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Consciousness and Anesthesia

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The purpose of general anesthesia is to render surgical patients unconscious, and thus insensitive to pain and oblivious to events occurring during the procedure. For this reason, anesthesia – like sleep and coma – often enters into philosophical and scientific discussions of consciousness. How do we know that the patient is unconscious? Appearances to the contrary notwithstanding, are there reasons to think that anesthetized patients are actually conscious after all? Assuming that they are actually unconscious, is it possible for them to acquire and retain unconscious memories of pain and surgical events? What can the biological mechanisms of general anesthesia tell us about the neural correlates of consciousness?

The Evolution of General Anesthesia

Up until the middle of the nineteenth century, anesthesia was not a feature of surgery. Instead, patients were simply required to withstand the pain of the procedure, perhaps with the aid of alcohol, opiates (such as laudanum), a bite-board, and physical restraints. Humphrey Davy (1778–1829), the pioneering electrochemist, discovered the effects of nitrous oxide on headache and dental pain during his research on respiratory physiology; but his report went unnoticed in the medical community and the substance was quickly consigned to use at "laughing gas" parties. In 1845, Horace Wells, an American dentist, attempted to use nitrous oxide for anesthesia during a dental extraction, but the demonstration failed. But on October 16, 1846, William Morton, another dentist, employed ether in the surgical removal of a tumor with no signs or reports of pain in the patient. That event is now celebrated in hospitals and medical schools throughout the world as "Ether Day" (Fenster 2001). Morton died in 1868, and his tombstone in Cambridge's Mount Auburn Cemetery carries the following epitaph, composed by Bigelow:

> Inventor and Revealer of Inhalation Anesthesia:
> Before Whom, in All Time, Surgery was Agony;
> By Whom, Pain in Surgery was Averted and Annulled;
> Since Whom, Science has Control of Pain.

Soon thereafter, chloroform was introduced as an alternative to ether, which had an unpleasant odor and other side effects. Anesthesia was also extended from surgery to obstetrics, although

some physicians had qualms about dangers to the neonate, Queen Victoria essentially ended the debate when she received chloroform for the birth of her eighth child, Prince Leopold. Nevertheless, some professionals and others continued to debate a "calculus of suffering" by which some individuals, and some conditions, were deemed more worthy of anesthesia than others (Pernick 1985).

Debates aside, progress in anesthesia continued. In 1868, nitrous oxide, mixed with oxygen to circumvent drug-induced asphyxia, was introduced to medicine – after having served for half a century as entertainment at "laughing gas" parties. Also that year, following the development of the hypodermic needle, morphine was added to the procedure to reduce the amount of inhalant required to produce anesthesia, and to prevent shock, nausea, and other negative sequelae. In 1876, the sequential use of nitrous oxide and oxygen to induce anesthesia, and ether or chloroform to maintain it, was introduced. In the mid-1880s, cocaine and its derivatives, such as novocaine, joined morphine as adjuncts to analgesic practice.

Throughout the twentieth century, the techniques for delivering and maintaining anesthesia were improved (Stoelting & Miller 2000). Beginning in the 1930s, a succession of drugs was introduced for the rapid induction of anesthesia: barbiturates such as thiopental (sodium pentothal), then benzodiazepines such as diazepam and midazolam began to substitute for barbiturates; and most recently propofol, a synthetic drug which also permits rapid recovery from anesthesia, with fewer lingering after-effects. Although inhaled anesthetics suppress voluntary responses to what are euphemistically called "surgical stimuli," curare was introduced in the 1940s to suppress involuntary, reflexive responses as well. It has since been replaced by drugs such as de-tubocurarine, vecuronium, and succinylcholine. A new generation of inhalational agents including halothane, enflurane, and isoflurane, which were less volatile than ether and less toxic than chloroform, came into use after World War II. More recently, intravenous opioid anesthetics such as fentanyl and sufentanyl, as well as new drugs to induce anesthesia, such as propofol, have emerged as alternatives to inhalational agents.

