

*Learning and Consciousness during General Anesthesia*

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**Introduction**

The recent interest in learning and memory during anesthesia shown by general medical journals,<sup>1-6</sup> editorials in specialty journals,<sup>7-10</sup> and the lay press, together with two recent conferences devoted to the subject<sup>11,12</sup> and another planned for 1992, indicate that the subject is of interest to physicians, psychologists, and the public media. Many strong claims about memory during anesthesia are being made. An editorial in *Lancet*<sup>2</sup> states: "There is now sufficient evidence to warrant the adoption of active measures to prevent every anesthetized patient from hearing conversation in the operating theatre. It is unlikely that unconscious auditory perception can be prevented by

pharmacological means." Another from the *British Medical Journal*<sup>5</sup> concludes: "Anaesthetists should assume that any anesthetized patient is capable of retaining verbal and other high level inputs in long term memory." A "viewpoint" in *Trends in Neuroscience*<sup>10</sup> with the title "Does anesthesia cause loss of consciousness?" concluded: "It is not possible to determine reliably whether or not a given anesthetized patient is conscious during surgery." Many other strong claims appearing recently indicate that an objective review of the subject is due.

The relevant literature can be divided into three types: 1) clinical surveys showing a low incidence of consciousness or explicit recall, together with numerous case reports of such occurrences, which form the bulk of the literature; 2) controlled studies using explicit memory tests for experimental stimuli presented during anesthesia, which have produced almost uniformly negative results, *i.e.*, absence of recall; and 3) controlled studies using indirect indicators of retention of experimental stimuli, which have yielded mixed results.

This literature can be integrated into two plausible viewpoints. 1) Conservative: Consciousness and explicit recall occur rarely, usually because of error on the part of the anesthesiologist, overly light anesthesia, or patients who are resistant to the effects of anesthetics. It is not surprising that they occur sometimes in patients who appear to be adequately anesthetized; judgments of depth of anesthesia are neither quantitatively precise nor infallible. These occasional instances do not reflect a more widespread phenomenon. 2) Liberal: The instances of consciousness and recall documented in the clinical reports are the "tip of the iceberg." In a much larger percentage of anesthetized patients, some information processing functions of the brain that are normally associated with awareness, such as language comprehension and learning, continue to function during adequate surgical anesthesia without awareness or subsequent explicit recall. Sensitive assessments would reveal widespread unconscious retention of auditory information presented during anesthesia.

**Definitions**

There is confusion in the anesthesia literature because of the unfortunate use of the words "awareness" and

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"memory" or "recall" in an interchangeable fashion. "Awareness is the quality or state of being aware; *i.e.*, watchful, vigilant, informed, cognizant, or conscious."<sup>a</sup> As we shall see, patients can respond to commands under anesthesia with no recall postoperatively, and the opposite is also possible; *i.e.*, patients may not follow commands but may exhibit some postoperative recall of intraoperative experience. An additional problem with the term became obvious with the identification of implicit or non-declarative memory as a separate form of memory.<sup>13-15</sup> Implicit memory is the influencing of a response by memory of a previous experience without the person knowing that he or she is being influenced. As we shall see, patients under anesthesia may show some evidence of implicit memory<sup>16,17</sup> without being "aware" or able to "monitor" their environment and without showing explicit recall (the deliberate recollection of an experience). On the other hand, many patients with organic amnesias display nearly normal implicit memory and severe problems with long-term retention of new explicit memories, but without awareness deficit.

Thus, the terms "memory" and "awareness" should be distinguished. (Awareness is often associated with or equated to short-term or working memory, *i.e.*, a limited-capacity memory that lasts only for seconds and contains whatever an individual is currently thinking about; this, however, should not be confused with long-term memory, which is what most people think of when they think of memory.) The term "memory"<sup>18</sup> usually includes the notions of acquisition of new information or learning, its storage, and its subsequent retrieval. For present purposes, we will equate "consciousness" with "awareness" and "wakefulness," although awareness can be dissociated from wakefulness in both normal subjects and neurologic patients. A normal subject can be awake but unaware of certain aspects of his or her environment. The neurovegetative patient can be awake but totally unaware.<sup>19</sup> The state of consciousness carries also some philosophical meanings,<sup>a</sup> which we will not address.

### Historical Perspective

The history of memory for events under anesthesia is as old as the history of anesthesia itself. Horace Wells failed to demonstrate the anesthetic properties of nitrous oxide at the Massachusetts General Hospital in 1845 when the patient complained and remembered feeling pain. One year later, William Morton, at the same hospital, succeeded in anesthetizing Gilbert Abbott with diethyl ether; Abbott later reported that he had been aware of the surgery but had experienced no pain.<sup>20</sup> A little over a month after Morton's successful demonstration, a patient was reported who, following amputation of an arm, "thought she had got a reaping hook in her arm and that

she heard the noise of sawing wood."<sup>21</sup> George Crile,<sup>22</sup> the pioneer surgeon, described vivid memory and recall in one of his patients who had received nitrous oxide anesthesia in 1908. Three years later, a similar incident with the same anesthetic was reported.<sup>23</sup>

However, despite these infrequent reports, a significant "problem of awareness during anesthesia" only appeared after the introduction of muscle relaxants in anesthesia practice by Griffith and Johnson<sup>24</sup> in 1942. Patients can become conscious while totally paralyzed because there is no measurement that guarantees unconsciousness in the paralyzed patient. It is interesting that the plight and misery of these unfortunate patients were prophesied by Claude Bernard in 1878 (as quoted by Blacher<sup>25</sup>) while discussing the effects of curare: "In all ages poetic fictions which seek to arouse our pity have presented us with sensitive beings locked in immobile bodies. Our imagination cannot conceive of anything more unhappy than beings provided with sensation, that is to say of being able to feel pleasure and pain, when they are deprived of the power to flee the one and yearn toward the other. The torture which the imaginations of poets have invented can be found produced in nature by the action of the American poison. We can even say that the fiction falls short of reality."

The case report by Winterbottom<sup>26</sup> in 1950 was followed by a voluminous literature on the subject, which consisted mainly of case reports and clinical studies. Hutchinson<sup>27</sup> was the first to investigate the magnitude of the problem through a prospective study by interviewing patients postoperatively. He reported that 8 of 656 patients (1.2%) had recall of some events of their surgery. Other similar studies<sup>28</sup> assessing the incidence under various premedicant and anesthetic regimens and after different types of surgery followed.

Cheek's reports<sup>29,30</sup> were the earliest in a series of studies that explored the use of hypnotic techniques to aid recall of intraoperative events. Levinson's study<sup>31</sup> of 1965 has often been cited as evidence of learning under "deep" levels of anesthesia. He exposed ten patients while under "deep" ether anesthesia to a suggestion indicative of a crisis. One month later the patients were hypnotized and regressed to the operation. Four were able to reproduce the words spoken by the anesthesiologist. Four became anxious and woke from the hypnosis.

Wolfe and Millett<sup>32</sup> and Hutchings<sup>33</sup> administered positive suggestions to patients under anesthesia and claimed highly therapeutic benefits for the patients. Bennett *et al.*<sup>17</sup> used a nonverbal postoperative response to a message administered intraoperatively and demonstrated some learning under anesthesia. Attempts to replicate these studies followed. The recent distinction between two types of memories—explicit or declarative memory and implicit or nondeclarative memory<sup>14</sup>—based largely

on studies in amnesic patients has been adopted by several investigators using specialized test procedures to explore learning under anesthesia.<sup>34,35</sup>

Serious objective studies of effects of subanesthetic concentrations of anesthetics on memory and behavior started with Steinberg's work<sup>36,37,b</sup> in the early 1950s on nitrous oxide. This was preceded by numerous clinical and incidental observations of the effects of this gas on behavior, *e.g.*, the observations of James.<sup>38</sup> The work of Parkhouse *et al.*<sup>39</sup> appeared several years later. More interest in the subject was rekindled in the 1970s and early 1980s<sup>40-46</sup> by studies of the residual effects of anesthetics on behavior, including the effects of pollution of operating rooms with trace concentrations of anesthetics, and illegal recreational use of these drugs.<sup>47,48,c</sup> At the same time that Steinberg was studying the effects of nitrous oxide, Artusio<sup>49,50</sup> was investigating Guedel's first stage of ether anesthesia for use during cardiac surgery. He divided it into three planes, in the deepest (plane 3) of which response to spoken commands was present together with total analgesia and absence of postoperative recall.

#### Effects of Subanesthetic Concentrations of Drugs on Memory

##### NITROUS OXIDE

Most literature on the effects of subanesthetic concentrations involves nitrous oxide. Substantial impairment of memory is observed when subjects learn and recall information during inhalation of subanesthetic concentrations of the drug.<sup>45</sup> The memory impairments do not vary greatly for different types of stimuli and memory testing procedures.<sup>39,45,46,51-55</sup> Digit span, (the longest sequence of digits that can be repeated immediately without error, in forward or reverse order), indicative of short-term memory, is also impaired.<sup>36,43</sup>

These studies involved overt memory tests in which subjects knew their memory was being assessed. *Implicit or covert tests* that indirectly assess memory may be more sensitive to low levels of learning than are explicit or overt tests,<sup>13</sup> as discussed in detail in a later section. Block *et al.*<sup>56</sup> administered three implicit tests to see if test performance resisted the memory-impairing effect of nitrous oxide. In each test, subjects heard a list of words. The words provided appropriate answers for some of the items on the test. For example, in the Constrained Associations Test, subjects were asked to give examples of a category like "metal." In the Free Associations test, for each of a series of words, *e.g.*, "king," subjects wrote the first word that came to mind, *e.g.*, "queen." In the Word Completion Test, for each of a series of three-letter word beginnings, *e.g.*, "BAL," subjects wrote a word starting with those letters, *e.g.*, "balance." Performance in two of the tests, Constrained Associations and Word Completion, showed

resistance to the memory-impairing effects of 30% nitrous oxide in oxygen.

All the results discussed so far pertain to memory impairment for new information presented to subjects under the influence of nitrous oxide. Would nitrous oxide also impair *memory for new information learned before its inhalation?* Ghoneim *et al.*<sup>45</sup> observed some impairments of this kind during gas inhalation in memory for lists of words, suggesting that the drug may affect memory retrieval as well as acquisition.

Some investigators have asked whether nitrous oxide produces "*state-dependent memory*." State-dependent memory refers to the phenomenon in which memories formed in one state may be better recalled in the same state than in a different one,<sup>55</sup> *e.g.*, information learned under the influence of nitrous oxide might be remembered better in the nitrous oxide than in the placebo state, whereas information learned in the placebo state might be remembered better in the placebo than the nitrous oxide state. This phenomenon is observed for some drugs using explicit memory tests. Ghoneim *et al.*<sup>45</sup> did not observe this symmetrical form of state-dependent memory with nitrous oxide. They demonstrated retrieval impairments that resembled an unusual form of asymmetrical state-dependent memory. This was confirmed in a subsequent study in which material learned while receiving placebo was poorly recalled on nitrous oxide, but material learned while receiving nitrous oxide could be recalled in either the placebo or drug state.<sup>55</sup>

##### ISOFLURANE, ENFLURANE, AND HALOTHANE

The effects of these drugs at subanesthetic concentrations have received less study than those of nitrous oxide. Cook *et al.*<sup>44</sup> examined effects of three concentrations of halothane (0.1, 0.2, and 0.4%) and enflurane (0.2, 0.42, and 0.54%). Both drugs produced dose-related impairments in digit span and two psychomotor tests. Memory functions also seemed to be impaired. Enflurane in an unspecified subanesthetic concentration has been reported<sup>57</sup> to slow overall choice reaction time without affecting the speed of searching for information in short-term memory.

