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Arousal Reactions during Anesthesia in Man

Jean Bimar, M.D., J. Weldon Bellville, M.D.†*

Power-spectrum analysis of the electroencephalogram and inhaled–exhaled concentrations of halothane (when used), nitrous oxide, and carbon dioxide of 36 patients during surgical operations under general anesthesia were monitored. Electroencephalographic arousal reactions were detected in 24 patients and these were accompanied by irregular respirations in nine patients. Cardiac arrhythmias occurred following an arousal reaction in eight patients. The authors conclude that this electroencephalographic arousal phenomenon occurs frequently and deserves further investigation to define its clinical implications and how it might be avoided. (Key words: Anesthesia, depth; Monitoring, electroencephalography, arousal reactions, computer analysis; Ventilation, patterns.)

SINCE 1966, we have utilized a technique of power-spectrum analysis of the electroencephalogram in the Laboratory of Applied Neurophysiology at Marseille. This work was continued at Stanford University, and the data reported in this paper were obtained during the conduct of a monitoring project wherein the electroencephalogram was transduced and the power spectra displayed. Additionally, the inspired and expired concentrations of halothane (when used), nitrous oxide, and carbon dioxide were monitored. This permitted us to make some observations of arousal reactions during general anesthesia in man that have not been previously reported.

Methods

TECHNIQUE AND APPLICATION

Electrical activity of the brain was recorded from the scalp by means of silver chloride electrode cups. The amplifier used had a flat frequency response between 1 and 40 Hz (cycles/sec). Bipolar records were made from frontal–temporal and temporal–occipital leads. These analog signals from the amplifier were processed on-line by means of a Xerox Data Systems Sigma 5 computer and displayed back to the anesthesiologist in the operating room on a television screen monitor.

The simultaneous display and recording on magnetic tape of inhaled–exhaled concentrations of halothane, nitrous oxide, and carbon dioxide, all transduced by Beckman® LB-1 infrared gas analyzers, made these values available for retrospective correlation with the electroencephalographic changes. Each analyzer was calibrated with a background of the other two gases (CO_2, 5 per cent, N_2O, 60 per cent; halothane, 1 per cent) and a computer algorithm was developed to correct for interference when any of the gases was outside this range.

SAMPLING CHOICE AND LENGTH OF PERIODS IN THE ANALYSIS

The choice of the sampling time depends upon two requirements. From a mathematical viewpoint, the resolution and permanence of the spectrum (hence its reliability) necessitate some relationship between analyzed frequency bands and the duration of the samples taken. There is also a constraint of a physiologic sort in that the analyzed sampling must be relatively short, so that processing in real time will reflect rapidly changing phenomena and warn the person in attendance of any abrupt change in the electroencephalographic trace.

For these reasons, we chose to display a spectrum every 8 seconds, based on the analysis of successive 8-second samples of the electroencephalogram. This choice depends on the number of samples per second allowed by the analog–digital converter (512 every 8 seconds) and its duty cycle in the total monitoring system.

APPEARANCE OF THE SPECTRUM

The autospectrum covers a range of frequencies from 0 to 32 Hz. The displayed spectrum is made up of the powers of frequency bands of .5 Hz; thus, 64 values are displayed. An important factor is the evaluation of the amplitude of the analog graph, whose value coincides on the spectrum with the repetition of the same frequency band during the period being analyzed. It is essential to select the appropriate amplification from the very beginning of anesthesia so that changes in power at a particular frequency can be appreciated. This choice is made more easily when the scale maximum is displayed, that is, the hypothetical value of the highest power of the spectrum (*e.g.*, 1,000; 2,000; 5,000; 10,000). This can usually be selected before the start of anesthesia based on the subject's resting EEG power spectrum.

This amplification must be maintained constant to enable one to evaluate correctly the variations in amplitude, whether as a whole or of a particular

* Professor of Anesthesia; Chairman, Hôpital Nord, Marseille, France.

† Professor of Anesthesia, University of California at Los Angeles, Los Angeles, California.

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Address reprint requests to Dr. Bellville: Department of Anesthesiology, UCLA School of Medicine, Los Angeles, California 90024.