In current practice, general anesthesia begins with a pre-operative visit by the anesthetist. Immediately before the operation, the patient typically receives a benzodiazepine sedative, followed by an infusion of oxygen to displace nitrogen in the lungs. In *rapid sequence induction*, a short-acting drug such as thiopental or propofol is employed to induce initial unconsciousness before administering neuromuscular blockade to produce muscle relaxation (the anesthetic euphemism for total paralysis of the skeletal musculature). In an alternative procedure, called *inhalation* or *mask induction*, the patient may receive nitrous oxide and oxygen plus a volatile anesthetic; in this case, however, anesthesia develops more slowly. Subsequently, inhalants such as isoflurane, desflurane, or sevoflurane may be used to maintain anesthesia induced by other drugs. In *intravenous anesthesia*, the inhalants are replaced by drugs such as sufentanyl and propofol. In any event, because of the use of muscle relaxants, the patient must be respirated through intubation of the trachea. At the end of the operation, the patient may receive a drug such as neostygmine to reverse the neuromuscular blockade and permit the resumption of normal breathing, as well as morphine to help alleviate postoperative pain. Any residual inhaled anesthetic is removed by the patient's normal respiration.

The technique just described, known as *balanced anesthesia*, achieves the tripartite goals of general anesthesia: sedation, loss of consciousness (sometimes referred to as "narcosis" or "hypnosis"), and muscle relaxation. By contrast, various forms of *local* or *regional anesthesia* can be achieved by injection of local anesthetics such as lidocaine into

the subarachnoid (*spinal anesthesia*) or epidural (*epidural anesthesia*) spaces of the spinal cord, or the peripheral nerves supplying some body part (*nerve block*). In such procedures, adequate anesthesia is defined more narrowly as a loss of tactile sensation, and there is no loss of consciousness. In *conscious sedation*, local or regional anesthetics are combined with benzodiazepine sedatives: again, there is no general loss of consciousness, though the use of benzodiazepines will likely render the patient amnesic for the procedure. In *hypesthesia*, subclinical doses of general anesthetics are administered to nonpatient volunteers for studies of learning and memory (Andrade 1996).

Mechanisms of Anesthesia

Although modern scientific medicine generally disdains "empirical" treatments that are known to be efficacious, even though their scientific bases are not known, the mechanisms underlying general anesthesia remain a matter of considerable mystery. As a first pass, it seems plausible that general anesthetics reversibly disrupt neural activity by inhibiting either neural excitability or synaptic activity. Beyond that, things get murky.

To complicate things further, the various classes of anesthetic agents appear to have somewhat different mechanisms of action (Stoelting & Miller 2000). For example, many intravenous "hypnotic" drugs – including propofol, barbiturates such as thiopental, and benzodiazepines such as diazepam – appear to interact with gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, to increase the time that chloride ion channels are open, resulting in a hyperpolarization of cell membranes. However, ketamine, another intravenous anesthetic, interacts with excitatory N-methyl-D-aspartate (NMDA) receptors instead. Natural and synthetic opioid anesthetics such as fentanyl, of course, act on opioid receptors, inhibiting presynaptic release of neurotransmitters such as acetylcholine and substance P. However, even in high doses these drugs do not, by themselves, induce loss of consciousness. For this purpose, they are often combined with nitrous oxide and oxygen. Nitrous oxide, for its part, has effects on NMDA receptors similar to those of ketamine. Current evidence is broadly consistent with anesthetic action on both synaptic excitation and inhibition, with the contribution of each process varying from agent to agent.

The molecular and cellular mechanisms by which inhaled anesthetics such as isoflurane achieve their effects have been the subject of intense investigation and debate (Franks & Lieb 1994). According to the Myer-Overton rule known since the late nineteenth century, there is a strong correlation between the potency of an anesthetic gas and its solubility in lipids, suggesting that the expansion of nerve cell membranes effectively might close the ion channels by which sodium enters the cell to induce an action potential. It is now believed that the inhalants bind directly to specific pockets of relevant proteins rather than altering the lipid bilayer itself. In this way, they create a dynamic block of channels involved in synaptic excitation; some anesthetics also intensify synaptic inhibition. Although the general view is that anesthetics act on the postsynaptic side, there are some indications that they inhibit presynaptic neurotransmitter release as well.