One study<sup>58</sup> using a word recognition test reported that state-dependent memory may occur with subanesthetic concentrations of isoflurane. Another study<sup>40</sup> examined effects on memory of anesthetic concentrations of isoflurane and nitrous oxide and of subanesthetic concentrations of isoflurane, enflurane, and other agents. It was claimed that anesthetics at low concentrations impaired verbal memory while sparing nonverbal memory and increased acoustic relative to semantic confusions in memory. The same investigator<sup>59</sup> also claimed that retrieval from memory of some types of material learned

under the effect of anesthetic agents was better at 1 week after learning than at 2 h.

Recently, Newton *et al.*<sup>60</sup> studied volunteers who inhaled isoflurane in concentrations of 0.1, 0.2, and 0.4 MAC. Response to verbal commands and recall and recognition at 1 h after inhalation for two word lists were tested. Each list included a "shock" word, which, because of its distinctiveness from the other words, was presumed to elicit greater attention and be remembered better. At 0.1 MAC, there was full compliance with commands, and memory was good. For 0.2 and 0.4 MAC, performance on the memory tests was no better than chance. Response to commands was impaired at 0.2 MAC and lost at 0.4. Half of the subjects remembered the "shock" words at 0.2 MAC, and none remembered them at 0.4. The abrupt change in performance between 0.1 and 0.2 MAC demonstrates a steep dose-response curve, as has been observed with nitrous oxide.<sup>55</sup>

More work is needed to determine whether different anesthetic agents have qualitatively similar effects on memory and whether equal fractions of MAC of different agents produce equal effects on memory. McMenamin and Parbrook<sup>61</sup> found that at approximately equipotent concentrations, isoflurane produced more cognitive and psychomotor impairments than nitrous oxide. Anecdotally, the "MAC for amnesia" is assumed to be lower than that for analgesia, because patients may move in response to a noxious stimulus without any evidence of recall postoperatively. However, MACs of anesthetics that prevent learning need to be determined.

#### THIOPENTAL

Although Dundee and Pandit<sup>62</sup> have suggested that both thiopental (6 mg/kg) and methohexital (4 mg/kg) have little effect on memory, a definitive study with thiopental using a paired associate task showed impairment. Osborn *et al.*<sup>63</sup> presented easily associated pairs of letters and words (*e.g.*, "C" and "camel"). In a later memory test, the cue letters alone were presented and subjects were instructed to supply the associated words. It was found that continuously infused 0.3% thiopental impaired learning and retention.

#### KETAMINE

Harris *et al.*<sup>64</sup> gave volunteers 0.4 mg/kg of the drug intravenously followed by one half of the dose at 15-min intervals. Ketamine appeared to impair some aspects of learning, whereas its effect on short-term memory was equivocal. Ghoneim *et al.*,<sup>65</sup> in a more analytical study, administered ketamine to healthy volunteers in subanesthetic doses of 0.25 and 0.5 mg/kg intramuscularly. The drug caused impairment of immediate and delayed recall. Most of the impairment was due to interference

with retrieval processes—a rare finding for a drug and quite different from effects produced by other drugs, *e.g.*, benzodiazepines, anticholinergics, marijuana, and alcohol. The latter drugs interfere with acquisition of new information but do not impair retrieval of information learned before drug administration.<sup>66–68</sup> (In drug research, impairments of long-term memory retrieval *versus* acquisition are commonly inferred from impairments in recall of information studied before *versus* during drug action. However, other methods of assessing drug effects on acquisition and retrieval sometimes yield discrepant results<sup>69</sup>).

#### BENZODIAZEPINES

Effects of benzodiazepines on memory have recently been reviewed.<sup>18</sup> These drugs impair the formation of new long-term memories and have relatively little influence on other aspects of memory. Implicit or nondeclarative memory is usually spared.<sup>70–72</sup>

#### Explicit Memory for Events during Anesthesia

##### INCIDENCE

The incidence of recall of events during anesthesia has been estimated by interviewing patients postoperatively. Utting,<sup>73</sup> in a series of 500 patients in whom 70% nitrous oxide in oxygen was the only drug used for maintenance of anesthesia, reported an incidence of recall of 2%. A similar incidence of 2–4% was reported when nitrous oxide was used in a concentration of some 60–67%.<sup>74–76</sup> Crawford,<sup>77</sup> using 67% nitrous oxide in obstetric cases, found an incidence between 2.5–4%, which increased to as much as 25% when a 50% concentration was used.

Using a variety of anesthetic regimens in patients undergoing a variety of surgeries, the incidence has been estimated at 1.2% by Hutchinson,<sup>27</sup> 1% by Wilson *et al.*,<sup>28</sup> and, very recently, 0.2% by Liu *et al.*<sup>78</sup> The latter incidence is lower than that found in previous studies<sup>79</sup> and may reflect changes in anesthetic practice away from very light anesthetics<sup>80</sup> as well as increased awareness of the problem by anesthesiologists. It is interesting that despite what appears to be a genuine decrease in incidence, the number of cases reported to the Medical Defence Union of the United Kingdom and Ireland has increased over the last 15 yr rather than decreased.<sup>81</sup> Perhaps the increasing public knowledge of the existence of the problem and the development of litigious attitudes in society towards health-care providers may account for this paradox. In a recent study<sup>82</sup> of 247 patients for causes of preoperative anxiety, about 50% expressed concern that they would not be asleep during the operation and more than 25% still were worried postoperatively about not being asleep during a future anesthetic even though they had been adequately anesthetized during the present one.

Higher incidences of recall have been reported in situations where light anesthesia is used, *e.g.*, obstetrics,<sup>83</sup> 7–28%; cases of major trauma,<sup>84</sup> 11–43%; cardiopulmonary bypass surgery,<sup>85</sup> as high as 23%; and bronchoscopy,<sup>86</sup> 8%.

When light anesthesia is used, the patient may recall “dreams” that appear to be associated with the anesthetic.<sup>74</sup> Some of the “dreams” are disturbing. “Dreams” are recalled considerably more often than actual events, *e.g.*, in Utting’s<sup>73</sup> series of 500 patients anesthetized with nitrous oxide, the incidence of “dreams” that the patients thought were the worst features of their perioperative experiences was 7% *versus* 2% for recall of intraoperative events, and in the recent series of Liu *et al.*<sup>78</sup> the incidences were 0.9% and 0.2%, respectively. Utting has suggested that there could be a continuum, with adequate anesthesia resulting in complete amnesia, lighter anesthesia resulting in “dream” recall, and still lighter anesthesia resulting in recall of actual events. Some investigators<sup>d</sup> who find the “sleep” metaphor of anesthesia objectionable believe that referring to “dreams” during anesthesia unjustifiably implies a resemblance to the dreams of normal sleep. They prefer to describe these experiences as altered states of awareness characterized by vivid thoughts and images, usually with a strong affective component, which appear autonomously to the patient.

The studies reviewed in this section vary in many respects, *e.g.*, the timing of the postoperative interview, its structure or lack of it, the identity of the interviewer (anesthesiologist, nurse anesthetist, clinical psychologist, research assistant, *etc.*), and the attempts made to verify the patients’ recollections or to eliminate confabulations. In all cases, the concentrations of gaseous and volatile anesthetics in inspired and expired air have not been monitored to verify the correct functioning of the anesthesia machine delivery system and to identify patients with pharmacokinetic abnormalities in whom adequate partial pressures of the anesthetics in alveolar air were not achieved.

### CAUSES

*Equipment factors.* An inadequate concentration of anesthetic may be delivered to the patient. This may be due to an empty vaporizer, empty cylinder of nitrous oxide, or entrainment of air by a ventilator. Equipment failure or misuse is less common nowadays but still happens despite the sophistication of modern anesthesia equipment.

*Overly light anesthesia.* For certain operations, such as caesarean section and for some patients, such as those sustaining major trauma, the anesthesiologist may aim at light anesthesia. Sometimes this may progress too far, to the point of consciousness and recall, which may not be surprising considering that judgments of depth of anesthesia are neither quantitatively precise nor infallible.

*Increased anesthetic requirement of some patients.* Although there have been no well-documented studies showing pharmacodynamic differences between patients in response to anesthetic drugs, it is not unreasonable to expect that some patients may be more “resistant” to the effects of anesthetics than others, analogous to the variability of responses seen with most drugs. It has been suggested that chronic alcoholism<sup>87–90</sup> and prior exposure to anesthetic agents<sup>91</sup> increase anesthetic requirements. Guerra<sup>92</sup> suggested that there may be a higher incidence of consciousness and recall in obese patients because of the use of higher concentrations of oxygen in nitrous oxide–oxygen mixtures and the administration of lower doses of drugs to avoid excessive postoperative respiratory depression. To our knowledge, the effects of obesity on the pharmacokinetics of anesthetic drugs have not been adequately studied.

### METHODS OF DETECTION

Anesthesiologists comment frequently about the need for an “awareness monitor,” yet there is often confusion because of terminology about what needs to be detected. Detection of learning and explicit memory under anesthesia requires questioning the patient postoperatively for recall and/or recognition of intraoperative events. Detection of wakefulness or consciousness during anesthesia depends on the validity of methods that claim to measure the depth of anesthesia or the degree of central nervous system depression. Table 1 summarizes these methods.

*Postoperative interview for intraoperative events.* Waiting for the patient to spontaneously volunteer that he or she was conscious during general anesthesia would underestimate the magnitude of the problem. The patient may be reluctant to discuss the experience with the physicians or nurses for fear of disbelief or ridicule or to avoid appearing critical.<sup>93</sup> Blacher<sup>94</sup> has also suggested that the overwhelming stress of awakening while paralyzed during surgery may cause amnesia for intraoperative events. A structured interview is therefore necessary.<sup>95,96</sup> A careful visit with the patient should include at least these questions<sup>74</sup>: What is the last thing you remember before going to sleep for your operation? What is the first thing you remember on waking after your operation? Do you remember anything in between? Did you have any dreams? Other detailed questioning and prompting is possible without inducing confabulation. An early interview, during the first 24 h, seems to be an appropriate time.

*Recall or recognition of stimuli presented during anesthesia.* Some researchers have presented words, stories, poems, pieces of music, and other sounds during anesthesia. Explicit memory tests administered postoperatively demonstrated no recall or recognition<sup>74,97–101</sup> except in two

TABLE 1. Methods That Have Been Suggested for Detection of Learning and Consciousness

Measures of explicit memory	Postoperative interview
Measures of implicit memory	Recall or recognition of stimuli
	Priming tasks
	Category production
	General information questionnaire
	Nonsense words
	Preference for unfamiliar melodies
	Spelling of homophones
	Word associations
	Word completion
	Behavioral suggestions tasks
	Therapeutic suggestions tasks
Measures of consciousness	Clinical signs of anesthesia
	Electroencephalography
	Isolated forearm
	Lower Esophageal contractility
	Sensory evoked responses
	Skin conductance responses
	Surface electromyography
	Time to correct response

studies. Patients in one study<sup>102</sup> who were played a list of words during anesthesia performed better on a later recognition test than did controls who were not played these words. In another study,<sup>16</sup> patients showed recognition of nonsense words that had been presented frequently during anesthesia. We argue below that these results support implicit rather than explicit memory under anesthesia. We do not interpret them as contradictory to other studies reporting no explicit memory following anesthesia.

#### Methods for Testing Wakefulness

The following methods do not measure learning during anesthesia but attempt to monitor the anesthetic state, specifically states of overly light anesthesia.

