

No Evidence of Classical Conditioning of Electrodermal Responses during Anesthesia

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Classical conditioning of skin conductance responses was studied in 26 healthy volunteers and 31 patients who received general anesthesia (0.5 MAC isoflurane-70% nitrous oxide) for minor gynecologic surgery to determine whether there was autonomic evidence of new learning during anesthesia. In the conditioning phase, a loud noise was paired with a target word (conditioned stimulus [CS]). Conditioning was established if the CS produced conditioned responses, *i.e.*, greater skin conductance responses than other, "filler words." In the subsequent elicitation phase, we investigated whether it was possible to elicit similar conditioned responses to the CS when it was presented without noise about 3 h later. Conditioning was established in the control group, who received no anesthesia. There were differences in response magnitudes of 0.32 and 0.27 μ siemen between responses to the CS and filler words, $P < 0.001$. In contrast, there was no evidence that conditioning was established during anesthesia. In the elicitation phase, conditioned responses to the CS could be elicited in volunteers; *i.e.*, response magnitudes were greater for the CS than other words (during the first two blocks of trials), with differences of 0.19 to 0.48 μ siemen, $P < 0.05$ to $P < 0.001$. In contrast, responses to the CS could not be elicited in patients after anesthesia. There was also no evidence of recognition of words that were presented during anesthesia in patients, but recognition was manifested in volunteers. Thus, in contrast to our previous demonstration of conditioning in subjects who received 30% nitrous oxide in oxygen, there was no evidence of conditioning in anesthetized patients. (Key words: Conditioning; classical conditioning. Memory, recognition; anesthesia. Skin conductance: electrodermal response; galvanic skin response.)

CLASSICAL OR PAVLOVIAN CONDITIONING¹ is recognized as a very basic type of learning that involves involuntary responses, such as emotions or physical reflexes.² This type of learning is called associative learning because of the formation of associations between stimuli or between stimuli and responses. For example, Pavlov began by presenting his dogs with a neutral stimulus, such as a tone, followed shortly by food. The dogs salivated in response to the dry food in the mouth. As the pairing of the tone and the food continued, the tone began to elicit salivation by itself, even when there was no food. In Pavlov's terms, the food in the mouth is the *unconditioned stimulus* (UCS), which elicits the *unconditioned response*

(UCR) of salivation. The word "unconditioned" indicates that the connection between this particular stimulus and response does not have to be learned. In contrast, the new stimulus that ultimately elicits salivation is called the *conditioned stimulus* (CS), and the animal's salivation response to it is called the *conditioned response* (CR). The word "conditioned" indicates that this new response is learned through an association (in this case an association between the tone and the food). Thus, the end result of a classical conditioning experiment is that a CS produces a response similar to the one produced by an UCS.

Patients suffering from organic amnesias have severe impairment of the ability to remember new events, yet some forms of new learning, grouped together as implicit memory, show little impairment.³ (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.) One example of implicit memory is classical conditioning. Even though these patients will deny any memory of the experiment, classical conditioning can be acquired and retained over long periods.⁴ In a previous study,⁵ we have shown that inhalation of 30% nitrous oxide in humans modified but did not abolish establishment and elicitation of conditioned responses to stimulus words, despite impairment of verbal recall.⁶ (Recall is a measure of explicit memory which requires conscious recollection by subjects.) We have also shown⁷ that other types of implicit memory, specifically priming and recall of behavioral suggestions, were possible during general anesthesia.

In the present study, we investigated whether it was possible to establish a CR during anesthesia and to elicit it afterward. If so, this would provide evidence of learning and responsiveness during anesthesia. The UCS was a loud noise that innately evoked a skin conductance response, the UCR, in the conscious subject. The noise was paired with a word (target word) as the CS (fig. 1). Conditioning was manifested if that target word came to elicit larger skin conductance responses than other, unrelated (filler) words.