The concept of balanced anesthesia implies that there are likely to be a number of separate mechanisms working together to produce analgesia (lack of pain), a sleep-like loss of consciousness (sometimes referred to as "hypnosis"), immobility (voluntary responses to surgical stimuli, as opposed to the spinal reflexes suppressed by muscle relaxants such as vecuronium), and amnesia (lack of memory for surgical events). According to one pro-

posal, inhalants such as isoflurane, which induce both immobility and amnesia, achieve these effects by different routes: immobility by acting on GABA receptors in the spinal cord, and amnesia by suppressing activity in the hippocampus.

As it happens, the specific proteins affected by inhaled anesthetics are receptors for GABA, among other neurotransmitters. Thus, the inhaled anesthetics may share a mechanism with the intravenous anesthetics after all. Along the same lines, the inhaled anesthetics share some pharmacological properties, such as tolerance, withdrawal, and cross-tolerance, with alcohol and sedative hypnotics such as barbiturates. However, there are now several anesthetic agents that violate the Meyer-Overton rule, and it is known that some gases can bind to the proteins implicated in anesthesia yet not cause anesthesia. Although much attention has focused on GABA, Hans Flohr has implicated NMDA instead (Flohr 2000). Both nitrous oxide and ketamine act as antagonists on NMDA receptors, blocking glutamate, an excitatory neurotransmitter – as does xenon, a newly developed anesthetic. Even if the intravenous anesthetics share a final common pathway with some inhaled anesthetics, other inhalants may achieve the same effects by rather different means.

Some theorists have sought to solve the mystery of anesthesia by invoking another mystery, namely quantum theory. Roger Penrose, a British mathematical physicist, and Stuart Hameroff, an American anesthesiologist, have famously speculated that consciousness is a product of certain processes described by quantum theory (Penrose 1994; Hameroff 1998). Briefly, quantum coherence (by which individual particles are unified into a wave function) produces a unified conscious self; non-local entanglement (which connects separate particles) is responsible for associative memory; quantum superposition (by which particles simultaneously exist in two or more states) produces alternative unconscious mental representations; and the collapse of the wave function (by which particles attain a definite state) brings one of these alternative mental states into conscious awareness. Within the context of this theory, Hameroff has further proposed that these processes take place in microtubules – proteins found in the walls of neurons that are shaped like hollow tubes.

Although the conventional view is that microtubules serve a structural function, supporting the structure of the cell, it is also true that they are built out of proteins – and certain proteins are known to be the site of anesthetic activity. Penrose and Hameroff contend that consciousness is actually a product of processes occurring in this microtubular cytoskeleton, which are in turn magnified by the neuron itself. In this view, anesthetics exert their effects on the specific proteins that make up these microtubules, disrupting the "quantum coherence" and thus the conscious awareness that it generates. As opposed to conventional theories of anesthesia, which focus on processes operating at the synapse, the Hameroff–Penrose theory shifts attention to processes operating inside the neural cell itself. The Penrose–Hameroff theory of both consciousness and anesthesia has attracted a great deal of interest, but at this stage it remains highly speculative, and has been criticized on both logical and empirical grounds (Grush & Churchland 1995).

Anesthesia and Awareness

Clinically, the success of general anesthesia is marked by three criteria:

- the patient's lack of response to intraoperative stimulation during the surgical procedure itself;

- upon awakening, the patient reports no awareness of pain during the procedure;
- nor does the patient report any memories of other surgical events.