*The isolated forearm technique.* Tunstall<sup>103</sup> isolated one forearm from the circulation before injection of muscle relaxants by inflating a pneumatic tourniquet and then verbally instructed the anesthetized patient to move the nonparalyzed arm. The tourniquet must be deflated after about 20 min to avoid pressure-induced nerve block or injury. It is sometimes difficult to distinguish responses to commands from reflex or involuntary muscle movements. There are no or low correlations between responses and clinical signs of light anesthesia—*e.g.*, blood pressure, pulse rate, sweating, and lacrimation<sup>104</sup>—demonstrating the lack of predictive value of clinical signs for wakefulness. Most patients who demonstrate responses show no evidence of recall of intraoperative events; *e.g.*, in Tunstall's<sup>103</sup> original series of 12 patients undergoing cesarean section, 9 responded with a sustained movement, and of those 9, 4 responded exactly to command, but no patient had any recall. The opposite is also true; *i.e.*, patients may report intraoperative recall but show no responses.<sup>83</sup>

*Time to "correct" response.* Cormack<sup>105</sup> discontinued the administration of nitrous oxide following reversal of neuromuscular blocking agents. Every 15 s patients were asked to open their mouths, and the time at which they responded appropriately was noted. As the nitrous oxide concentration in the brain is unlikely to decrease appreciably within 15 s of its discontinuation, an appropriate response within this time was taken as an indication that consciousness had occurred. This method gives retrospective information, which only relates to the depth of anesthesia at the end of the operation.

*Clinical signs of light anesthesia.* When anesthesia becomes too light during surgery, the patient may move and exhibit signs of sympathetic activity, *i.e.*, tachycardia, hypertension, sweating, pupillary dilatation and reaction, lacrimation, and pallor. These signs may be absent due to treatment with muscle relaxants, opioids, cholinergic and  $\beta$ -adrenergic antagonists, vasodilators, and antihypertensive agents. Their utility as indicators to deepen the anesthesia may be missed by anesthesiologists who may interpret a purposeful muscle movement as a reflex somatic response and tachycardia and hypertension as due to causes other than light anesthesia. Their value as signals for impending consciousness and recall is further dampened by the anesthesiologist's daily experience that they may occur without the patient complaining postoperatively of consciousness and recall, while the latter complaints may occur in the absence of these signs.

*Electroencephalography.* Many studies have tried to use the electroencephalograph (EEG) as a monitor for depth of anesthesia. Clark and Rosner<sup>106</sup> and Stockard and Bickford<sup>107</sup> have drawn attention to the problems of finding an EEG derivative that is universally affected by different anesthetics at equipotent concentrations and the influence of other variables which complicate its interpretation, *e.g.*,  $\text{PaCO}_2$ , body temperature, and afferent central nervous system input. The EEG, either raw or processed as spectral array,<sup>107</sup> period-amplitude analysis,<sup>108</sup> spectral edge frequency,<sup>109</sup> median frequency,<sup>110</sup> cerebral function analysis monitor,<sup>111</sup> or others, has not proved to be of practical value in predicting or identifying consciousness with or without postoperative recall. While some EEG patterns (*e.g.*, burst suppression and isoelectricity) always indicate unconsciousness, there are no patterns that prove consciousness is present.<sup>112</sup> Stanski, in an extensive review of the subject,<sup>113</sup> attributed the limitations of the EEG to the lack of understanding of the effects of combination of several drugs as occurs in clinical practice, inability to choose the most appropriate parameter, and lack of a "gold standard" for consciousness.<sup>114</sup>

*Sensory evoked responses.* Three evoked potential techniques have been used: auditory, somatosensory, and visual. There have been only a few studies of the effects of anesthetics on visual (VEP) and somatosensory (SEP) evoked

potentials. Uhl *et al.*<sup>115</sup> showed that the latency of VEP was prolonged with an increased concentration of halothane. Chi and Field<sup>116</sup> found similar response with isoflurane. However, neither group of investigators showed any significant differences among the different concentrations of anesthetics, indicating that VEP would not be a useful monitor for depth of anesthesia. Sebel *et al.*<sup>117</sup> showed that nitrous oxide had a dose-related effect on the amplitudes of cortical VEP, although no consistent influence was found by Chi and Field.<sup>116</sup> Peterson *et al.*<sup>118</sup> studied the effect of halothane, enflurane, isoflurane, and nitrous oxide on the SEP and showed dose-related changes in amplitude and latency of the cortical components. Sebel *et al.*<sup>119</sup> showed that isoflurane produced dose-related changes in the amplitude and latencies of SEP, but only up to 1.65% end-tidal concentration. In order for the evoked responses to be used as measures of anesthetic depth, they must be sensitive to changes in surgical stimulation as well as to anesthetic concentration. This remains to be confirmed for the VEP and SEP.<sup>120</sup> Perhaps even more important, they must be shown to be sensitive to changes in the level of consciousness.

The auditory evoked potentials (AEP) have received more attention as a determinant of anesthetic depth (fig. 1). The early cortical waves or the middle latency range of the AEP (middle latency evoked response [MLR]) show dose-related changes with all the anesthetics which have been studied so far,<sup>121-127</sup> specifically prolongation of latencies and reduction of amplitudes. This uniformity is in marked contrast with the EEG effects. The earlier brainstem part of the AEP responds in a graded fashion to changing doses of volatile anesthetics but not to some intravenous anesthetics.<sup>128-130</sup> Surgical stimulation at a steady state of light inhalation anesthesia increases the amplitude of the MLRs.<sup>131</sup> Thornton *et al.*<sup>132</sup> combined the recording of AEP with the isolated forearm test<sup>103</sup> in patients receiving varying concentrations of nitrous oxide. When the latency of the Nb wave of the MLR was less than 44.5 ms, four of seven patients moved their hands in response to commands, indicating wakefulness. This lack of consistency may be due in part to problems with the isolated forearm technique. Nevertheless, the MLR was not affected during anesthesia with high-dose fentanyl<sup>133</sup> despite the production of unresponsiveness.

Extra and intracellular recordings in neurons demonstrate the existence of a 40-Hz oscillatory activity in the brain, which can be observed also in the spontaneous EEG and in sensory-evoked potentials.<sup>134-136</sup> The dominance of the 40-Hz oscillations is represented in the MLRs. Two groups of investigators examined the effects of general anesthesia on this evoked and fast cerebral rhythmic activity. Plourde and Picton<sup>137</sup> used the auditory steady-state response (ASSR), which results from superimposition of individual MLRs when the rate of stimulation is sufficiently rapid.

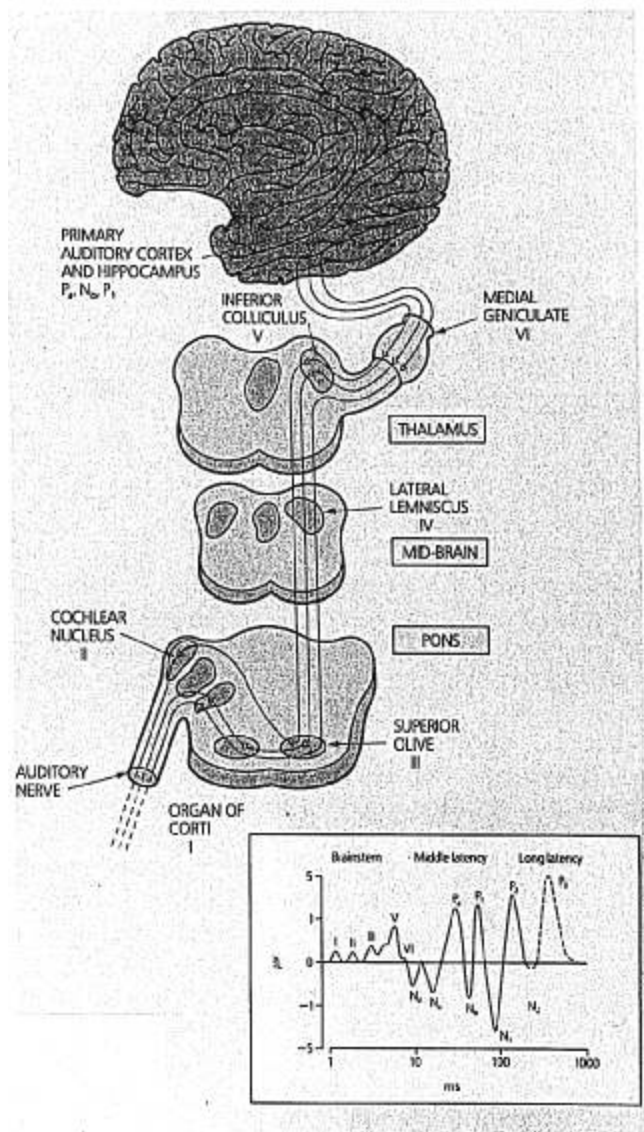


FIG. 1. The brain stem pathway of the auditory signal. Waves I-VI in the auditory evoked potential are believed to arise in the relay stations shown. The middle latency waves arise in the primary auditory cortex and longer latency waves in other cortical association areas. (Reproduced from Jones JG: Awareness under anaesthesia, Anaesthesia Rounds. Number 21. ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, England, 1988, p 19.)

They correlated the 40-Hz activity with an auditory stimulus detection task as an index of the level of consciousness. The attenuation of ASSR by anesthesia (thiopental, fentanyl, and isoflurane with or without nitrous oxide) paralleled the level of consciousness. Plourde and Boylan<sup>138</sup> studied the ASSR during sufentanil anesthesia. The ASSR was severely attenuated or abolished with loss of consciousness. This contrasts with the absence of an effect of high-dose fentanyl on the MLR.<sup>133</sup>



Madler *et al.*<sup>139</sup> used the MLR for evoking the 40-Hz rhythms. They correlated the latter with the dose of isoflurane. They found a dose-dependent decrease in frequency of oscillations (fig. 2). The MLR and 40-Hz rhythms share a common weakness: both can be recorded in comatose patients.<sup>140,141</sup> Their presence, therefore, does not prove that consciousness is preserved.<sup>112</sup>

Certain longer latency potentials may be associated with cognitive processes, such as perception of or preparation for events. The P3 (or P300) is generated when subjects attend to and discriminate stimulus events that differ from one another in some dimension. It may reflect memory-updating processes and access to consciousness.<sup>142,143</sup> Plourde *et al.*,<sup>144,145</sup> evaluated the P3 as an index of consciousness in the perianesthetic period. It disappeared with loss of responsiveness during induction of anesthesia and reappeared later during recovery after other signs of awakening. Jessop *et al.*<sup>146</sup> measured the P3 in subjects breathing different concentrations of nitrous oxide. As the nitrous oxide concentration increased, there was a decrease in amplitude and increase in latency of the P3. However, even absence of the P3 does not mean that the subject is unconscious, since there may be no P3 if the subject is not attentive to the stimuli. The *contingent negative variation* (CNV) is a slowly increasing negative potential occurring during the interval between two successive stimuli, when the subject notices a contingency or association between two stimuli.<sup>147</sup> The CNV predicted responsiveness to verbal command during the administration of 40% nitrous oxide.<sup>148</sup> It has not been evaluated in the perianesthetic period.