TABLE 1. Patients Studied and Results

Patient	Operation	Anesthetic Method*	Arousal†	Cardiac Arrhythmias‡	Respiratory Abnormalities§
1	Pyelotomy	Thiopental/succinylcholine/methoxyflurane			
2	Hysterectomy	Thiopental/*d*-tubocurarine/halothane/fentanyl/ mechanical ventilation			
3	Dilatation and curettage	Thiopental/halothane			
4	Laparotomy	Thiopental/succinylcholine/halothane/ *d*-tubocurarine	+++		++
5	Left mandibular biopsy	Halothane			
6	Vaginal fistula	Methohexital/methoxyflurane/succinylcholine	++		
7	Hysterectomy	Methohexital/halothane/succinylcholine	++	++	
8	Tubuloplasty	Methohexital/succinylcholine/*d*-tubocurarine/halothane	+++	++	+
9	Hysterectomy	Thiopental/halothane	++		
10	Hysterectomy	Thiopental/halothane	++		++
11	Colectomy	Thiopental/halothane/succinylcholine/ mechanical ventilation	++		
12	Tubal ligation	Thiopental/succinylcholine/halothane	+		
13	Abdominal hysterectomy	Thiopental/succinylcholine/halothane/ mechanical ventilation	+++	++	
14	Portocaval anastomosis	Halothane/tubocurarine	++	++	
15	Mammary carcinoma	Thiopental/halothane			
16	Splenectomy	Thiopental/halothane/mechanical ventilation	++	+	
17	Dilatation and curettage	Thiopental/halothane			
18	Dilatation and curettage	Thiopental/halothane			
19	Tubuloplasty	Thiopental/halothane/*d*-tubocurarine	+		+
20	Splenectomy	Thiopental/succinylcholine/halothane	++		++
21	Splenectomy; biopsy	Thiopental/halothane/*d*-tubocurarine/ mechanical ventilation			
22	Splenectomy	Thiopental/halothane/*d*-tubocurarine/ mechanical ventilation	++		
23	Tubal ligation	Thiopental/succinylcholine/halothane	++		+
24	Cardiac surgery (bypass)	Thiopental/morphine/*d*-tubocurarine/ mechanical ventilation	+		
25	Carcinoma of pharynx	Thiopental/halothane	++		
26	Skin grafts	Ketamine			
27	Splenectomy	Thiopental/halothane/*d*-tubocurarine/ mechanical ventilation	++		
28	Melanoma, metastatic	Thiopental/succinylcholine/halothane	+++	+	++
29	Laparotomy	Thiopental/halothane/*d*-tubocurarine	+		
30	Hernia	Thiopental/halothane			
31	Groin skin grafts	Thiopental/halothane	++		+
32	Dilatation and curettage; biopsy	Thiopental/halothane			
33	Breast biopsy	Thiopental/meperidine	++		
34	Hysterectomy	Thiopental/*d*-tubocurarine/meperidine	+++	++	
35	Bowel resection	Thiopental/*d*-tubocurarine/fentanyl/ mechanical ventilation			
36	Laparotomy	Thiopental/*d*-tubocurarine/fentanyl/ mechanical ventilation	++	+	

* All patients received nitrous oxide, oxygen, and the drugs listed.
† Arousal: +++ = large number of arousals; ++ = numerous arousals; + = some arousals.
‡ Cardiac arrhythmias: ++ = cardiac arrhythmias of long duration (with arousal); + = some premature beats.
§ Respiratory abnormalities (during arousal): ++ = frequent; + = of short duration.

frequency band, that occur during anesthesia or coma. This makes it easier to detect quickly certain characteristic traces, for example, slow waves of large amplitude.

The changes that occur in the electroencephalographic tracing during anesthesia have been described in detail.[1] These range from the activation stage during induction with thiopental to the burst

suppression seen with deep anesthesia. The ongoing power spectral analysis very accurately translates each of these stages and often allows for more detailed analysis. For example, when a drug effect changes the dominant frequency band, which is difficult to recognize by eye, it is very readily appreciated in the computer display of the power spectrum. Furthermore, the appearance of very slow waves produces a marked disappearance of the fast activity in the power-spectrum display. This disappearance of all fast activity, as well as a considerable increase in the power of the slow frequencies, is an alarm signal and may be the result of an overdose of anesthetic or a hypoxic event.