Information relevant to these issues is typically gleaned from a brief post-operative interview in which the patient is asked such questions as "What was the last thing you remember before you went to sleep? What is the first thing you remember after you woke up? Can you remember anything in between these two periods? Did you dream during your operation?" Evaluated in these terms, anesthesia is almost always successful. Nevertheless, the use of muscle relaxants in balanced anesthesia makes it possible to perform surgery under lighter doses of anesthetic agents – increasing the risk of intraoperative awareness and postoperative recall at the same time as they decrease the risk of anesthetic morbidity. It was also recognized early on that the use of muscle relaxants increased the risks further, by preventing inadequately anesthetized patients from communicating their intraoperative awareness to the surgical team – a situation reminiscent of Harlan Ellison's science-fiction classic, *I Have No Mouth and I Must Scream* (1967).

Nevertheless, the incidence of anesthetic awareness is extremely low, with recent estimates of surgical awareness hovering around 0.2 percent of general surgical cases (Jones & Aggarwal 2001). A "closed case" analysis of 5,480 malpractice claims against anesthesiologists from 1970 to 1999 found only 22 cases of alleged intraoperative awareness and another 78 cases of postoperative recall. Occasionally, the incident is so serious as to result in post-traumatic stress disorder; but more commonly, the patient is left with only vague – and nondistressing – memories of intraoperative events. In general surgery, intraoperative awareness and postoperative recall are usually attributable to light anesthesia, machine malfunction, errors of anesthetic technique, and increased anesthetic requirements – for example, on the part of patients who are obese or abuse alcohol or drugs. The incidence of surgical recall arises in special circumstances, such as trauma, cardiac, or obstetrical surgery, where cardiovascular circumstances dictate lighter planes of anesthesia. Even then, the incidence of surgical recall is remarkably low – in part because even in the absence of anesthesia, the benzodiazepines often used for sedation are themselves amnesic agents (Polster 1993). In fact, modern anesthetic practice may underestimate the incidence of *intraoperative awareness* by interfering with *postoperative memory*. That is to say, an inadequately anesthetized patient may be aware of surgical events at the time they occur, but be unable to remember them later because of sedative-induced anterograde amnesia.

However low, the possibility of surgical awareness means that, in addition to monitoring various aspects of vital function during the operation, the anesthetist must also monitor the patient's state of consciousness, or *anesthetic depth* (Ghoneim 2001a). This task would be made easier if psychology and cognitive science could reach consensus on the neural or behavioral correlates of consciousness. In the absence of such criteria, anesthesiologists have often been forced to improvise. One set of standards simply relies on measures of anesthetic potency. Research has determined the *minimum alveolar concentration* (MAC) of inhalant which prevents movement in response to surgical stimulation in 50 percent of patients; *MAC-aware* is the concentration required to eliminate awareness of the stimulation. As a rule, MAC-aware is roughly half of MAC, suggesting that some of the movement in response to surgical stimulation is mediated by subcortical structures, and does not necessarily reflect conscious awareness. Similar standards for adequate anesthesia, based on blood plasma levels, have been worked out for intravenous drugs such as propofol.

It should be noted that the operational definition of MAC-aware means that 50 percent

of patients will be aware of surgical events despite the presence of anesthetic – although a dose amounting to about 1.3 MAC does seem to do the trick. Nevertheless, it is important to supplement knowledge of dose-response levels with more direct evaluations of the patient's conscious awareness. Unfortunately, many obvious clinical signs of consciousness – such as talking or muscle movement in response to surgical stimulation are obviated by the use of muscle relaxants. Accordingly, some anesthesiologists rely on presumed autonomic signs of consciousness, such as the *PRST score* based on the patient's blood pressure, heart rate, sweating, and secretion of tears.