**Surface electromyography (EMG).** Frontalis muscle activity has been investigated as an index of depth of anesthesia.<sup>149,150</sup> The frontalis muscle has been chosen because of its innervation by visceral efferent fibers of the facial nerve and its lesser sensitivity than the hypothenar muscles

to the effects of muscle relaxants. A decrease in tonic muscle activity occurs during induction of anesthesia as the patient loses consciousness, and an increase occurs with awakening. However, a decrease in EMG activity by itself may not be sufficient to indicate loss of consciousness during opioid administration.<sup>151</sup> Occasional phasic increases in activity may occur at times of noxious stimulation, such as endotracheal intubation, when associated with light anesthesia. These sudden increases of the EMG may serve as a warning for impending wakefulness, although they often occur after the patient moves. The wide variability in EMG values among patients prevents the adoption of a single value as an indicator of inadequate anesthesia.<sup>152</sup>

**Lower esophageal contractility (LEC).** Measurement of LEC has been suggested as a guide to the depth or adequacy of anesthesia.<sup>153</sup> The smooth muscles of the lower esophagus remain active despite the skeletal muscle paralysis produced by muscle relaxants. When the concentration of anesthetic is increased, the rate and amplitude of contractions are reduced.<sup>154,155</sup> An increase in LEC also occurs in response to surgical stimulation.<sup>156</sup> However, inter- and inpatient variability in esophageal activity and variability in relation to the type of surgery, type of anesthetic, and adjuvant medication<sup>156-159</sup> may prevent the development of an index predictive of inadequate anesthesia. Of particular concern is the unreliability of LEC at the interface between consciousness and unconsciousness.<sup>157</sup>

**Skin conductance responses.** The amount of sweating, controlled by the autonomic nervous system, largely determines the electrical conductance of the skin. Few studies have been done to explore the effects of anesthesia on electrodermal responsiveness. Generally, all anesthetics depress to a variable degree the resting activity in the sudomotor system.<sup>160-163</sup> Some anecdotal reports have

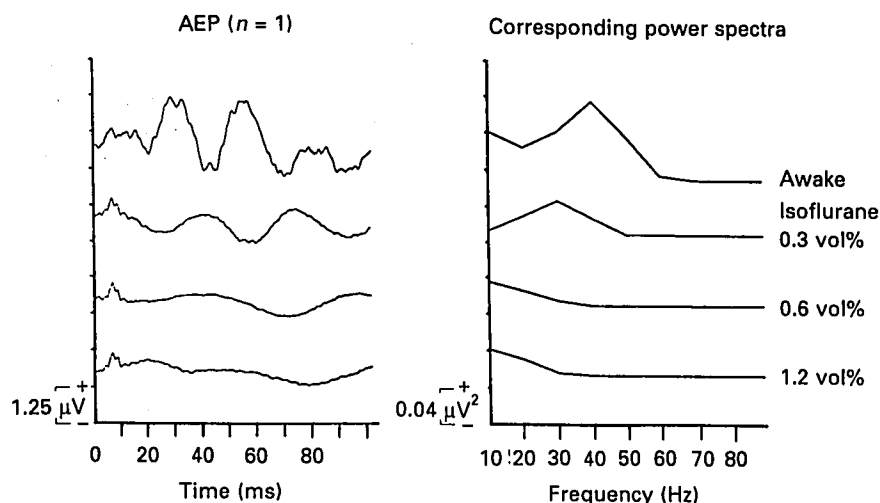


FIG. 2. Auditory evoked potentials (AEP) and corresponding power spectra from a single patient. The graph shows data from the awake state before induction of anesthesia and during different concentrations of isoflurane. The midlatency components of the AEP were reduced in amplitude and prolonged in latency with increasing doses of isoflurane. The midlatency oscillation had a dominant frequency of 40 Hz in the awake state. The frequency decreased to 30 Hz during inhalation of 0.3% isoflurane, and to 10 Hz during 0.6 and 1.2% isoflurane. (From Madler C, Keller I, Schwender D, Pöppel E: Sensory information processing during general anaesthesia: Effect of isoflurane on auditory evoked neuronal oscillations. *Br J Anaesth* 66:81-87, 1991.)



suggested changes in tonic levels of skin conductance and/or responses evoked by endotracheal intubation and surgical manipulations, whereas others have not.<sup>164,165</sup> Responses to auditory stimuli have sometimes been reported and sometimes not.<sup>164,165</sup> Common to these anecdotal reports have been lack of standardization of anesthetic regimen, level of anesthesia, and method of measurement of skin conductance. Sudomotor responses, like some of the clinical signs of anesthesia and LEC measurements, reflect the state of the autonomic nervous system, which has not been successful as a reliable index of anesthetic depth.

### MEDICOLEGAL CONSEQUENCES

*Frequency of legal claims.* The possibility of consciousness and recall during general anesthesia has received different levels of legal attention in the United States and across the Atlantic. Recent medicolegal interest in this subject in the United Kingdom has been promoted by two widely publicized successful claims brought by two patients in 1985 and 1989 who sued their anaesthetists because they were awake during a caesarean section performed under general anesthesia.<sup>9,166,167</sup> These cases have led to a number of similar claims. The Medical Defence Union, which defends physicians in the United Kingdom, has been receiving an average of four or five cases of consciousness and recall per year.<sup>168</sup> The situation has been different in the United States. Thompson,<sup>169</sup> reviewing the subject in 1987, found only one reported lawsuit in the United States. The number of cases that were started and then settled out of court is unknown. The Committee on Professional Liability of the American Society of Anesthesiologists has been conducting studies of closed malpractice claims related to anesthetic care, which are available from insurance carriers.<sup>170</sup> A closed claims analysis of cases of explicit memory may improve our understanding of the causes, suggest effective preventive strategies, and document the process of malpractice claim settlement or litigation, including its financial cost, in the United States.

*Basis of litigation.* A patient who sues because of consciousness during general anesthesia is most likely to sue for *medical malpractice*. The patient will have to convince the jury or judge that he or she was indeed conscious and that this consciousness resulted from the anesthesiologist's negligence. To do so, the patient will need the support of expert witnesses unless he or she argues the doctrine of *res ipsa loquitur*, i.e., that the patient would not ordinarily be conscious under anesthesia unless the anesthesiologist had been negligent. Powers and Gore<sup>171</sup> suggest that such a doctrine may apply in these cases, whereas Thompson<sup>169</sup> suggests that courts may be reticent to apply it, particularly when the case involves disputes over the choice of a treatment, e.g., the choice between using light levels of anes-

thesia with a risk of consciousness and using deeper levels of anesthesia with their alternative dangers. The patient can also sue for *breach of contract* if the anesthesiologist had promised the patient during the preoperative visit that he or she would not be conscious during the operation, even if the breach was not the result of malpractice. A third cause for a lawsuit is *lack of informed consent*. The patient may sue on the ground that he or she was not told of and did not consent to the possibility of being conscious during surgery, feeling pain, or listening to alarming sounds and conversations. This subject has been reviewed previously.<sup>166,167,169</sup>

*Prevention.* Legal experts are in agreement that apart from good medical practice, the best way in which anesthesiologists can stay out of court is through proper communication with their patients. Except when there are valid reasons not to discuss the possibility of consciousness with the patient (which should be documented in the patient's chart), the anesthesiologist may want to discuss this possibility during the preoperative visit whenever such a risk is relatively high. Some may argue, however, that this may cause undue anxiety to the patient. A carefully written and detailed anesthesia record is essential if the burden of proof of causation will fall on the shoulders of the anesthesiologist to show that he or she was not negligent. If the anesthesiologist suspects during anesthesia that the patient may be conscious, talking to the patient in a reassuring way while reinducing unconsciousness is a reasonable course of action.

If the patient complains of consciousness during the postoperative visit, the anesthesiologist should try through questioning to establish the accuracy of the patient's recall. Dreaming may occur at any time in the perioperative period and pain in the immediate postoperative period may be assumed, in confusion, to have happened during surgery. Remembering specific intraoperative events that can be corroborated as authentic confirms the patient's complaint. The anesthesiologist should acknowledge that the patient's account of events is genuine. He or she should explain that consciousness can occur without fault during anesthesia in which muscle relaxants are used, because of the desire to avoid high and potentially toxic doses of anesthetic drugs and because of difficulty in interpreting clinical signs. He or she should apologize to the patient and sympathize with any pain or suffering caused. If it is clear that an avoidable error caused consciousness, it may be argued that it should not be acknowledged lest this is taken to imply negligence. However, if such an error is admitted, this may reduce the patient's fears about future surgery, an important consideration.<sup>9</sup>

The time spent with the patient at this stage is well spent because there are some indications that legal proceedings might have been avoided in some cases if the anesthesiologists concerned had listened sympathetically

to the patients and explained honestly what went wrong.<sup>9</sup> Lastly, the anesthesiologist should be ready to refer the patient to a psychiatrist or clinical psychologist with expertise in this area if the patient's distress continues.

#### PREVENTION OF RECALL OF EVENTS DURING ANESTHESIA

Prevention of recall of events during anesthesia should be feasible in most cases. Meticulous checking of the anesthesia machine, continuous monitoring of the composition of inspired and expired gases, and vigilance during the course of anesthesia should eliminate cases due to failure of anesthesia equipment. Guidelines to eliminate cases due to inadequate anesthesia have been suggested.<sup>168,172</sup> These include: 1) premedicating the patient with amnesic drugs (e.g., scopolamine or benzodiazepines); 2) administering more than a "sleep dose" of induction agents if they will be followed immediately by succinylcholine and tracheal intubation (and giving additional doses in cases of difficult intubation); 3) avoiding muscle paralysis unless it is needed for intubation and/or surgery and even then avoiding total paralysis; and 4) supplementing nitrous oxide and opioid anesthesia with volatile agents to maintain their end-tidal concentrations at least at 0.6% MAC when using 60% nitrous oxide or more. Eger *et al.*<sup>173</sup> have suggested the use of at least 0.8-1 MAC when inhalation agents are used alone. It should be remembered that these figures are tentative and may need to be reconsidered when the concentrations of drugs that prevent learning and recall are defined.

Hug<sup>174,175</sup> has recently reviewed the limitations of opioids as anesthetics and stressed the need for their supplementation. Although such supplementation of "pure opioid anesthesia" may result in hypotension, this usually can be treated promptly and satisfactorily by administration of a vasopressor or a noxious stimulus (e.g., intubation or surgical incision). For this reason, physicians administering anesthesia to severely ill patients and major trauma patients are best served by heeding the advice of Hug<sup>175</sup>: "Unless patient survival is critically dependent on avoiding even momentary hypotension, my first priority is to assure unconsciousness." Aldrete and Wright<sup>176</sup> have expressed a similar sentiment, suggesting that the anesthesiologist's armamentarium includes drugs that can be used in small doses under circumstances of hemodynamic instability to produce at least amnesia. In obstetric practice, the use of scopolamine as a premedicant and one of the potent inhalational agents at least at 0.6 MAC concentration in 50% nitrous oxide and oxygen before delivery usually prevents consciousness and recall with no detriment to the fetus,<sup>177</sup> provided that the output of the vaporizer is monitored.

Total intravenous anesthesia carries the risk of consciousness and recall if the plasma concentration of the drug is allowed to decrease too low in proportion to the arousal intensity of a specific surgical stimulus. This risk should be reduced by the use of computer technology<sup>178,179</sup> to design and control variable rate infusion schemes so that stable drug concentrations can be achieved almost instantaneously and proportional changes in the concentrations can be made with equal rapidity according to patient's requirements. Lastly, playing white noise, music, neutral sounds, or therapeutic suggestions through headphones or using earplugs may prevent the patient from hearing the sounds in the operating room.

#### Recall of Intraoperative Events during Hypnosis

Cheek<sup>29</sup> investigated patients who had complaints dating from previous surgery. When these patients were hypnotized, he reported that they recalled negative statements that had been made about them during surgery by members of the surgical team, and this recall was followed by a complete remission of their symptoms. Levinson,<sup>31</sup> in an often-quoted work, made statements concerning a spurious crisis during dental surgery in ten patients receiving ether anesthesia. None of these patients had any recall of the incident in the postoperative period. However, when they were interviewed under hypnosis, four patients were reported to give verbatim or near-verbatim recall of the bogus incident. Four others became anxious and emerged from hypnosis. Bennett,<sup>180</sup> Goldmann *et al.*,<sup>85</sup> and Howard<sup>181</sup> reported similar cases of recall under hypnosis of events during anesthesia.

The investigators who advocate the use of hypnosis for enhancement of recall of events under anesthesia attribute its success to various causes, including establishment of rapport with the patients, removal of a repression barrier to recall of traumatic events, and exploitation of state-dependent memory. As mentioned previously, state-dependent memory refers to the phenomenon that memories formed in one state will be better recalled in the same state than in a different one.<sup>182</sup> Mismatching of states during acquisition and recall may decrease the accessibility of information. If learning during anesthesia is state-dependent, then the material that is learned may not be accessible for retrieval unless a similar altered state of consciousness is introduced. State-dependency is a well-documented finding in the animal literature, although its demonstration in humans has been rather inconsistent. The evidence for state-dependent memory with administration of subanesthetic concentrations of inhalation anesthetics is either weak or atypical.<sup>55,58</sup> One must also question the analogy between the state of general anesthesia and that induced by hypnosis.