Arousal Reaction

The classic reaction of awakening[2,3] by stimulation of the reticular formation in animals is now very frequently encountered (24 of 36 patients) with the present techniques of light anesthesia. However, it is rarely recognized that arousal does occur during the course of general anesthesia in man, for two reasons: first, because the electroencephalogram is not routinely monitored, and second, because arousal has not generally been recognized by anesthesiologists or investigated in man in detail.

Power-spectrum analysis of relatively brief electroencephalographic samples enables one to detect such an arousal reaction; a decrease in the total power and a marked shift in the dominant frequency to high-frequency (18–30 Hz) activity. However, the classic reaction of awakening very often changes either with the duration of anesthesia or with the drugs used. Also, we observed the reaction of reverse arousal described by Brazier and others.[1] It is thus evident that the sudden slowing seen in the electroencephalogram is an indication of a sudden shift of the power spectrum to the low (1–3 Hz) frequencies. This modification is difficult to distinguish from shifts to slower spectra whose etiologies are entirely different, for instance, the shifts seen with severe hypoxia and during deep inhalational anesthesia. Both resemble reverse arousal.

Patients Studied

Thirty-six patients (mean age 37 years) were selected for study from among those scheduled for surgical procedures in the operating room equipped for the monitoring project. All patients were ASA Class 1 or 2. Fourteen were male, while 22 were female. Halothane was the primary anesthetic used for 28 of the 36 patients studied. The electroencephalographic power-spectrum data, analog electroencephalogram, and gas recordings and electrocardiogram were reviewed retrospectively. These data and the characteristics of each patient, operative procedure, and anesthetic technique are tabulated in table 1.

Results

In table 1, the occurrence of arousal and respiratory irregularities and the incidence of cardiac arrhythmias are listed. The intensity of arousal is rated on a scale from 1 to 3+. Irregular respirations were observed in association with arousal in nine of 25 patients whose lungs were not ventilated mechanically and cardiac arrhythmias associated with arousal were observed in five patients.

To illustrate the changes observed in the electroencephalographic power spectra and respiratory patterns, selected illustrative electroencephalographic power spectra and analog traces from one patient (patient 28) are shown (figs. 1–3).

Discussion

The effects of anesthetics on the brain have been reviewed recently by Winters and Ferrar-Allado, who have postulated that different anesthetics have different mechanism of action and produce anesthesia by different means.[4] This is not a new concept, and there are many papers showing differences in effects at many sites in the central nervous system.[3–7] This was emphasized by Darbinjan, Golovchinsky and Plehotkina, who studied the effects of anesthetics on the reticular formation, as well as on the cerebral cortex.[6,7]

The arousal reaction in the electroencephalogram was described in 1930 by Berger.[2] He found that when a subject's eyes were closed the alpha rhythm (10–12 Hz) was dominant, but upon opening the eyes, desynchronization took place. This desynchronization, or arousal, was characterized by electroencephalographic changes wherein the alpha rhythm was replaced with low-voltage waves of higher (18–24 Hz) frequency. The magnitude of the electrical change paralleled the extent of the transition, and has been referred to either as alpha-wave blockade or as arousal reaction. Later, other investigators showed that desynchronization of the electroencephalogram could be produced by any type of afferent stimulus that arouses the subject to alertness.

In 1949, these findings were reviewed and extended by Moruzzi and Magoun,[3] who used bipolar electrodes implanted in cats under chloralose anesthesia or in *encephale isole* preparations and showed that the arousal reaction could be produced by direct stimulation of the reticular formation of the brain stem. This led to the realization of the importance of the reticular activating system in the maintenance of the conscious state, and also led them to postulate the unified theory for the production of anesthesia, related to blocking the reticular activating system.