In modern practice, most methods for monitoring the depth of anesthesia involve the central nervous system. Analyses of the EEG power spectrum (derived by a fast Fourier transform of the raw EEG signal) show that anesthetized patients typically have a median EEG frequency of 2–3 Hz or less, with "spectral edge frequencies," at the very high end of the distribution, within or below the range of alpha activity (8–12 Hz). Another derivative of the raw EEG is provided by bispectral analysis, which employs a complicated set of transformations to yield a *bispectral index* (BIS) that ranges from close to 100 in subjects who are normally awake, to values well under 60 in patients who are adequately anesthetized. Another common monitoring technique employs event-related potentials (ERPs, also known as evoked potentials, or EPs) elicited in the EEG by weak somatosensory, auditory, or even visual stimulation. Adequate anesthesia reduces the amplitude of the various peaks and troughs in the ERP, as well as the latency of various components representing brainstem response and early and late cortical responses. Of course, the late "cognitive" components of the ERP would be expected to disappear entirely during adequate anesthesia. An *AEP index* of consciousness reflects the degree to which three "midlatency" components of the auditory ERP are delayed with respect to their normal occurrence between 20 and 45 milliseconds after the stimulus.

Although most physiological indices of anesthetic depth have been validated against such criteria as movement in response to painful surgical stimulation, they have also been compared to various aspects of memory performance (Kerssens & Sebel 2001). In one study, a 0.2 percent end-tidal concentration (a measure related to MAC) of isoflurane produced a substantial impairment of performance on a continuous recognition test even over retention intervals as short as 8 seconds, while a 0.4 percent end-tidal concentration reduced recognition after 32 seconds to zero. Another study showed similar effects for low and high doses of propofol. In a study comparing midazolam, isoflurane, alfentanyl, and propofol, a 50 percent reduction in recall was associated with an average BIS score of 86, while an average BIS of 64 yielded reductions of 95 percent.

Of course, the simple fact that anesthesia impairs recall does not mean that anesthetized patients lack on-line awareness of what is going on around them. In principle, at least, they could experience an anterograde amnesia for surgical events similar to that which occurs in conscious sedation. In the absence of a reliable and valid physiological index of conscious awareness – something that is not likely to be available any time soon – what is needed is some kind of direct behavioral measure of awareness, such as the patient's self-report. In balanced anesthesia, of course, such reports are precluded by the use of muscle relaxants. But a variant on balanced anesthesia known as the *isolated forearm technique* (IFT) actually permits surgical patients to directly report their level of awareness in response to commands and queries (Russell 1989). Because muscle relaxants tend to bind relatively quickly to receptors in the skeletal musculature, if the flow of blood is temporarily restricted to one forearm by means of a tourniquet, the muscles in that part of the body will not be paralyzed.

And therefore, the patient can respond to the anesthetist's instruction to squeeze his or her hand, or raise their fingers – that is, if they are aware of the command in the first place.

Interestingly, response to the IFT is not highly correlated with ostensible clinical signs of consciousness. Nor does it predict postoperative recollection of intraoperative events. In one study, more than 40 percent of patients receiving general anesthesia for caesarian section responded positively to commands; yet only about 2 percent had even fragmentary recollections of the procedure. On the assumption that a patient who responds discriminatively to verbal commands is clearly conscious to some extent, the IFT indicates that intraoperative awareness is somewhat greater than has previously been believed. However, discriminative behavior also occurs in the absence of perceptual awareness, as in cases of "subliminal" perception, masked priming, and blindsight (see Merikle, chapter 40; Weiskrantz, chapter 13). Estimates of intraoperative awareness may indeed be suppressed by an anterograde amnesia, which effectively prevents patients from remembering, and thus reporting, any awareness that they experienced during surgery.

Unconscious Processing during Anesthesia

While adequate general anesthesia abolishes conscious recollection of surgical events by definition, it is possible that unconscious (or, for that matter, conscious) intraoperative perception may lead to unconscious postoperative memory that influences the patient's subsequent experience, thought, and action outside of phenomenal awareness. Although clinical lore within anesthesiology includes the "fat lady syndrome," in which an overweight patient's postoperative dislike of her surgeon is traced to unkind remarks he made about her body while she was anesthetized, documented cases are hard to find. In the late 1950s and early 1960s David Cheek, a Los Angeles physician and hypnotherapist, described a number of patients who, when hypnotized, remembered meaningful sounds that occurred in the operating room – particularly negative remarks. Cheek claimed to have corroborated these reports, and attributed unexpectedly poor postoperative outcomes to unconscious memories of untoward surgical events. Unfortunately, the interview method he employed, hypnotic "ideomotor signaling," is highly susceptible to experimenter bias, and information that would corroborate such memories is not always available. Accordingly, the possibility cannot be excluded that patients' postoperative "memories," recovered through this technique, are confabulations.