Materials and Methods

PARTICIPANTS

Forty-four patients (all women) and a control group of twenty-six volunteers (24 women and 2 men) were re-

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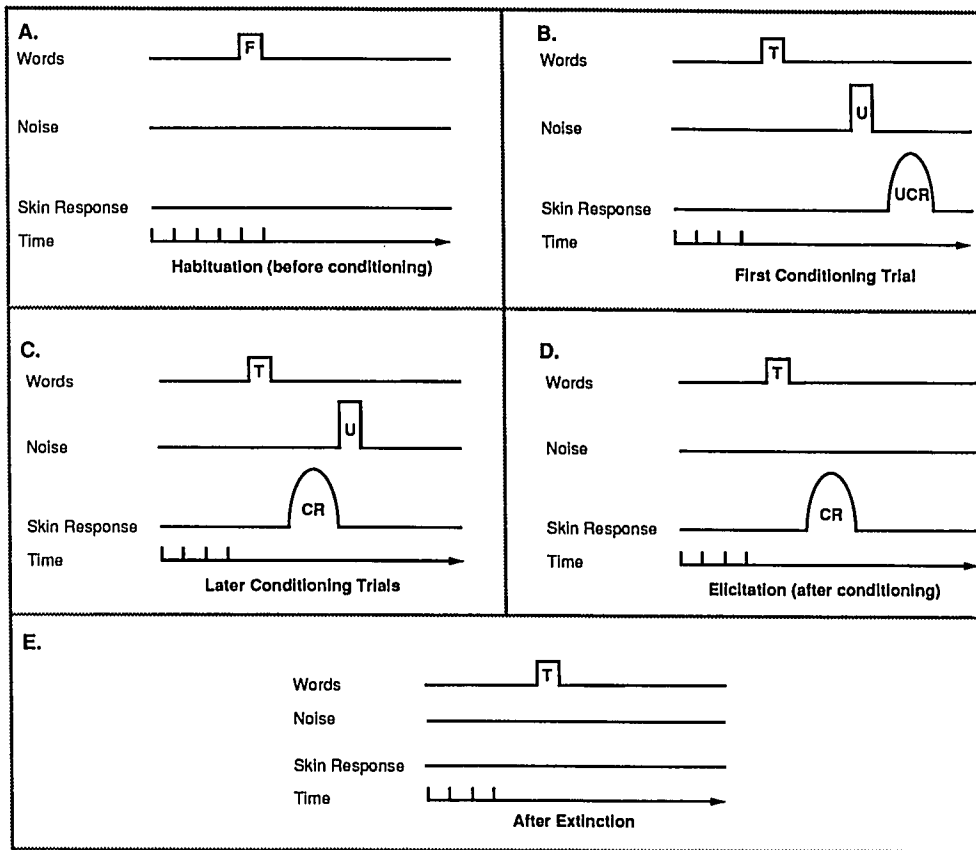


FIG. 1. The relationship of events in the classical conditioning procedure used. Upward deflection of the trace indicates stimulus or response onset; downward deflection indicates offset. F = filler or neutral word; T = target word or conditioned stimulus; U = unconditioned stimulus; UCR = unconditioned response; CR = conditioned response. The tick marks on the time scale and the durations of words, noises, and skin conductance responses are approximate. *A*: Habituation (before conditioning): after presentation of several words to attenuate any response to words in general, words that are neutral in pleasantness elicit no skin conductance responses. *B*: First conditioning trial: a specific target word (in this study "light") is paired with noise (the unconditioned stimulus). The latter elicits the unconditioned response, *i.e.*, a change in skin conductance. *C*: Later conditioning trials: repeated pairing of the noise with the target word elicits changes in skin conductance in response to the target word (as well as to the noise, which for the sake of simplicity is shown only in *B*). When the target word which at first (*B*) did not cause a change in skin conductance produces such a change, it functions as a conditioned stimulus and the change in skin conductance that it produces is a conditioned response. *D*: Elicitation (after conditioning): after a conditioned response has been established, presentation of the target word alone is sufficient to elicit a change in skin conductance. *E*: After extinction: after the target word has been presented repeatedly without the noise, it no longer produces a change in skin conductance, as was the case before conditioning.