The clinical case reports of recall of events under anes-

thetia aided by hypnosis make fascinating reading, but their value as support for learning under anesthesia is limited. They were not controlled experiments involving randomized, prospective assignment of patients to experimental and control groups under double-blind conditions. Attempts to control the depth of anesthesia or measurements of the end-expired concentrations of inhalation anesthetics were usually lacking. Even when an attempt was made to control the depth of anesthesia, the results were dubious. For example, Levinson<sup>31</sup> believed that the EEG tracings from his patients indicated a level of "very deep anaesthesia." Yet, Eger *et al.*<sup>173</sup> recently drew attention to the fact that the tracings showed slow-frequency, high-voltage activity that changed to a lower voltage and a higher frequency with stimulation, characteristics consistent with a light level of anesthesia.

Another problem is that much of the material "re-called" under hypnosis is incorrect.<sup>183,184</sup> A panel of the council on Scientific Affairs of the American Medical Association<sup>185</sup> reviewed the evidence concerning the effect of hypnosis on memory and concluded that "recollections obtained during hypnosis can involve confabulations and pseudomemories, and not only fail to be more accurate, but actually appear to be less reliable than non-hypnotic recall." It is, therefore, worrisome that most of the reports did not use techniques that would exclude confabulation as the basis for "memories" that were hypnotically retrieved. Also, details concerning the interview between hypnotist and patient were usually insufficient to establish if leading questions were asked and if the patient's recall was accurate.

It is hard to distinguish accurate from spurious recall without specific stimuli to score. Few studies have used measures more objective than the free recall "of spontaneously occurring events." Terrell *et al.*<sup>186</sup> used hypnosis to aid recall of specific verbal stimuli that were presented under anesthesia. There was no evidence of recall. Bennett<sup>17</sup> tested the recall of suggestions to touch the ear that were administered during anesthesia; Goldmann and Levey<sup>165</sup> and Goldmann<sup>187</sup> tested recognition of cues given under anesthesia. They all reported that hypnosis did not enhance recall. It therefore seems unlikely that hypnosis will be a useful tool in assessing learning and recall in the operative period.

### Medical Consequences of Recall of Events during Anesthesia

#### SYMPTOMATOLOGY

Awakening during surgery and remembering postoperatively the events that transpired can be a horrible experience that may cause acute psychic trauma. The patients may be anxious and irritable and have repetitive

nightmares, a preoccupation with death, and a reluctance to discuss their symptoms because of a concern with their sanity. Depression and rage are common reactions when the topic is broached.<sup>7,92,94,188</sup> Stress-induced perioperative myocardial infarction has also been claimed as a consequence.<sup>1</sup> Some patients either deny the significance of the trauma or suffer no long-term sequelae, apart perhaps from a nagging fear that it may happen again if they require anesthesia in the future.<sup>189-192</sup>

What determines the response of the patient is not clear. Guerra<sup>190</sup> suggested that his or her personality, emotional response to the illness, and reason for the surgery may be factors. Physicians who suffered the experience<sup>189,193</sup> seemed to have been spared the effects of postoperative psychic trauma. Perhaps their medical knowledge gave them insight to appreciate what was happening at the time. Blacher<sup>25</sup> claimed that patients who are wide awake, although they may suffer greatly during the procedure, may have fewer traumatic symptoms afterward than those who are in an obtunded state, perhaps because while awake what happens is not in doubt.

#### CAUSES OF DISTRESS

Apart from the acute pain that may be experienced, what seems to be most traumatic are: the lack of control; lying passively at the receiving end; the feeling that things must have gone terribly wrong, or else she or he would not be in that state; and inability to communicate the distress, either during surgery, because of the muscle paralysis, or afterward with the medical staff, other patients, relatives, and friends. Patients' inability to communicate their distress after surgery may be caused by the medical staff's disbelieving the patient or avoiding discussion of the issue, perhaps because of feelings of guilt or embarrassment and/or possible future litigation. Lay people may not believe that consciousness can happen during a planned general anesthetic. The patients may also be tormented, if they were in an obtunded state, by doubts as to whether what they experienced really happened or whether there is something wrong with their minds.<sup>25,190,188</sup>

#### MANAGEMENT

Management of these cases involves a candid explanation of what happened to the patient and its reasons at the earliest possible time in the postoperative period. Sympathy with the patient's reactions and reassurances about nonrepetition of the same mishaps with future anesthetics should be expressed. Maintenance of personal contact with the patient is necessary for some time.<sup>25,92,194</sup> Guerra<sup>190</sup> maintains that in some cases, psychotherapy may be necessary to help the patient deal with the event. Referral to a psychiatrist or psychologist should not be

delayed, if it becomes apparent that the patient continues to experience panic attacks, recurrent nightmares, or other related symptoms.

### HYPNOTICALLY AIDED RECALL

In addition to the phenomenon of awakening during anesthesia with subsequent recall, there have been case studies<sup>29,181</sup> of patients who under hypnosis were able to recall negative statements made about them during surgery, followed by remission of their symptoms. Blacher<sup>25,94</sup> described several cases where the symptoms of the patients were relieved by psychoanalysis, during which it was explained that the symptoms resulted from wakefulness during surgery. Common denominators are apparent through these case studies: the symptoms developed very shortly after surgery; no other cause was found to account for them; they were relieved after their origin during anesthesia was clarified through hypnosis or psychoanalysis; and they apparently did not recur.

Although these reports may alert physicians to investigate patients with unexplained symptoms dating from a recent surgery by referring the patients to psychologists or psychiatrists, their contribution to the study of learning during anesthesia is limited. Because of their anecdotal nature and lack of control, a cause-and-effect relationship cannot be established. In almost all cases, there is no evidence that the patient woke up during anesthesia, and description of the anesthetic is absent or very sketchy.<sup>195</sup> In most cases, there is no confirmation of the alleged intraoperative conversations. Lastly, remission of the patient's symptoms through hypnosis or psychoanalysis may be due to causes other than the bringing of intraoperative events into consciousness. Surgery is a stressful life event that may affect the psychological well being of patients.<sup>196-198</sup>

### Implicit Memory for Events during Anesthesia

#### DEFINITION

Although memory was traditionally believed to be a unitary process of the mind, most researchers nowadays have adopted the hypothesis that memory consists of a number of different systems and subsystems.<sup>199</sup> Two distinct systems, explicit or declarative memory and implicit or nondeclarative memory, have been identified based initially on studies of amnesic patients. Explicit memory is measured by recall and recognition tests, which require conscious and deliberate retrieval of information. Implicit memory is measured by facilitation of performance on completion, identification, skill-learning, and other tests by prior exposure to target materials. Such facilitation does not require conscious or intentional recollection of specific prior exposure.<sup>13-15</sup> A striking feature about these

tasks is that amnesic patients usually deny having performed the task before and at the same time show evidence of good learning. Patients who suffer from organic amnesias, elderly subjects, and subjects under the influence of benzodiazepines, alcohol, scopolamine, and sub-anesthetic concentrations (30%) of nitrous oxide have impaired explicit memory but intact or largely spared implicit memory.<sup>56,70-72,200-206,c</sup> If there is any analogy in memory capabilities between these populations and anesthetized patients, retention of events under anesthesia might rarely be evident in tests that require remembering to be intentional, whereas it might be revealed in tests that do not demand awareness of remembering.

### TASKS

Most of the tasks used to test implicit memory under anesthesia probe for "priming" effects rather than the learning of motor skills, which of course is impossible in an unconscious subject. In priming tasks, patients are presented during anesthesia with target stimuli. Target stimuli have included words, nonsense words, and unfamiliar melodies. After anesthesia, patients are given a test that does not explicitly involve remembering but on which the target stimuli provide some appropriate answers.

For example, the test might consist of a number of three-letter word stems, with the patient asked to supply a word beginning with those letters for each. One of the items might be "PEN" and a possible answer like "PENSION" might have been presented during anesthesia. "Priming" is said to occur, providing evidence of learning during anesthesia, if presentation of "PENSION" increases the likelihood of giving this word on the test. Differences between performance on the target items and nonpresented control items can be used to measure the magnitude of the priming effect.<sup>207</sup> In the absence of any priming, patients will tend to give some answers more often than others; *e.g.*, they may give "PENCIL" more often than "PENSION" or "PENINSULA". Generally, it is advisable to use target stimuli that are not the most "dominant" or most common correct responses. This can be determined from norms, which are available for some tests using verbal material.<sup>208</sup>

The instructions given to the subjects are crucial. Graf *et al.*<sup>13</sup> found that when subjects were instructed in the word-completion task to use the three-letter word stems as cues to recall previously presented words, amnesic patients performed more poorly than control subjects. However, when subjects were instructed to use the word stems to form the first word that came to mind, amnesic patients and control subjects performed the same. With dissociation between the integrities of the explicit and implicit memory systems, priming is observed, but recall and recognition for target items is poor.

# STUDIES DURING ANESTHESIA

For their implicit test, Eich *et al.*<sup>209</sup> used homophones, words that are pronounced alike but that are different in spelling, such as "earn"/"urn" and "ate"/"eight." They presented to the anesthetized patient a series of short, descriptive phrases (*e.g.*, grecian urn, dinner at eight) that were intended to influence patients toward giving a particular spelling on a spelling test administered postoperatively. Although Jacoby and Witherspoon<sup>210</sup> found that performance of amnesic Korsakoff patients on a similar task was at least as good as that of healthy volunteers, and although Eich<sup>34</sup> had obtained promising results with this task in a previous "shadowing" study involving healthy volunteers, no such influence during anesthesia was observed.<sup>209</sup> Possibly, the high level of cognitive skill required for the success of this task, *i.e.*, inferring the intended meaning and spelling from associative context, may be more than can be supported by the faint registration of information and its subsequent fragile storage under anesthesia. It is also possible that the considerable delay between presentation of the material and the spelling test (4–5 days) may have been detrimental.

Block *et al.*<sup>16</sup> used two priming tasks, a Word Completion test requiring patients to give words beginning with specified three-letter word stems, and a Constrained Associations or Category Production test, in which patients were given the names of six categories, such as "military title" and were asked to give instances for each, such as "general." A list of words that had been previously presented during anesthesia provided some appropriate answers for Word Completion and instances for Category Production, the latter chosen from normative data tabulating the frequencies with which different instances of a category are given as examples.<sup>208</sup> Priming was demonstrated in the Word Completion test but not in the Category Production test (fig. 3).