Despite these methodological problems, Cheek's suggestion was subsequently supported by Bernard Levinson, who as an experiment staged a bogus crisis during surgery. After the anesthesia had been established (with ether), the anesthesiologist, following a script, asked the surgeon to stop because the patient's lips were turning blue. After announcing that he was going to give oxygen, and making appropriate sounds around the respirator, he informed the surgeon that he could carry on as before. One month later, Levinson hypnotized each of the patients – all of whom had been selected for high hypnotizability and ability to experience hypnotic age regression – and took them back to the time of their operation. Levinson reported that four of the ten patients had verbatim memory for the incident, while another four became agitated and anxious; the remaining two patients seemed reluctant to relive the experience. Levinson's provocative experiment suggested that surgical events could be perceived by at least some anesthetized patients, and preserved in memory – even if the memories were ordinarily unconscious, and accessible only under hypnosis.

Despite Levinson's report, unconscious perception during general anesthesia remained largely unexplored territory until the matter was revived by Henry Bennett. Inspired by the apparent success of Cheek's "ideomotor signaling" technique for revealing unconscious memories, Bennett gave anesthetized surgical patients a tape-recorded suggestion that, when interviewed postoperatively, they would perform a specific behavioral response, such as lifting their index finger or pulling on their ears. Although no patient reported any conscious recollection of the suggestion, approximately 80 percent of the patients responded appropriately to the experimenter's cue. Bennett, following Cheek, suggested that unconscious memories were more likely to be revealed with nonverbal than with verbal responses.

At about the same time, Evans and Richardson reported that intraoperative suggestions, delivered during general anesthesia, led to improved patient outcome on a number of variables, including a significantly shorter postoperative hospital stay. Again, the patients had no conscious recollection of receiving these suggestions. Although this study was not concerned with memory per se, the apparent effects of suggestions on post-surgical recovery certainly implied that the suggestions themselves had been processed, if unconsciously, at the time they occurred.

As it happens, subsequent studies have failed to confirm the findings of either Bennett et al. or Evans and Richardson. And more recently, a double-blind study inspired by Levinson's report, in which nonpatient volunteers received subanesthetic concentrations of either desflurane or propofol, failed to obtain any evidence of memory for a staged crisis. Nevertheless, these pioneering studies, combined with an increasing interest in consciousness and unconscious processing within the wider field of psychology and cognitive science, stimulated a revival of interest in questions of awareness, perception, and memory during and after surgical anesthesia, which have been carried out with progressively improved paradigms.

Of particular importance to this revival was the articulation, in the 1980s, of the distinction between two different expressions of episodic memory – explicit and implicit (Schacter 1987). Explicit memory is conscious recollection, as exemplified by the individual's ability to recall or recognize some past event. Implicit memory, by contrast, refers to any change in experience, thought, or action that is attributable to a past event – for example, savings in relearning or priming effects. From the 1960s through the 1980s, a growing body of evidence indicated that explicit and implicit memory were dissociable. For example, amnesic patients show priming effects even though they cannot remember the priming events themselves; and they can learn new cognitive and motor skills, even though they do not remember the learning experience. Similarly, normal subjects show savings in relearning material that they can neither recall nor recognize as having been learned before. And, again in normal subjects, priming is relatively unaffected by many experimental manipulations that have profound effects on recall and recognition. In a very real sense, then, implicit memory is unconscious memory, occurring in the absence of, or at least independent of, the individual's conscious recollection of the past (see also Kihlstrom, Dorfman, & Park, chapter 41). Accordingly, the experimental paradigms developed for studying implicit memory in amnesic patients and normal subjects were soon adapted to the question of unconscious processing of intraoperative events in anesthesia (Kihlstrom 1993; Kihlstrom & Schacter 1990).