cruited to participate in the study. The volunteers were recruited from advertisements in a local newspaper. The patients were scheduled to undergo minor gynecologic surgery in our ambulatory surgery center. Subjects were excluded if they had hearing or severe visual impairments; mental impairment or disease; diseases that might affect the autonomic nervous system; or any severe disease in general (ASA physical status 3–5); or if they were taking medication with autonomic properties that may affect the activity of the sweat glands. Several subjects were excluded in the initial part of the study: six because of problems with instruments, four because of changes in protocol, and three because of reluctance to be tested postoperatively.

PROCEDURES

Prior to participation, subjects read and signed a consent form that explained the study, which had been approved by the institutional review board. Subjects were told that they would hear a number of words interspersed with occasional loud noises. Subjects were tested individually in a quiet room (volunteers) or during anesthesia in the operating room (patients). The habituation and conditioning trials of the tape (see below) were played first to the volunteers. (The term "trials" refers to presentations of words, with or without noise on the tape, that related to different aspects of the conditioning paradigm.) In the case of patients, half of them were played a blank

tape for 10 min, followed by the habituation and conditioning tape (which took the same time); the other half had the sequence reversed. The allocation to a particular sequence was done randomly. This counterbalancing was done to control for the possibility that surgical stimuli of varying intensities from the initial part of the operation, compared to the later part, might affect skin conductance. These recordings were started 5 min after achieving and maintaining the desired anesthetic concentrations. The subsequent recordings of the elicitation/generalization trials and extinction trials, were played to the patients immediately before they left the ambulatory surgery center for home. These recordings were played to volunteers about 3 h after the first part of the tape.

STIMULI

A set of three words ("light/dark/line") was selected from word association norms.⁸ The word "light" was the stimulus or target word, "dark" was its most common response, and "line" was a word which sounded like it (*i.e.*, differed in only one phoneme) but did not occur as a response to it. These were used as the CS, semantic generalization word, and phonemic generalization word, respectively. We wanted to assess whether during anesthesia, words were processed for meaning or just as sounds. No two words in the remaining part of the list were closely related to one another associatively, semantically, or phonemically, and all words were neutral in pleasantness according to normative ratings.⁹

A list of trials was prepared for four successive phases of the assessment: habituation, conditioning, elicitation/generalization, and extinction (fig. 1). 1) The *habituation trials* involved presentation of eight filler words and were included to attenuate any responding to words in general. 2) The 30 *conditioning trials* consisted of 10 repetitions of the CS (followed by the UCS) interspersed with 20 filler words. There were from one to three filler words before each occurrence of the CS. 3) The *elicitation/generalization trials* consisted of four blocks of six trials each. Each block included one trial with the CS (without the UCS), one with the semantic generalization word, one with the phonemic generalization word, and three with other filler words (none used as filler words from the conditioning or habituation trials). 4) The *extinction trials* consisted of seven consecutively repeated presentations of the CS (without the UCS or other words) and were expected to attenuate any remaining CR.

The filler words were not closely related to any of the CS or generalization words but were comparable to these words in mean frequency and rated pleasantness.¹⁰ All the words were used in a previous experiment,⁵ were re-

corded on cassettes, and were played through headphones.

Within each phase, the interval between the onset of successive words varied from 12 to 15 s (averaging 13.5 s), except for trials during the conditioning phase in which the UCS was presented; similar intervals, *e.g.*, 10 to 16 s, have been used in prior studies.^{5,11} In trials involving UCS presentation, onset of the UCS occurred 10 s after onset of the CS and was followed 12 to 15 s later by the next word. The UCS, which was presented only during the conditioning phase, was a 1-s white noise amplified to 110 dB (0.0002 dyne/cm², calibrated at the position of the headphone). The words, which were recorded on a separate channel of the tape, were presented at normal but loud speaking volume.

