Rats	Pentobarbital	Conditioned food aversion	+	Uncertainties
Dariola <i>et al.</i> ¹³²	Rats	Thiopental	Conditioned fear (lick suppression)	+	Learning only occurred in rats that were treated with epinephrine
Ghoneim <i>et al.</i> ¹³³	Rabbits	Ketamine	Conditioned nictitating membrane response	+	Marginal results
El-Zahaby <i>et al.</i> ¹³⁴	Rabbits	Isoflurane	Conditioned nictitating membrane response	-	Epinephrine did not enhance retention
Pang <i>et al.</i> ¹³⁵	Mice	Halothane	Conditioned fear (lick suppression)	+	Halothane was not measured in the experimental chamber
Kandel <i>et al.</i> ¹³⁶	Rats	Desflurane and two nonanesthetics	Conditioned fear (fear-potentiated startle)	-	Desflurane, perfloropentane, and 1, 2-dichloroperflorocyclobutane abolished learning at subanesthetic concentrations or their equivalents

+ = positive results; - = negative results.

the conditioned response (fig. 4). Food aversions can be conditioned with very long interstimulus intervals of several hours between conditioned stimulus and unconditioned stimulus. When an animal consumes a flavored fluid and becomes nauseated afterward, it will acquire a conditioned flavor aversion associating the flavor with sickness.

Current Literature

The literature on the effects of anesthetics on learning and memory in animals is limited (table 4). The results of the studies cover a wide spectrum, including findings of no learning during anesthesia, learning only when epinephrine is administered, learning during ketamine anesthesia in which there is sympathetic nerve stimulation, and learning without epinephrine or apparent sympathetic nerve stimulation (fig. 5). Conditioned flavor aversion was demonstrated when lithium was administered during anesthesia.

Critiques and Conclusions

The development of flavor aversions when the nauseating agent is administered during anesthesia can provide evidence for learning during anesthesia. However, none of the available reports^{131,137-140} provide a compel-

ling result. The depth and duration of anesthesia produced by bolus doses of pentobarbital or urethane are difficult to determine, as are the durations of actions of nauseating agents such as lithium chloride or apomorphine. It is possible that the effects of the latter may linger during recovery from anesthesia.

Classical conditioning may be the best method available to investigate learning and memory during anesthesia in animals. Fear conditioning has been more successful in providing evidence of learning during anesthesia than conditioning of a skeletal muscle response, such as eye-blink conditioning. The application of a strong, painful, potentially life-threatening and anesthesia-lightening unconditioned stimulus compared with a slight electrocutaneous one might account for the different results. However, a recent study¹³⁶ that used conditioned fear reported negative findings. The question of the possibility of learning during "adequate" anesthesia in animals has yet to be answered.

Wakefulness without Explicit Recall and Psychosomatic Disorders after Anesthesia

Wakefulness during anesthesia without postoperative explicit recall may occur during light anesthesia and is

MEMORY IN ANESTHESIA

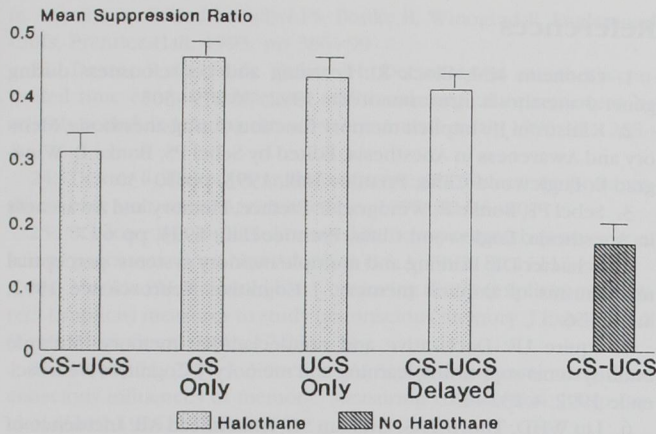


Fig. 5. Conditioned fear was measured by suppression of drinking in mice 24 h after training and recovery from anesthesia. The figure shows mean suppression ratios \pm SEM; that is, the duration of drinking in the presence of a tone-conditioned stimulus (CS), divided by duration of drinking in the absence of the tone. Lower values reflect greater conditioning. Four groups of animals were anesthetized. One group (CS-UCS group at left) was conditioned during anesthesia by pairing of CS with an unconditioned stimulus (UCS), an electric shock. The other three anesthetized groups (CS Only, UCS Only, and CS-UCS Delayed) were controls and were not conditioned. An additional group in which the animals were conditioned in the absence of anesthesia (CS-UCS group at right) was included to evaluate the strength of conditioning in unanesthetized animals. The group that was conditioned during anesthesia (CS-UCS group at left) showed significant conditioning as assessed by the suppression ratio compared with the three anesthetized control groups. (Reproduced with permission from Pang *et al.*¹³⁵).