In our first study, patients receiving isoflurane anesthesia for elective surgery were played, through earphones, an auditory list of 15 paired associates consisting of a familiar word as the cue and its closest semantic associate as the target – for example, *ocean–water*

(Kihlstrom et al. 1990). The stimulus tape was presented continuously from the first incision to the last stitch, for an average of 67 repetitions over an average of 50 minutes. In the recovery room, the patients were read the cue terms from the stimulus list, as well as a closely matched set of cues from a control list of paired associates, and asked to recall the word with which each cue had been paired on the list read during surgery: this constituted the test of explicit memory. For the test of implicit memory, they were read the same cues again, and asked simply to respond with the first word that came to mind. The subjects recalled no more target words from the presented list than from a control list, thus showing that they had very poor explicit memory for the experience. On the free-association test, however, they were more likely to produce the targeted response from the presented list, compared to control targets, thus displaying a priming effect. Compared to explicit memory, which was grossly impaired (as would be expected with adequate anesthesia), implicit memory was relatively spared.

Despite this early success, subsequent studies employing similar paradigms produced a mix of positive and negative results. For example, we precisely replicated the procedure described above with another group of patients receiving sufentanyl, and found that explicit and implicit memory were equally impaired (Cork, Kihlstrom, & Schacter 1992). Although the two studies, taken together, suggested the interesting hypothesis that different anesthetic agents might have different effects on implicit memory, a more parsimonious conclusion might have been that the isoflurane effects were spurious. In a debate at the Second International Symposium on Memory and Awareness in Anesthesia, held in 1992, experimental psychologists and anesthesiologists agreed that memory for events during anesthesia had not yet been convincingly demonstrated. Over the next few years, however, the literature began to settle, so that a comprehensive quantitative review of 44 studies could conclude that adequately anesthetized patients can, indeed, show postoperative memory for unconsciously processed intraoperative events (see also Bonebakker et al. 1996; Merikle & Daneman 1996; Cork, Couture, & Kihlstrom 1997).

The Limits of Implicit Memory in Anesthesia

Although the more recent literature continues to contain a mix of positive and negative results, there are simply too many positive findings to be ignored (Ghoneim 2001b). At the same time, the literature contains enough negative studies, and other anomalous results, to warrant further investigation. For example, Merikle and Daneman concluded that the evidence for unconscious processing during general anesthesia was not limited to "indirect" measures of implicit memory, and extended to "direct" measures of explicit memory as well (Merikle & Daneman 1996). This is a surprising statement, given that adequately anesthetized patients lack conscious recollection by definition. However, these authors included in their survey only the few tests of explicit memory that encouraged guessing, and excluded the many studies that discouraged guessing. While guessing yields a more exhaustive measure of conscious recollection, it is also true that guessing can be biased, unconsciously, by priming itself. Therefore, it is likely that some of the "explicit" memory identified by Merikle and Daneman is, in fact, contaminated by implicit memory. In support of this idea, a study employing the "process dissociation" procedure confirmed that postoperative memory was confined to automatic priming effects, and did not involve conscious recollection (Lubke et al. 1999).

A persisting issue is whether postoperative implicit memory might be an artifact of fluctuations in anesthetic depth which occur naturally during surgery. In the study just described, even implicit memory varied as a function of the patient's level of anesthesia. Patients showed more priming for words presented at BIS levels above 60, and no priming for items presented at BIS levels below 40. A subsequent study from the same group, which confined stimulus presentation to BIS levels ranging from 40 to 60, yielded no evidence of implicit memory (Kerssens, Ouchi, & Sebel 2005). Although implicit memory may be spared at a depth of anesthesia sufficient to abolish explicit memory, implicit memory itself may be abolished at deeper levels. Still, it is not clear that the abolition of implicit memory is a benefit worth the risks of maintaining very deep levels of anesthesia throughout surgery.