MEASUREMENT OF SKIN CONDUCTANCE

The methodology for measuring skin conductance followed the recommendations of a committee studying publication standards for electrodermal measurements.¹² The same methods were used in a previous study⁵ and have been described in detail. Briefly, skin conductance recordings were obtained using silver-silver chloride electrodes and an electrode paste. A constant 0.5-V potential was applied across the two recording sites and a 1000-ohm series resistor, with the subject's conductance estimated from the voltage generated across the series resistor. Tonic level control circuitry (Wheatstone bridge) was used to increase the sensitivity of detection. The two electrodes were placed on the thenar and hypothenar eminences of the palm of the subject's nondominant hand. Testing was not begun until 10 min after application of the electrode paste. The signal, after amplification, was recorded on one channel of a multichannel Lafayette Datagraph Physiological Recording System (Lafayette Instrument Company, Lafayette, IN). In addition to time markers, event markers, indicating the time of onset of the words and the UCS, were automatically recorded on another channel. The research assistant observed the subjects and noted any movement artifacts on the tracing.

When recording skin conductance during the elicitation/generalization and extinction phases in the postoperative period in the first few patients, we noticed that responses to the words were almost absent. We thought that this might be due to fatigue or residual sedation, which was manifested when the patients were placed in a quiet room and isolated from the surrounding environment by the headphones. To increase the amplitude of the responses, we attempted to keep the subjects alert and awake by asking the first 12 patients to pronounce each word as they heard it, and asking the remaining 20

patients and all volunteers to raise the index finger of the dominant hand slightly each time they heard a word.

ANESTHESIA AND RECOVERY

The patients group received no premedication. The blood pressure cuff, intravenous cannula, oximeter pad, and nerve stimulator electrodes were placed on the arm that was not used for recording skin conductance. Anesthesia was induced with propofol (Diprivan), approximately 40 mg every 10 s until the patient failed to respond to commands (138 ± 42 mg, mean \pm SD). Anesthesia was maintained with 1 MAC isoflurane in nitrous oxide, *i.e.* 0.5% isoflurane (end-tidal) in nitrous oxide (70%) and oxygen. Atracurium was used for muscle relaxation. We avoided complete neuromuscular blockade in order to assess depth of anesthesia by spontaneous movement of the patient. If the baseline blood pressure or heart rate was exceeded by 30% or if the patient showed some movement, bolus doses of alfentanil 10 μ g/kg were given. In 8 patients at the end of surgery, residual muscle paralysis was antagonized by atropine (0.4 ± 0.1 mg) and edrophonium (36 ± 13 mg). These drugs were always administered after the end of the skin conductance recording for that phase of the experiment.

Morphine (16 patients) or non-opioid analgesics (14 patients) were administered during recovery from anesthesia for pain relief. Metoclopramide (6 patients) was administered as an antiemetic when needed.

EXPLICIT MEMORY TESTS

Before the postoperative skin conductance assessment was started, patients were asked whether they had heard anything while asleep, had dreamt or had any fantasies or other experiences while asleep, or could remember any sounds or words which were included in the recording? They were encouraged to guess. After the postoperative skin conductance assessment was completed, patients and volunteers were given a recognition test. Subjects were presented with 58 words ("long" recognition questionnaire), which included the words played during the habituation and conditioning trials. Subjects were asked to indicate whether or not each word had been presented during anesthesia (or during the first session, in the case of controls) and to rate their confidence in each answer on a three-point scale ("very sure," "likely," or "guess"). Lastly, they were given a sheet of paper containing the CS word and its semantic and phonemic generalization words, *i.e.*, "light," "dark," and "line," mixed with three other words used as a similar set in another experiment,⁵ *i.e.*, "slow," "fast," "slope" ("short" recognition questionnaire). Patients were told that some of the words had been followed by a loud noise and some

had not. They were asked to indicate for each word whether or not it had been followed by a loud noise and to rate their confidence on a three-point scale similar to the one used in the preceding recognition task. A schedule of the experimental procedures is shown in table 1.