Another test that was used, the Nonsense Words task, is not as commonly used as an implicit test. Patients were presented during anesthesia with a list of nonsense words, *e.g.*, "goral," that were repeated with varying frequencies up to 16 times. In the postoperative period, the patients heard pairs consisting of one nonsense word that had been played during anesthesia and one that had not; they guessed which had been played and, during a separate presentation, decided which sounded more pleasant. Patients both preferred and more accurately guessed the nonsense words that had been played to them most frequently (16 times) during anesthesia, relative to those played less frequently, but showed no such patterns in additional control tests (fig. 4). Whereas the preference score reflected implicit memory, the recognition task was expected to probe explicit memory. Relative to unfamiliar stimuli, normal subjects and amnesic patients prefer stim-

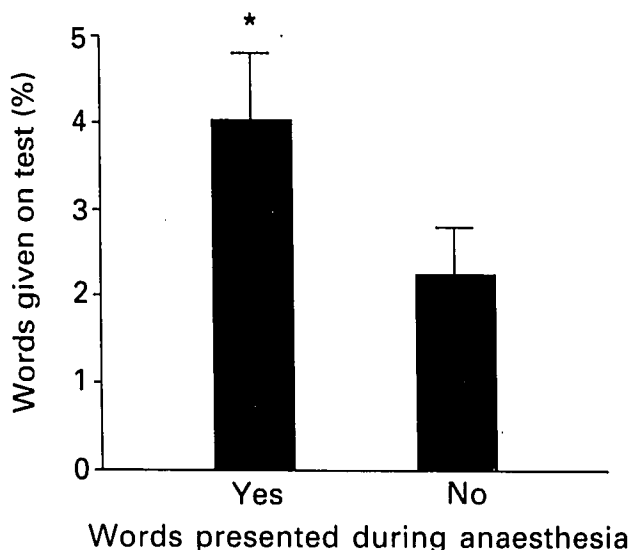


FIG. 3. Performance in the word completion task on the day after general anesthesia and surgery. The values are the percentages of words given on the test by the average patient from the list that had been played to her during anesthesia ("Yes") and from the list not played to her ("No"). The priming effect is the difference between these values. Error bars indicate 1 SE. \* $P < 0.05$  by analysis of variance. (From Block RI, Ghoneim MM, Sum Ping ST, Ali MA: Human learning during general anaesthesia and surgery. *Br J Anaesth* 66:170–178, 1991).

uli to which they have been exposed, even in the absence of recall of the previously presented stimuli.<sup>211,212</sup>

However, as Block *et al.*<sup>16</sup> noted, the results of the recognition task, rather than suggesting conscious memory, may possibly apply more to implicit memory. The patients were instructed to guess if unsure which nonsense word was played previously; later questioning by the research assistant indicated that they generally viewed their recognition judgments as pure guesswork rather than memory of prior occurrence. Frequency of stimulus presentation affects performance in many memory tests, including recognition and preference judgments.<sup>211,213,214</sup> Information about frequency of stimulus presentation may be encoded automatically and independently of types of memory processing that involve intention and cognitive effort.<sup>215,216</sup> Such automatically encoded frequency information may have been sufficient to mediate recognition of nonsense words presented 16 times but not those presented less frequently.

On recognition tests, performance may be mediated by two different processes.<sup>217</sup> Subjects may explicitly retrieve an event from the past or they may *judge* that an event had occurred previously because it "rings a bell." This latter judgment is reminiscent of implicit memory, although whether subjects are able to rely solely on implicit memory for recognition when the level of explicit memory is low remains controversial.<sup>218</sup> Finally, the re-

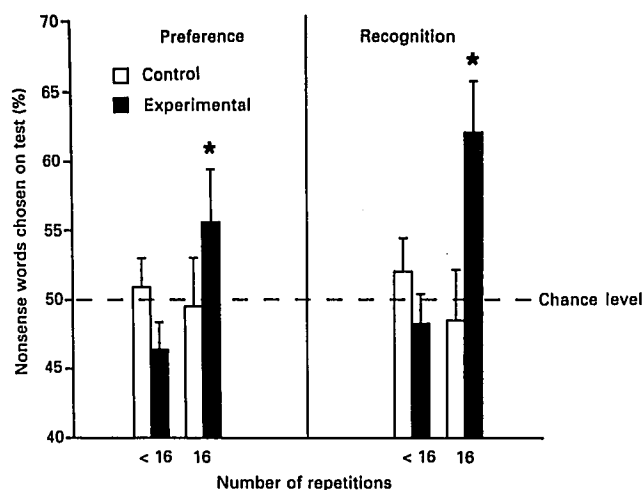


FIG. 4. Performance in the nonsense words task on the day after surgery. Values are the percentages of nonsense words chosen by the average patient on the preference and recognition tests for nonsense words from the list that had been played to her during anesthesia ("Experimental") and from the list not played to her ("Control"). Different nonsense words were repeated with varying frequencies. The maximum number of repetitions was 16. The dotted line shows the expected values if patients had guessed randomly (50%). Error bars indicate 1 SE. \* $P < 0.05$  by analysis of variance. (From Block RI, Ghoneim MM, Sum Ping ST, Ali MA: Human learning during general anaesthesia and surgery. *Br J Anaesth* 66:170-178, 1991.)

sults were consistent with those of a previous study,<sup>56</sup> which investigated the effects of a subanesthetic concentration of nitrous oxide (30%). In contrast to drug-induced impairment in explicit memory for meaningful words, recognizing how nonsense words sounded resisted the drug's effect, as did other implicit assessments of memory.

Millar<sup>219</sup> described very briefly the use of a category production task in anesthetized patients. Six tape-recorded lists of words were prepared such that each list defined a distinct semantic category (e.g., flowers or animals) within which the words were moderately common category instances. Patients were allocated at random to one of the lists, which was repeated during anesthesia. Following recovery, patients were required to generate examples of each of the six category names. Words in the lists presented during anesthesia were more likely to be generated earlier in the retrieval sequence than were the "control" words in the nonpresented lists, suggesting that intra-anesthetic exposure to the words raised their priority for retrieval.

Roodra-Hrdlicková *et al.*<sup>220</sup> and Jelacic *et al.*,<sup>221</sup> two groups of investigators at the same institution, used the same category production task. Patients in the experimental group were presented with four target words, "yellow," "banana," "green" and "pear" during nitrous oxide and isoflurane anesthesia in the study of Roodra-Hrdlicková *et al.*, and during nitrous oxide supplemented

with fentanyl or sufentanil in the study of Jelacic *et al.* Postoperatively, patients were asked to give three examples of the categories "fruit" and "colors." The experimental group demonstrated priming effects for the target words that had been presented, compared to the control group, which had been presented with seaside sounds. Thus, the implicit memory task that showed no evidence of learning in the study of Block *et al.*<sup>16</sup> proved successful for these investigators.<sup>220,221</sup>

Two important differences in these studies can be observed. The first is the type of categories used. Roodra-Hrdlicková *et al.*<sup>220</sup> and Jelacic *et al.*<sup>221</sup> used easy categories, whereas Block *et al.* used difficult categories, e.g., "type of wood," "type of male clothing," for which it was harder to generate exemplars (targets included "hickory," and "walnut" and "vest" and "coat," respectively). The second difference was the time of testing. Block *et al.* tested the patients on the day after anesthesia, whereas Roodra-Hrdlicková *et al.* and Jelacic *et al.* tested them at a mean time of 203 min and 81 min postanesthesia, respectively.

Standen *et al.*<sup>222</sup> also used a category production task in children who had a combination of local anesthetic block and halothane anesthesia. Patients were presented during anesthesia with words, each chosen from a different category. Patients were tested within 24 h by administration of a series of cues: first, the words' categories, then their initial letters, and then more specific characteristics, e.g., "you find it on the farm" for the word "tractor." There was no difference between the performance of the experimental group and the control group, who was not exposed to the test material. The patients were heavily premedicated, having received either diazepam (0.5 mg/kg) or trimeprazine (2 mg/kg), with or without droperidol (0.2 mg/kg). Although diazepam in smaller doses (0.2-0.3 mg/kg) may spare implicit memory,<sup>70-72</sup> larger doses may impair it.

It was recently reported<sup>212</sup> that initially unfamiliar melodies became more preferred following brief exposure. A similar shift in preference occurred in both amnesic patients and control subjects, even though the amnesic patients performed poorly in recognizing the melodies that had been presented. Winograd *et al.*<sup>223</sup> presented patients during nitrous oxide, oxygen, isoflurane, and fentanyl anesthesia with different selections of music from cultures around the world. The control group consisted of students who had no anesthesia or surgery. While the control group preferred melodies that had been heard before, no such effect was found for the anesthetized patients.

Recently, Kihlstrom *et al.*<sup>f</sup> used an association task. During isoflurane anesthesia, patients were presented with stimulus words and the corresponding response words given most frequently to each stimulus. Postoperatively, they showed evidence of priming, compared to their per-

formance on control words, which had not been presented. Although the task has been reported before<sup>201</sup> to be successful in showing evidence of intact implicit memory in amnesic patients, Block *et al.*<sup>56</sup> did not get analogous results in volunteers inhaling 30% nitrous oxide in oxygen.

As described in a brief report, Goldmann<sup>187</sup> administered to patients before anesthesia a questionnaire that included questions such as "What is the blood pressure of an octopus?". Patients were played the answers during anesthesia. Postoperatively, they performed better on a recognition test on those items whose answers they had heard under anesthesia, although they did not recall hearing the answers.

Millar and Watkinson<sup>102</sup> administered a list of ten low-frequency words to patients during nitrous oxide and halothane anesthesia. They performed better during the postoperative period on a recognition test than did control patients. Whereas a recognition task is usually considered a measure of explicit memory, we take the same position that we took before regarding recognition of nonsense words in the study of Block *et al.*<sup>16</sup>—namely, that the performance of the patients most likely reflected implicit rather than explicit memory of a previous episode. This position is supported by Kihlstrom and Schacter.<sup>224</sup> Millar and Watkinson<sup>102</sup> found that correct recognition performance revealed no significant difference between the groups when patients were asked to select the target words from a long list. However, the experimental group scored significantly higher in discriminating between presented and nonpresented words.

*Comments on studies in the anesthesia literature.* Thus, some studies have provided evidence of implicit memory during anesthesia, and others have not. Comparison of the methodologies in these studies does not reveal any clear explanation of the discrepancies. Some implicit memory tasks may be sensitive to learning during anesthesia, whereas others are not. Implicit memory tasks differ in various characteristics such as the types of test, stimuli, and retrieval cues. The effects of differences in implicit memory tasks have received a great deal of attention in the psychology literature.<sup>207,225-228</sup> For example, the extent to which performance in implicit memory tasks may be facilitated on the basis of perceptual information as opposed to conceptual, semantic information has been examined. In amnesic patients and healthy individuals, priming is greater when the target materials and the implicit test are presented in the same sensory modality (both auditory) than in different sensory modalities (visual *vs.* auditory), although priming still occurs in the latter situation.<sup>229</sup> In studying learning under anesthesia, both visual and auditory implicit tests have been used, as have both "perceptual" stimuli, such as music and "conceptual" stimuli, such as instances of categories. Some theorists believe that perceptual and conceptual priming are dis-

tinct and derive from separate memory systems, with the former based on a presemantic "perceptual representation system" and the latter on "semantic memory."<sup>207</sup> It has been hypothesized<sup>224</sup> that intraoperative stimulus registration reflects automatic activation of old knowledge and that it is unlikely that anesthetized patients would be able to execute the higher cognitive processing required to encode new memory traces. However, some evidence suggests that new memory traces of nonsense words<sup>16</sup> and proper names<sup>8</sup> can be formed during anesthesia.

Another factor that may have contributed to discrepancies among studies of implicit memory during anesthesia are the marked variations in anesthesia methods used. Cork *et al.*<sup>h</sup> found evidence for implicit memory in patients who received isoflurane but not nitrous oxide and sufentanil, although the Jelacic and Bonke group<sup>8</sup> found evidence for implicit memory in patients anesthetized with nitrous oxide and alfentanil. Block *et al.*<sup>16</sup> found that method or "depth" of anesthesia did not affect implicit memory, although it remains possible that implicit memory may be spared by certain anesthetics and certain drugs at lower doses but not at higher doses.

Finally, the unconscious enactment of behavioral or therapeutic suggestions presented during anesthesia, as described in the following sections, can be regarded as implicit memory in that the patients do not have conscious access to the source of the influence, which nevertheless affects their behavior.

#### **Recall of Behavioral Suggestions Administered during Anesthesia**

Cheek and Le Cron<sup>230</sup> suggested that nonverbal responses (raising one finger for "yes" and a different finger for "no") were more trustworthy than verbal responses for hypnotic recollection of meaningful sounds heard during anesthesia. Patients were often unaware of their nonverbal responses. Bennett *et al.*,<sup>17</sup> following on this suggestion, measured learning during anesthesia using a postanesthetic motor behavior. In an important departure from previous work, Bennett *et al.* performed a randomized and double-blind study in which patients were assigned to either suggestion or control groups. The suggestion patients were exposed during anesthesia to statements of the importance of touching their ear during a postoperative interview. Compared with controls, they touched their ear more frequently, though they were amnesic for the spoken message, both without and under hypnosis.