Explicit and implicit memory are also dissociated in *conscious sedation*, an anesthetic technique that is increasingly popular in outpatient surgery. In conscious sedation, the patient receives medication for analgesia and sedation, and perhaps regional anesthesia, but remains conscious throughout the procedure. It is well known that high doses of sedative drugs have amnesic effects on their own, such that patients often have poor memory for events that occurred during the procedure. As it happens, sedative amnesia produced by drugs such as diazepam or propofol also dissociates explicit and implicit memory (Polster 1993; Cork, Heaton, & Kihlstrom 1996). As with general anesthesia, studies employing the process-dissociation procedure confirm that sedative amnesia impairs conscious recollection, but spares automatic priming effects.

Most work on implicit memory employs tests of *repetition priming*, such as stem- or fragment-completion, in which the target item recapitulates, in whole or in part, the prime itself – for example, when the word *ashtray* primes completion of the stem *ash-*. Repetition priming can be mediated by a perception-based representation of the prime, which holds information about the physical properties of the item, but not about its meaning. But there are other forms of priming, such as semantic priming, where the relationship between prime and target is based on "deeper" processing of the prime – for example, when the prime *cigarette* primes completion of the stem *ash-* with *-tray* as opposed to *-can*. Semantic priming requires more than physical similarity between prime and target, and must be mediated by a meaning-based representation of the prime. The distinction between repetition and semantic priming is sometimes subtle. For example, in the isoflurane study described earlier, the paired associates presented as primes were linked by meaning, but because both elements of the pair were presented at the time of study, the priming effect observed could have been mediated by a perception-based representation, rather than a meaning-based one. The point is that implicit memory following surgical anesthesia is fairly well established when it comes to repetition priming, but conclusions about semantic priming are much less secure. Fewer studies have employed semantic priming paradigms, and relatively few of these studies have yielded unambiguously positive results (Ghoneim 2001b). If semantic priming occurs at all following general anesthesia, it is most likely to occur for items presented at relatively light levels of anesthesia, as indicated by indices such as BIS. At deeper planes of anesthesia, implicit memory – if it occurs at all – is likely to be limited to repetition priming.

The distinction between perception-based and meaning-based priming may have implications for the use of intraoperative suggestions to improve post-surgical outcome. If implicit memory following anesthesia is limited to repetition priming, implying that the anesthetized patient's state of consciousness does not permit semantic analysis of the intraoperative message, it is hard to see how such suggestions could have any effects at all. In

fact, a comparative study found that intraoperative suggestions had no more effect on post-operative pain than did *pre*-operative suggestions of the same sort – or, for that matter, the pre- and intraoperative reading of short stories. Intraoperative suggestions will do no harm, and patients may derive some "placebo" benefit from the simple knowledge that they are receiving them during surgery. To the extent that intraoperative suggestions do some good, the limitations on information processing during anesthesia may mean that any positive effects are more likely to be mediated by their prosody, and other physical features, than by their meaning: a soothing voice may be more important that what the voice says. If anesthesiologists want patients to respond to the specific semantic content of therapeutic messages, such messages are probably better delivered while patients are awake, during the pre-operative visit that is already established as the standard of care.

Implicit Memory or Implicit Perception?

Priming effects are evidence of implicit memory, but they can also serve as evidence of implicit perception – a term coined to refer to the effect of an event on experience, thought, and action, that is attributable to a stimulus event, in the absence of (or independent of) conscious perception of that event (Kihlstrom, Barnhardt, & Tataryn 1992). Implicit perception is exemplified by "subliminal" perception of degraded stimuli, as well as neurological syndromes such as "blindsight" and neglect (see Merikle, chapter 40; Weiskrantz, chapter 13). In general anesthesia, the patients are presumably unaware of the priming events at the time they occurred. For that reason, evidence of implicit memory following general anesthesia is also evidence of implicit perception.

See also 7 Normal and abnormal states of consciousness; 41 Implicit and explicit memory and learning; 46 Global disorders of consciousness.

Further Readings

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