SCORING

As is customary, skin conductance responses following onset of a word were scored separately for two time intervals, one shortly after the word and one later. Responses in the first and second intervals have been labelled "orienting responses" and "anticipatory responses".¹³ While the psychological significance of CRs in the two intervals is controversial,^{11,14-16} common interpretations are that CRs in the second interval reflect anticipation of the forthcoming UCS and CRs in the first interval are orienting responses to the CS, which during the course of conditioning come to reflect recognition of the signal value of the CS in predicting the UCS.

Orienting response magnitude and anticipatory response magnitude were defined as the largest conductance changes beginning within 1 to 4 s and 4 to 11 s after stimulus onset, respectively. When more than one response began in an interval, their combined magnitude was scored. Magnitudes were scored as zero for intervals not showing any response.

STATISTICAL ANALYSES

Magnitudes of orienting and anticipatory skin conductance responses were analyzed separately for patients and volunteers. The data were skewed because of numerous nonresponses, and the distribution assumption of normality for parametric tests was not satisfied, so nonparametric tests were used. The analyses of the conditioning phase compared responses to the CS and the immediately preceding filler word using Wilcoxon's signed rank test (one-tailed). Individual analyses were done for each of the ten presentations of the CS, and analyses were done averaging over all 10 presentations. Preliminary analyses of the elicitation/generalization phase showed that no generalization of CRs to semantic or phonemic generalization words occurred. Therefore, for clarity and max-

TABLE 1. Schedule of Experimental Procedures

Procedure	Time (min)
Consent and placement of skin electrodes	-20
Induction of anesthesia in patients	-15
Habituation and conditioning	0
Recovery from anesthesia in patients	
Elicitation/generalization and extinction	≈ 180
Recognition tests	≈ 190

imum sensitivity, the final analyses compared responses to the CS with mean responses to all other words combined. These analyses were done separately for each of the four blocks of trials, using Wilcoxon's signed rank test (one-tailed).

The percentage of words on the long recognition questionnaire that each subject indicated had been presented previously (for patients, during anesthesia), was calculated separately for words that had actually been presented during the habituation or conditioning phases (excluding the CS) and words that had not been presented. Separate analyses for patients and volunteers using paired *t* tests (one-tailed) were done to compare the differences between these percentages. On the short recognition questionnaire, the number of patients who correctly identified the CS as having been followed by noise and did not incorrectly identify more than one other word as having been followed by noise was determined. An exact computation using the binomial probability distribution was done to calculate the probability that this many patients or more would meet the specified criterion of performance due to chance alone. A similar computation was done for volunteers.

The ages of patients and volunteers were compared by *t* tests, as were their years of education.

Results

CHARACTERISTICS OF SUBJECTS

The patients were all in ASA Physical Status 1. None reported a history of awareness during anesthesia in the past. Their weight was 66.2 ± 14.8 kg. The ages of the patients and volunteers did not differ significantly, being 29.0 ± 6.8 yr and 24.9 ± 9.9 yr, respectively. The patients were less educated than the volunteers, with 12.8 ± 1.4 yr and 14.9 ± 2.2 yr of school, respectively, $P < 0.001$.

DURATIONS OF PROCEDURES

For the patients, the mean durations of anesthesia and surgery were 58 ± 20 min and 43 ± 20 min, respectively. The duration of the interval between the conditioning phase and the elicitation/generalization phase was 194 ± 67 min for the patients.