This fascinating study has, however, been criticized. First, there was no baseline assessment of "ear pulling" frequency. Second, the difference between groups was due to the extreme reaction of two patients. If these two "outliers" were excluded, the difference between groups would not be significant.<sup>231</sup> Third, Wilson and



Spiegelhalter<sup>232</sup> criticized the statistical analysis, claiming that the *P* value using appropriate statistical tests should have been 0.08 and not 0.05. Fourth, the patients' levels of anesthesia or their end-expired concentrations of inhalation anesthetics were not measured, raising the question of whether some patients could have been too "lightly" anesthetized while receiving the suggestions.<sup>173</sup>

Goldmann<sup>233</sup> was initially unsuccessful in replicating the findings of Bennett *et al.* The British patients, for unknown reasons, were reluctant to touch their ears. However, when the experimental group was instructed during surgery to touch their chins postoperatively, they did so more often than did the control group.<sup>85</sup> One criticism of this study, in addition to the absence of preanesthetic baseline assessment of the frequency of chin-touching, is the state of anesthesia during which the suggestion was presented to the patients. Patients were undergoing cardiac surgery, and the tape was presented near the end of bypass after the patients regained normothermia. The use of "light" anesthesia toward the end of bypass to avoid myocardial depression is common. In the study of Goldmann *et al.*, the state of anesthesia was so "light" that some patients (23%) explicitly recalled intraoperative events that were later confirmed to have happened. The results may, therefore, represent more than "unconscious" hearing and retention.

Lastly, Block *et al.*<sup>16</sup> used a similar task with some modification. Although they also did not have a preanesthetic assessment, they introduced an additional control. They gave a suggestion during anesthesia to touch the ear to half the patients and a suggestion to touch the nose to the remainder, and then measured both ear-touching and nose-touching in all patients during the postoperative interview. The patients who were given a suggestion to touch the ear provided a measure of nose-touching in the absence of a suggestion to touch the nose, and *vice versa*. Patients touched the "correct" (suggested) body part longer than the "incorrect" (not suggested) body part. The number of touches showed a marginal trend in the same direction ( $P = 0.06$ ) (fig. 5). Similar to the results of Bennett *et al.*<sup>17</sup> and Goldmann *et al.*,<sup>85</sup> a few patients showed very long durations of touching the "correct" body part, although the effect was not caused solely by these long durations skewing the data. Similar, also, to the other results, the patients could not guess accurately which body part they had been asked to touch during anesthesia.

The results of Bennett *et al.*<sup>17</sup> have, therefore, been replicated. However, because the evidence for learning has been modest, further studies would be useful. Such studies should involve preanesthetic measurement of the behaviors to be tested, stipulation of different behaviors for different patients, and highly accurate, reliable measurement of the postoperative behaviors.

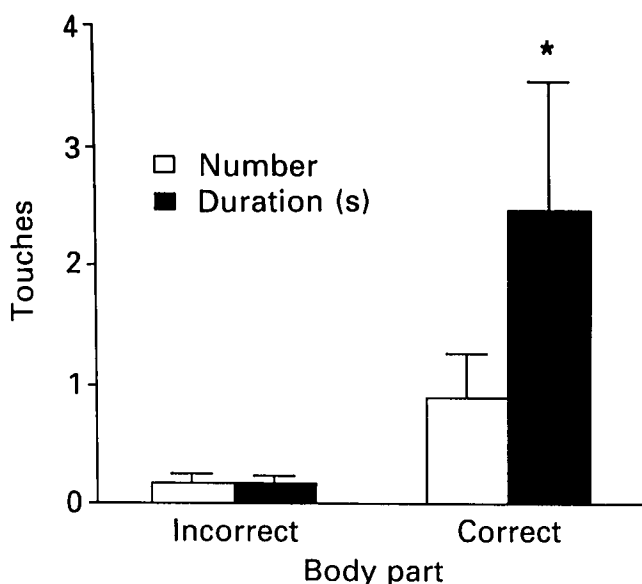


FIG. 5. Performance in the behavioral suggestions task during 4 min of postoperative questioning on the day of surgery. The values are the number and duration of touches by the average patient of the body part that had been specified (ear or nose) in the suggestion played to her during anesthesia ("Correct") and of the other body part ("Incorrect"). Error bars indicate 1 SE. \* $P < 0.05$  by analysis of variance. (From Block RI, Ghoneim MM, Sum Ping ST, Ali MA: Human learning during general anaesthesia and surgery. *Br J Anaesth* 66:170-178, 1991.)

### Efficacy of Therapeutic Suggestions Administered during Anesthesia

#### RATIONALE

Perhaps the most important clinical application of research on learning under anesthesia is the possibility of improving the postoperative course of patients by presentation during anesthesia of therapeutic suggestions predicting a rapid and comfortable postoperative recovery. There is well-documented evidence that psychological and behavioral preparation prior to surgery can affect postoperative recovery.<sup>234</sup> It is also probable that continuation of the preoperative interventions in the postoperative period would be even more helpful to patients. One of the important modalities of treatment is the guiding of patients, through suggestions, to behave in a manner conducive to optimal postoperative recovery. Such suggestions or communications may be delivered either during or without hypnosis. The efficacy of suggestions are enhanced when subjects feel at ease and are not distracted; feel they are in a special kind of expectancy situation in which unusual events may occur; and can feel,

remember, think, imagine, and experience in new or unusual ways.<sup>235</sup> It has also been claimed that hypnosis produces more profound bodily relaxation than do waking-state interventions, elicits greater clarity of visual imagery, and increases responsiveness to suggestions for therapeutic change.<sup>236</sup> It has been speculated that suggestions administered during anesthesia might incorporate some of the desirable conditions that increase their efficacy.

*If therapeutic suggestions are effective, how might they work?* Barber,<sup>235</sup> in a review of the literature on physiologic effects of suggestions, concluded that if they are effectively communicated and accepted at a "deep" level, they could influence cellular (especially vascular and immunologic) functioning to conform to the suggested alterations. Supposedly, by becoming deeply absorbed in the imagined physiologic change as a result of the suggestions, the feelings that accompanied the actual physiologic change would be reinstated, and these feelings would stimulate the cells to produce the actual change. Wadden and Anderson,<sup>236</sup> in a review of the clinical use of hypnosis, concluded that hypnosis was more effective in treating nonvoluntary disorders such as pain than disorders involving self-initiated behavior such as overeating. The authors suggested this might be because pain, unlike eating, was not affectively rewarding and there would be no conflicting motivation concerning its avoidance, as there might be with food. Consequently, individuals suffering from nonvoluntary disorders might be highly motivated to accept therapeutic suggestions. Such acceptance would be negatively reinforced by diminution of an ongoing aversive experience. However, the analogy between the hypnotic and anesthetized states is limited, and it remains to be established that suggestions can be helpful when administered to an unconscious patient.

### STUDIES

Two uncontrolled studies<sup>32,33</sup> found that therapeutic suggestions improved patients' postoperative recovery. Pearson<sup>237</sup> found that patients who were presented during anesthesia with therapeutic suggestions were discharged from the hospital an average of 2.4 days sooner than were those played music or blank tape, but the experimental and control groups were not matched for type of surgery. The differences in hospital stay of patients undergoing different operations made comparisons between the groups difficult. Bonke *et al.*<sup>238</sup> also found shorter postoperative hospital stays for patients receiving therapeutic suggestions who had cholecystectomies. They compared the postoperative recovery of patients who had been exposed either to therapeutic suggestions, "noise," or to operating room sounds during surgery. The shorter hospital stay was significant only for patients older than 55 yr and was evident mostly in comparison to one of the

two control groups. There may have been a trend for the group who was exposed only to noise to fare worse than the other two groups on indices of recovery. Because the therapeutic suggestions were interspersed with the same type of noise on the tape, one may ask: Is it possible that the full potentiality of the positive impact of suggestions was undermined?

This question seems to have been answered by a later study from the same institution.<sup>239</sup> The investigators could not replicate the earlier beneficial effects. Among the reasons which were cited for those discrepant results was the failure of the earlier study to account for the surgical performance of choledochotomies in some patients, which entailed a longer hospital stay. Two other studies<sup>240,241</sup> could not find beneficial effects of therapeutic suggestions, although they may be criticized because of the small sample sizes that were used.

However, a recent study<sup>242</sup> that was conducted under double-blind, randomized conditions in 39 hysterectomy patients obtained positive results: patients who had been played therapeutic suggestions during anesthesia conducted with a wide variety of anesthetic drugs had shorter postoperative stays (15%) and periods of pyrexia (44%) and were rated by nurses as having made a better than expected recovery compared to patients in the non-suggestion control group. On a variety of other outcome measures, there were nonsignificant differences, mostly in the expected direction.

These encouraging results left a few unanswered questions: Were there patients suffering from malignancy in the sample, and were their numbers equal in the control and suggestion groups? There was no information about the physical status of patients before surgery; patients with poor physical state are more likely to stay longer in the hospital. It is also possible that patients with poor socioeconomic status may stay longer in the hospital.<sup>243</sup> These patients suffer from a higher risk of infection.<sup>244</sup> There was no information on this point, except that the authors reported on the ethnic origin of their patients: there were 13 Caucasians in the suggestion group *versus* 9 in the control group, and there were 6 Afro-Caribbeans in the suggestion group *versus* 11 in the control group. It is also surprising that there were shorter periods of postoperative pyrexia in the suggestion group in the absence of relevant instructions on the tape recording, whereas there were no differences in pain intensity, nausea and vomiting, and urinary difficulties between the two groups, despite the presence of explicit instructions in the tape about these symptoms. The authors suggested that large individual variabilities in these symptoms and enhancement of immune function through a better psychological adaptation to the stress of surgery might account for these results. Yet there were no differences in the mood and anxiety scores postoperatively between the two groups.

Until recently there were no reports that positive suggestions administered during anesthesia influenced measures such as pain ratings, dosages of opioids administered, and incidence of nausea and vomiting. Münch and Zug<sup>245</sup> studied patients undergoing thyroidectomies. The incidence and magnitude of pain, nausea, and vomiting were not changed by suggestions, although the experimental group rated their well-being as better than the control group. However, many details of the management and assessment of patients postoperatively were absent from this short report. In a small pilot study, Furlong<sup>246</sup> reported that patients exposed to positive suggestions required less pain medication than did the control group. However, details of the management and assessment of patients' postoperative course are missing. McLintock *et al.*<sup>247</sup> studied 63 patients undergoing abdominal hysterectomy who were played either a tape of positive suggestions or a blank tape during the operation. Analgesic requirements using patient-controlled analgesia and intensity of pain during the first 24 h postsurgery were assessed. Patients who were played positive suggestions required a mean of 14.6 mg less morphine than did controls. Pain scores were similar in the two groups.

However, Block *et al.*<sup>248</sup> failed to replicate the results of Evans and Richardson<sup>242</sup> and McLintock *et al.*<sup>247</sup> Therapeutic suggestions or a blank, control tape were played to 209 patients undergoing various operations. Numerous assessments of postoperative recovery showed no meaningful, significant differences between patients receiving therapeutic suggestions and controls.

Although the reports of beneficial effects of therapeutic suggestions support the proposition that meaningful information is registered while patients are under general anesthesia (table 2), reports of no benefits do not preclude this possibility. Acquisition, storage and retrieval of events may occur without facilitating compliance with suggestions or physiologic mechanisms that promote healing.