The differences in the sensitivities of the cerebral

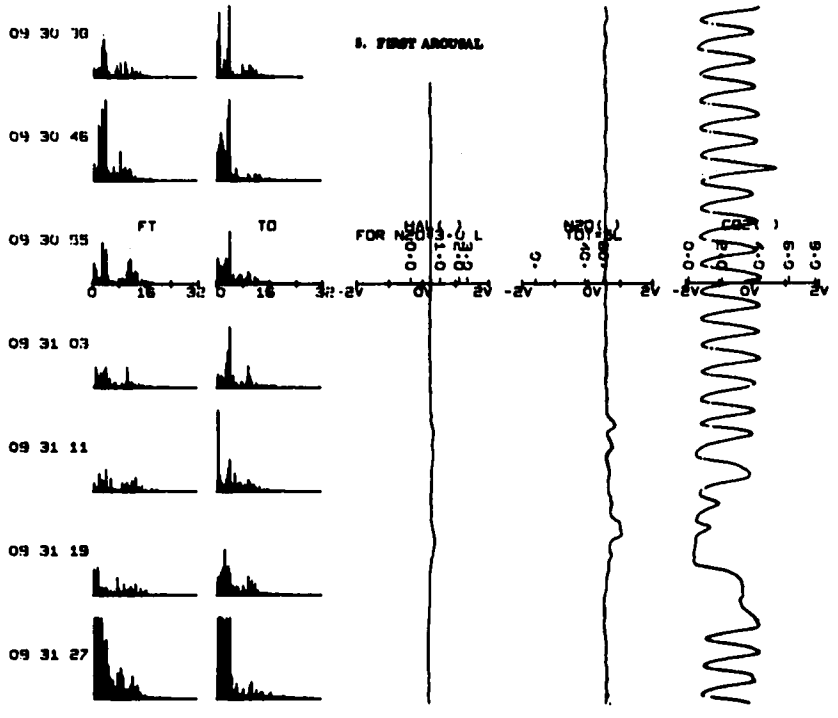

FIG. 1. Tracings recorded starting just prior to induction with thiopental given intravenously at 07-28-36 and continuing throughout the anesthesia. The first column on the left indicates the output of a real time clock, showing the hour, minute, and second. This is followed by the power-spectrum analysis (0–36 Hz) for an 8-second epoch from the frontal–temporal and temporal–occipital leads (from left to right). The next trace indicates the inhaled–exhaled halothane concentration in vol per cent and the next trace, the inhaled–exhaled nitrous oxide concentration (vol per cent). The last tracing records the inhaled–exhaled CO_2 concentrations. Thus, this figure represents the data analyzed over seven 8-second epochs (09-30-36 to 09-31-27) and the 22 breaths that took place during that time while oxygen, nitrous oxide and halothane were being administered.

This pattern appears constant and stable as anesthesia was maintained and is reflected in the power-spectrum display for 09-30-38 and 09-30-46. However, at 09-30-55, there was an abrupt change in the power-spectrum display, in that there was a marked decrease in the low-frequency content and a shift to higher frequencies. The total power in the electroencephalogram decreased further in the display at 09-31-03 and 09-31-11. This occurred 1.5 hours after stabilization of the anesthesia, and represents the first arousal reaction. This is also reflected at 09-31-11 by changes in the respiratory rate wherein the subject took a few shallow breaths before the arousal reaction was terminated some time after 09-31-19. There was a return to the pre-arousal electroencephalographic pattern.