CONDITIONING

There was no evidence of conditioning during anesthesia in any patient. Only one patient showed a few erratic responses, the rest never responded at all. In contrast, the volunteers showed conditioning, *i.e.*, greater responses to the CS than to the preceding filler words. Table 2 shows results for each of the ten trials. Averaged over all

TABLE 2. Conditioning in Volunteers on Successive Trials of the Conditioning Phase

Trial	Difference of Responses to Conditioned Stimulus and Preceding Filler Word	
	Orienting Responses (μ Siemen)	Anticipatory Responses (μ Siemen)
1	-0.12	-0.02
2	-0.08	0.07
3	0.11	-0.06
4	0.53*	0.40
5	0.49*	0.22†
6	0.55‡	0.42*
7	0.48‡	0.39†
8	0.47*	0.57*
9	0.35*	0.35*
10	0.36‡	0.34*

Values are the mean magnitude of responses to the conditioned stimulus, minus the mean magnitude of responses to the preceding filler word. Establishment of the conditioned response is indicated by positive differences, *i.e.*, greater responses to the conditioned stimulus than to the filler word. Significance levels according to Wilcoxon's signed rank test (one-tailed) are indicated.

* $P < 0.01$.

† $P < 0.05$.

‡ $P < 0.001$.

trials, the mean orienting response magnitudes were 0.47μ siemen (The microsiemen is a unit of electrical conductance. It is 0.001 siemen. A siemen used to be called a mho and is the reciprocal of resistance in ohms) for the CS, compared to only 0.15μ siemen for the filler words, a conditioning effect (*i.e.*, difference) of 0.32μ siemen, $P < 0.001$. The corresponding anticipatory response magnitudes were 0.38μ siemen for the CS and 0.11μ siemen for the filler words, a conditioning effect of 0.27μ siemen, $P < 0.001$.

ELICITATION

Table 3 shows results of the elicitation/generalization phase. CRs could not be elicited in patients. In contrast, CRs could be elicited in volunteers: volunteers' orienting responses to the CS were greater in magnitude than their orienting responses to other words during the first and second of the four blocks of trials and their anticipatory responses to the CS were greater in magnitude than their anticipatory responses to other words during the first block of trials. Neither orienting nor anticipatory responses showed evidence of conditioning during the third and fourth blocks of trials. This was not surprising; it presumably reflected extinction of the CR following presentation of the CS unaccompanied by the noise.

RECOGNITION

The patients showed no recognition of words presented during anesthesia on the long recognition questionnaire.

TABLE 3. Elicitation of Conditioned Responses in Successive Blocks of Trials of the Elicitation/Generalization Phase

Block	Orienting Responses (μ Siemen)			Anticipatory Responses (μ Siemen)		
	Conditioned Stimulus	Other Words	Difference	Conditioned Stimulus	Other Words	Difference
Volunteers						
1	0.76	0.44	0.33*	0.25	0.07	0.19†
2	0.69	0.21	0.48‡	0.07	0.08	-0.01
3	0.29	0.17	0.13	0.04	0.11	-0.06
4	0.19	0.15	0.04	0.08	0.05	0.02
Patients						
1	0.15	0.28	-0.13	0.01	0.03	-0.02
2	0.06	0.08	-0.01	0.07	0.07	0.01
3	0.11	0.06	0.05	0.02	0.06	-0.03
4	0.05	0.07	-0.02	0.06	0.09	-0.03

Values are the mean magnitude of responses to the conditioned stimulus, the mean magnitude of responses to the five other words in each block of trials, and their difference. Elicitation of the conditioned response is indicated by positive differences, *i.e.*, greater responses to the conditioned stimulus than to other words. The result of subtracting the value for other words from the value for the conditioned stimulus

may vary by 0.01 from the indicated difference, due to rounding error. Significance levels according to Wilcoxon's signed rank test (one-tailed) are indicated.

* $P < 0.05$.

† $P < 0.01$.

‡ $P < 0.001$.

They "recognized" as having been presented during anesthesia (*i.e.*, selected) $32\% \pm 27\%$ of the words that had been presented during anesthesia and a similar percentage, $31\% \pm 25\%$, of the words that had not been presented, $P = NS$. Volunteers, in contrast, showed recognition. They recognized (*i.e.*, selected) $70\% \pm 16\%$ of the words that had been presented during the habituation or conditioning phases, compared to only $32\% \pm 18\%$ of the words that had not been presented, $P < 0.001$.