confirmed by studies using the isolated forearm technique.^{17-20,141} The amnesia is due to the effects of anesthetics on acquisition, retrieval, or both. Blockade of retrieval may also be due to the traumatic nature of information that is acquired during surgery, state-dependency (state-dependent retrieval refers to the improved memory when recall and learning occur in the same context), or both.^{142,143} Are episodes of intraoperative consciousness without subsequent explicit recall harmful? It is possible that if memories of intraoperative events cannot be consciously recollected, they may exert a stronger influence on emotions than in the normal waking state for two reasons. First, anesthetized patients are less able to defend themselves against the implications of what they have "heard"; that is, to use normal, conscious cognitive processes to rationalize or cope with "bad news." Second, information that bypasses consciousness may activate complexes (repressed systems of emotionally charged ideas), with unfortunate psychological consequences, such as postoperative anxiety or depression.¹⁴⁴⁻¹⁴⁷

The evidence for negative effects resulting from unfavorable comments voiced during anesthesia remains circumstantial.^{15,21,148} Case reports, however, cannot serve to establish a phenomenon or substitute for controlled studies, particularly in cases in which suggestive techniques such as hypnosis were used. Unfortunately, controlled studies, for ethical and legal reasons, use neutral stimuli. Some investigators^{15,149-150} claim that meaningfulness of the material to be learned is of paramount importance, and it is difficult in controlled studies to use personally meaningful or emotional materials comparable to those mentioned in some case reports. Therein lies a dilemma. Case reports cannot establish a cause-and-effect relation between unconscious learning during anesthesia and a patient's psychological disorder or determine the frequency of such occurrences. But neither should they be dismissed, particularly if there is corroborating evidence from persons other than the patient and the therapist concerning the remembered intraoperative events. For several years, there have been no new reports linking unconscious learning during anesthesia and postoperative psychosomatic disorders.

General Conclusions

We have summarized the recent literature in the context of earlier studies. We have also highlighted some of the pitfalls and shortcomings and in some cases provided suggestions for future studies. Several conclusions can be drawn:

1. Conscious recall of intraoperative events is rare. It appears to be a dose-related phenomenon and is at highest risk during concomitant use of muscle relaxants. The epidemiologic nature of and possible measures to prevent post-traumatic stress disorder, which sometimes follows, must be studied. The need to develop an "awareness monitor" and the justification for its cost are controversial.
2. Studies of anesthetized patients using implicit tests of memory continue to generate positive and negative results. Studies using auditory evoked responses or other methods to measure anesthetic depth or using an experimental manipulation that is thought to produce one effect on explicit tasks and another effect on implicit tasks may elucidate the nature of memory for events during anesthesia. The influence of experimental variables that determine the positive outcome of studies need to be explored. Replication of successful results is important and should be at-

tempted within the framework of new studies. For example, if investigators want to determine whether patients have unconscious memory for material presented while the patient was anesthetized with a particular anesthetic regimen, they should study another group of patients anesthetized with another regimen, which, in a previous study using the same memory task(s), showed evidence of unconscious memory.

We can speculate that unconscious memory occurs only in few patients, only some of the time, and during light levels of anesthesia. Learning may be more perceptual than engaging in elaborate processing of complex information and may be limited to single, relatively familiar words. Memory may be more evident if tested as soon as possible after surgery.

3. Some recent studies of the efficacy of administration of therapeutic suggestions during anesthesia have reported positive results. However, methodologic and statistical concerns plague some of this work.
4. A concentration of 0.4% end-expired isoflurane prevents both recall and responses to commands in volunteers; 60% nitrous oxide does not completely prevent explicit memory or responses to commands. The effect of surgical stimulation and salience of the stimuli in raising the concentrations that prevent memory is unknown. Neither auditory-evoked responses nor bispectral analyses of the electroencephalograph have yet provided clear evidence of concentrations at which consciousness ceases. Use of brain imaging techniques may provide important information.
5. Animal studies, which may allow tight control of experimental procedures, have nevertheless produced contradictory results concerning learning and memory during anesthesia. Fear conditioning, together with precise control of the anesthetic concentrations, may be the most promising method.
6. It has been reported that psychic trauma may result from the unconscious storage of traumatic events experienced during anesthesia. However, for this hypothesis to be generally accepted, we need more evidence than anecdotal case reports.
7. Interest in the subject of learning and memory during anesthesia continues to be strong and shows no sign of abating. A dedicated group of anesthesiologists, psychologists, and others are working to unravel some of the mysteries surrounding this subject.

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