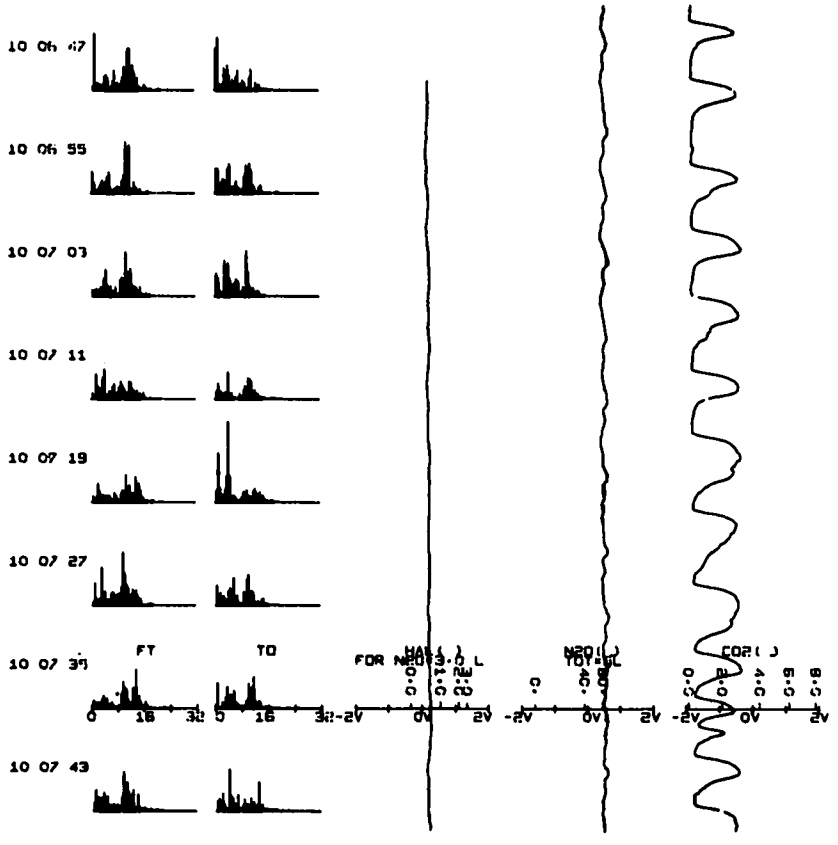

FIG. 2. The electroencephalographic power spectrum from 10-06-47 through 10-07-43. The concentrations of halothane and nitrous oxide are maintained as before. However, the electroencephalographic power spectrum is characteristic of the patient who is essentially awake, and there is an absence of the slow-wave activity associated with light halothane anesthesia and a predominance of fast activity with a peak in the 10–12 cycles/sec activity. There is hyperventilation in that end-expired CO_2 was decreased to 2.8 per cent. The electroencephalographic change, as well as the hyperventilation, indicates an arousal reaction. This essentially "awake" state, as judged from the electroencephalogram, continued through 10-14-23.

cortex to diethyl ether and to barbiturates have been studied extensively by Golovchinsky and Plehotkina.[7] They were able to show that even at stage 3 of ether anesthesia, electrical stimulation of the reticular formation induced typical electroencephalographic arousal (dysynchronization) accompanied by a