The patients also showed no recognition on the short recognition questionnaire. Six patients (19%) identified the CS as having been followed by noise and did not incorrectly identify more than one other word as having been followed by noise, but this many patients or more would have been expected to meet the specified criterion of performance due to chance alone, $P > 0.05$. Volunteers, in contrast, showed recognition. Sixteen volunteers (62%) met the foregoing criterion and the probability of this many or more meeting the criterion due to chance was negligible, $P < 0.001$. Of these volunteers, 13 identified the CS as having been followed by noise and did not incorrectly identify any other word as having been followed by noise. None of the patients was this accurate.

Discussion

The amount of sweating, controlled by the sympathetic branch of the autonomic nervous system, largely determines the electrical conductance of the skin. Generally, all anesthetics depress to a variable degree the resting activity in the sudomotor system.¹⁷⁻²⁰ Some anecdotal reports have suggested changes in tonic levels of skin conductance and/or responses evoked by endotracheal intubation and surgical manipulations, while others have

not.^{21,22} § Responses to auditory stimuli have sometimes been reported and sometimes not.^{22,*} Common to these anecdotal reports has been lack of standardization of anesthetic regimen, level of anesthesia, and method of measurement of skin conductance.

Using anesthetized rats, Weinberger *et al.*²³ demonstrated that epinephrine enabled the learning of a Pavlovian-conditioned fear response, despite adequate barbiturate and chloral hydrate anesthesia. The investigators used electric shock as the UCS and a noise as the CS during anesthesia. Although behavioral and physiological responses to the CS and UCS were absent during anesthesia, a post-anesthesia test showed that learning had occurred; *i.e.*, the CS had become an effective conditioned suppressor of water drinking. In a more recent study,²⁴ there was retention of a CS-UCS association learned under ketamine anesthesia in rats, although the level of anesthesia could not be ascertained.

Several lines of investigation have suggested that electrodermal responding and conditioning can occur even in the absence of conscious awareness of the stimuli-eliciting responses. Tranel and Damasio²⁵ studied patients with prosopagnosia, the inability to recognize visually the faces of familiar persons. Two such patients generated frequent and large electrodermal skin conductance responses to faces of persons they had previously known but were now unable to recognize. In a more recent study,²⁶ an amnesic patient showed electrodermal evidence of learning a word list, although learning was not evident in explicit recall or recognition tests. These results suggested that an early step of the physiological process of recognition or learning was still taking place in these

§ Ruder CB, Weinreich AI: Arousal during general anesthesia. *Anesthesiology Review* 29:29-32, 1976.

patients, without their awareness but with an autonomic index. Nitrous oxide in a 30% concentration appeared to prevent new CRs from being established during its inhalation, but learning evidently took place, since anticipatory CRs could be elicited after nitrous oxide inhalation had ceased.⁵ Goldmann and Levey²² claimed that their patients showed distinct skin conductance responses when the name of the leader of the miners' union, which was on strike at that time, was mentioned during anesthesia, although other information more personal to the patients failed to evoke responses.

In the present study, although conditioning occurred in awake volunteers, it was absent in patients who were anesthetized and there was no autonomic evidence of learning during anesthesia, despite evidence that women acquire classically conditioned electrodermal responses more readily than men.²⁷⁻²⁹ We did not find evidence for either explicit or implicit memory during anesthesia using the anesthetic agents specified above. It could be argued that multiple conditioning sessions may be needed to induce a CR during anesthesia. Although multiple consecutive conditioning sessions under anesthesia are not feasible in humans, they can be readily accomplished in laboratory animals. Parallel studies in humans and animals using the associative learning paradigm need to be done. These studies would determine the concentrations of the different anesthetic agents which prevent learning and/or recall. They would also investigate factors that may shift the dose-response curves for learning and memory during anesthesia. The hypothesis that implicit memory may resist the impairing effects of anesthetics should also be tested using both the classical conditioning preparations and priming tasks.^{3,7} These proposed studies should clear some of the enigmas surrounding the subject.

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