#### COMMENTS FOR FUTURE STUDIES

Clearly, replication of the positive studies is needed. Many details of the studies need to be considered if adequate replication is to be achieved. Some researchers<sup>249</sup> stress the importance of gaining close rapport with the patients during the preoperative interview to enhance motivation for the study and convince them of its relevance for their well-being. Some researchers believe that the message should use the patient's preferred name; should be presented slowly, but at normal listening volumes; should be phrased in direct, grammatically simple and affirmative statements; and should be repeated continuously during anesthesia. Clinical hypnotists<sup>245,i</sup> stress the importance of using positive terms (such as "comfortable" or "fine") and avoiding the use of negative ones

(such as "no pain" or "no trouble") to maximize benefits to the patients. This is based on the argument that the unconscious mind may not register sounds and words in the same way as the conscious mind, and inclusion of negative terms like "pain" or "trouble," albeit denied, may influence the patient negatively. To our knowledge, this belief has not yet been tested. The text may contain direct suggestions, *e.g.*, "You are completely relaxed"; third person suggestions simulating positive comments made by surgeons, *e.g.*, "Great . . . That looks excellent, very good indeed"; and suggestions on the best way to cope with postoperative sequelae, *e.g.*, "You will swallow to clear your throat and everything will go one way, straight down . . . so that you can get good food to make you strong after the operation, your stomach and intestines will begin churning and gurgling soon after your operation." Some researchers think that the tape should be recorded by the interviewer or the patient's own anesthesiologist or surgeon. (Woo *et al.*,<sup>241</sup> in a novel but unsuccessful approach, asked patients in one group to record the positive message in their own voices.)

The contents of the tape presented to the control group has varied. Some investigators have presented a blank tape (or simply plugged the ears), whereas some have played noise, sea sounds, or similar neutral sounds, or sounds of the operating room. The latter may have been the sounds during the patient's own operation or prerecorded operating room sounds. Each option has its merits and disadvantages. For example, recording and playing the patient's actual operating room sounds may be disturbing to some members of the operating room team and may contain pessimistic statements, which if registered by the patient's mind may be detrimental to his or her well-being. Noise might affect the patient negatively.

#### Recall of Unfavorable Comments Voiced during Anesthesia

If therapeutic suggestions are beneficial, it is tenable that unfavorable comments about patients voiced during anesthesia may cause them harm. There is a persistent tradition in the literature that unfavorable comments are particularly likely to be recalled.<sup>31,250</sup> The evidence is anecdotal. Sometimes memories of pessimistic or derogatory operating room conversations may only be apparent with the aid of hypnosis.<sup>180,181</sup> However, disparaging remarks may also be recalled without hypnosis.<sup>209</sup> This brings into focus the question of pertinence or significance of the material "heard" during anesthesia to the patient. For some investigators,<sup>251,233</sup> this is a very important factor that determines the probability of recollection of events under anesthesia. Blacher<sup>25</sup> claimed that he and others could replicate the results of Levinson<sup>31</sup> by creating a similar bogus crisis during anesthesia, but were unsuccessful.

TABLE 2. Variables That Have Been Reported to Respond to Suggestions Administered during Anesthesia

Variable and Study	Control Group	Suggestion Group
Postoperative stay (days) (Evans and Richardson <sup>242</sup> )	8.4	7.1
Pyrexia (half-days)	3.9	2.2
Difficulties with bowels (visual analogue rating scale, 0–100)	55.7	31.3
Nurse's assessment of recovery: Better than expected	6	16
Morphine requirement (mg) over the first postoperative day (McLintock <i>et al.</i> <sup>247</sup> )	65.7	51.0
Patient's assessment of well-being (visual analogue rating scale, 0–10) (Münch and Zug <sup>245</sup> )	4.5	3.4

cessful when they administered “benign” stimuli (he supplied no details).

Thus, remarks pertinent to the patients and their well-being, according to this view, are more liable to be retrieved than a list of meaningless words presented during surgery. For obvious ethical and legal reasons, this contention is hard to test. It is difficult also because of ambiguity about what constitutes meaningful information for the patient. For example, Goldmann and Levey<sup>165</sup> invoked this reasoning to explain the results of a study in which they measured galvanic skin responses during anesthesia. They found no orienting responses when they called the patient's name or during conversations pertinent to the operation. Only when they called the name of the leader of the Mine-workers union, which was on strike at that time in Britain, were responses obtained.

### Comments and Conclusions

#### MONITORING THE LEVEL OF CONSCIOUSNESS

If patients are to be spared the distressing and inadvertent occurrence of consciousness during surgery and explicit recall, some reliable means to evaluate the state of consciousness of the patient or depth of anesthesia are required. It is a sobering commentary that after 145 yr, it is not always possible to determine with certainty whether a given anesthetized patient is conscious during surgery.<sup>10</sup> *Monitoring the MLR or 30–40-Hz neuronal oscillations* seems at present to be the most promising indicator. Evoked neuronal oscillations would be particularly relevant if it can be proved that these oscillatory electrical activities in the brain are indeed the mediators of sensory information processing<sup>252</sup> and consciousness.<sup>1</sup> It has been proposed<sup>253</sup> that as long as 30–40-Hz oscillations are present, the patient is still conscious, although, as mentioned before, these fast oscillations can be recorded in comatose patients.<sup>141</sup> However, it is possible that disap-

pearance of fast rhythms caused by anesthetics may indicate unconsciousness, and the reappearance of these rhythms may signal the regaining of consciousness.<sup>112</sup> These propositions need to be tested with different drugs and regimens used in anesthesia. Future work should also look for correlations between changes in the MLR and fast oscillations and learning during anesthesia using explicit and implicit memory tests.

The concentrations of the commonly used inhalation and intravenous anesthetics that prevent learning and/or recall in humans and animals need to be determined. This information is necessary for many clinical situations in which patients can only tolerate “light” anesthesia. Factors that may shift the dose-response curves for learning and memory during anesthesia need to be studied. These include the effects of premedicants, stress hormones (epinephrine, norepinephrine, adrenocorticotrophic hormone, and vasopressin), and aging. Investigators need to determine whether equal fractions of MAC of different drugs produce the same or different degrees of memory impairment and whether combinations with nitrous oxide are additive or synergistic. The mechanisms of actions of these drugs on memory must also be analyzed in detail.

#### ANIMAL MODELS OF LEARNING AND RECALL

There are tests of learning and memory in animals. Working with animals provides an opportunity to make manipulations and conduct analyses that are not feasible in humans. There are similarities between some types of memories in different species.<sup>254</sup> One type of associative learning, classical or Pavlovian conditioning, may be particularly useful for the study of anesthetic drugs. Classical conditioning of discrete behavioral responses, like eyelid closure, exhibits the same basic properties of associative learning in rabbits, humans, and other mammals. Some neural mechanisms for this form of learning and memory have been identified,<sup>255,256</sup> unlike for other types of memory. It thus may be possible to relate a drug effect on learning to an effect at a particular anatomic locus. Weinberger *et al.*<sup>257</sup> showed that rats learned a conditioned fear response when injected with epinephrine during anesthesia. Thus, it may be possible to extend in animals the work of Levinson<sup>31</sup> (who created a bogus crisis during anesthesia in humans), which for ethical reasons cannot be done in humans.

Is there implicit memory for events that take place during adequate anesthesia, outside of conscious awareness? The answer is “possibly yes.” There is some evidence, not robust but probably valid, that supports this contention. Replication of these findings is necessary, as it is for what Kihlstrom and Schacter<sup>224</sup> have described as “taming of the phenomenon and bringing it under experimental control.” This might be facilitated by adop-

tion of a standardized protocol, which might include: motivating the patient before the experiment by conveying the importance of the experiment and the likelihood of a successful result; omitting premedication; using a simple and standardized anesthetic regimen; calling the patient by name before presentation of the stimuli; recording the tape in the voice of a person familiar to the patient, possibly an authoritative figure; continuing presentation of the tape during anesthesia in a slow and comfortable hearing volume; and administering postoperative tests at a fixed time. The studies in this area are mosaics of different methods and procedures, with different outcomes. It is impossible to determine if differences among studies with positive and negative results are attributable to differences in the tests, the anesthetic regimens, the number of repetitions, durations, and complexity of stimulus presentations, or other factors.

#### PRACTICAL IMPLICATIONS OF IMPLICIT MEMORY IN THE ANESTHETIZED PATIENT

There are two practical implications of implicit memory under anesthesia—the possibilities of influencing a patient's postoperative course either favorably or negatively. *The efficacy of therapeutic suggestions* for improved postoperative recovery presented during general anesthesia is more doubtful than the occurrence of implicit memory. There are several studies with negative outcomes that cannot easily be reconciled, with the two studies reporting positive results. A recommendation that taped messages be played during anesthesia to patients should be postponed until adequate replication of the previously published positive studies. In the meantime, additional studies should be aimed at optimizing the delivery of positive communications, as stated before. Targeting different types of surgeries and different types of patients should be attempted. One important characteristic varying among patients is degree of hypnotic susceptibility, assessed with a standardized instrument. Highly hypnotizable subjects may have a better capacity for unconscious perception and greater ability to manifest the positive psychophysiologic effects of suggestions than subjects of low hypnotizability.<sup>235,258</sup> It is possible that synergistic or at least additive benefits may be obtained if therapeutic suggestions are presented to patients preoperatively, while partially conscious during the early recovery phase and during the remaining phase of hospitalization. Even if therapeutic suggestions delivered during anesthesia and thus available only to implicit memory are effective, there is no compelling reason to assume that they are more effective than therapeutic suggestions delivered in a waking state, which would be available both to implicit and explicit memory. Only a direct comparison could establish this.

That *unfavorable comments voiced during anesthesia* may affect the patient's postoperative recovery negatively is probably more likely than improvement through positive therapeutic suggestions. Although the evidence for effects of negative comments is circumstantial, if implicit memory does occur, then unconscious retention of some information voiced during anesthesia is to be expected. In the absence of solid data supporting the danger of unfavorable comments, it will be difficult to change the behavior of the operating room team while the patient is anesthetized. Nevertheless, it may be reasonable to caution anesthesiologists, nurses, and surgeons to exercise restraint in their conversations and assume that some of these conversations may be retained by the unconscious patient. This would not be a high price to pay for possible prevention of some postoperative complications.

#### IMPLICATIONS OF IMPLICIT MEMORY DURING ANESTHESIA FOR COGNITIVE PSYCHOLOGY

There may be theoretical significance to the presence of implicit memory under anesthesia. We are still at the demonstration stage, but once reliable effects have been established, learning under anesthesia may provide a good testing ground for investigating the influence of various tasks and conditions on implicit memory and the neural substrates of this memory. It would be interesting to determine how closely implicit memory during anesthesia resembles implicit memory found in organic amnesias in various tasks, considering the advantages of studying the phenomenon in large numbers of individuals under controlled anesthetic conditions rather than in rare amnesic patients with uncontrolled premorbid factors.

#### USE OF ANESTHETICS AS PHARMACOLOGIC PROBES

More information is available about memory and consciousness at the cognitive or functional level than at the biologic one. Psychologists and cognitive scientists use data derived from experiments to formulate theories and models. Attempts are then made to map different aspects of the models onto what is known about the neuroanatomy and neurophysiology of the brain. Neuropsychologists, by studying patients with focal brain lesions, have made some progress in understanding memory, language, and perception. Yet, clear answers to old questions, such as "Why do we forget?" and "How did I come up with this name?" have yet to be found. Information at the neural level is needed. Some information about the neural mechanisms of memory and consciousness is available. Roles for protein kinase C-mediated phosphorylation of identified protein substrates in the hippocampus<sup>255,259</sup> and for long-term potentiation at the synapses<sup>260</sup> have been described. Extra- and intracellular recordings in neurons demonstrate the existence of a 40-Hz oscillatory activity

in the brain in response to auditory and visual stimuli.<sup>134,252,261</sup> Crick and Koch<sup>1</sup> have proposed that these oscillations may be the mediators of consciousness, binding together all the neurons distributed throughout the brain that relate to various aspects of a perceived object. One approach for bridging the gap between the psychological and the biologic levels is to use anesthetic drugs as pharmacologic probes to study their effects on consciousness and memory in humans and animals, and on neural responses in animals under similar conditions. This approach may provide insights both into these biologic mechanisms and the effects of anesthetics on them.

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# Footnotes

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