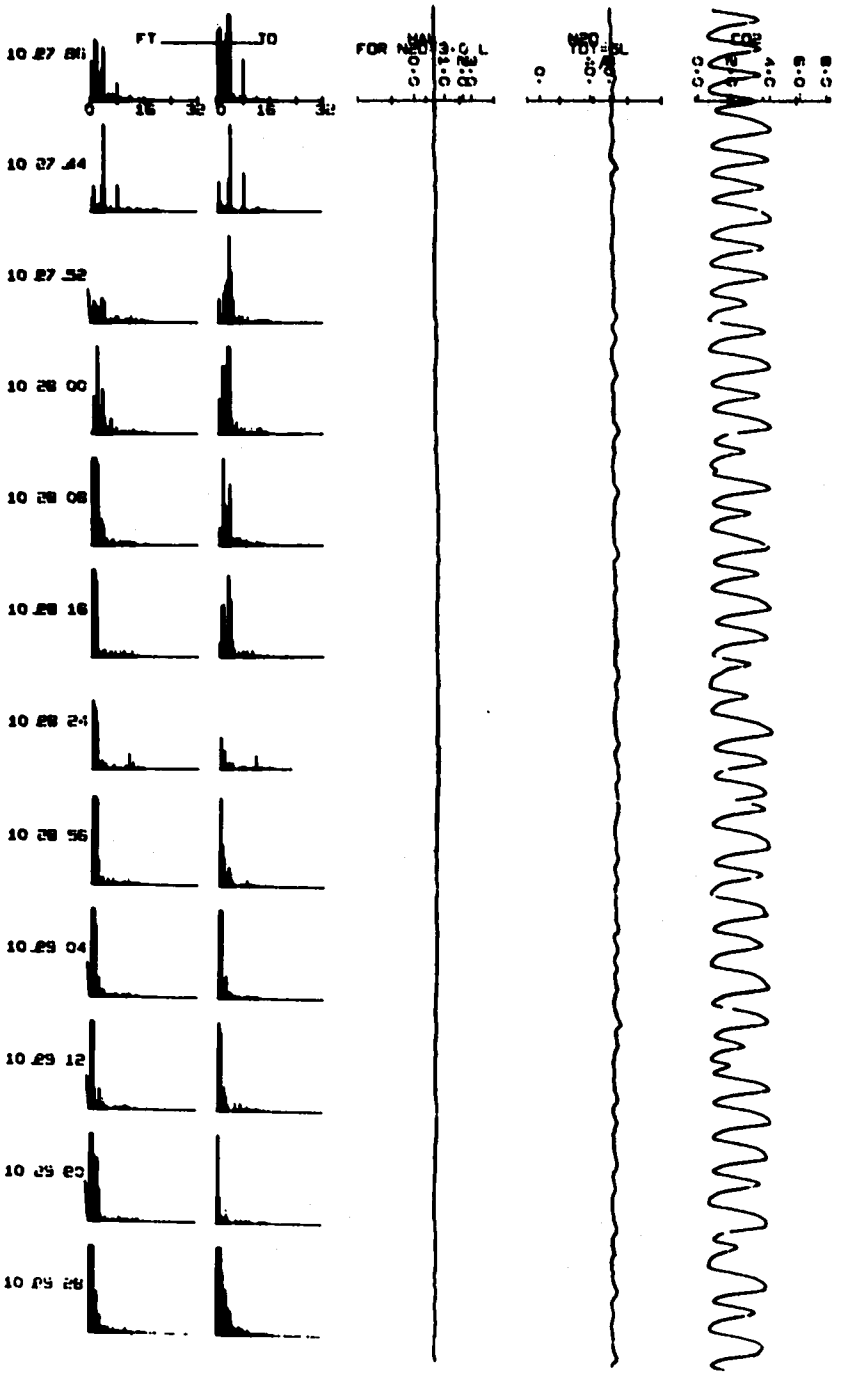

FIG. 3. This figure shows the phenomenon called "reverse arousal," described by Brazier,[1] which has been observed during very painful surgical procedures; it is often seen after brain trauma. At this time, the respiratory rate was markedly increased with a low tidal volume and end-expired CO_2 had returned to approximately 4 per cent while the halothane concentration was maintained at .75 per cent. The decrease in CO_2 at first led us to interpret the graphic electroencephalographic manifestations as hypocapnic narcosis. From 10-28-00, the analog trace and the power-spectrum analysis show considerable increase in the power of the slow waves. Upon reviewing the analog trace alone with the power-spectrum analysis, it was realized that this record represents a deepening anesthesia and was in fact a "reverse arousal."

marked shift of electrical oscillations towards higher frequencies of low amplitude. These results may be considered proof that even during deep ether anesthesia, reticular neurons can respond to direct and probably to transsynaptic activation.

Less attention has been given to the effects of anesthetics upon the electroencephalographic pattern of slow synchrony or "reverse arousal" than to the study of the arousal of desynchronization response.[8] Prince and Shanger[9] observed that either electroencephalographic desynchronization or synchronization could be produced by high-frequency reticular stimulation. The high-voltage slow-wave response they observed they believed to be unrelated to hypoxia, since it was abolished by artificially induced hypoxia. They considered several interpretations of this phenomenon and observed that in chronic unrestrained preparations, a much altered form of behavioral arousal could occur coincident with the high-voltage slow-wave response, in that the animals often moved spontaneously after stimulation and appeared to be at lighter levels of anesthesia for short periods.

The results of Kaada *et al.*[10] are similar. They reported the occurrence of high-voltage slow-wave activity following high-frequency reticular stimulation only in animals under relatively light anesthesia (chloralose–pentobarbital, chloralose–urethane, urethane–pentobarbital, or pentobarbital).

The arousal reaction has been studied extensively by neurophysiologists, who, in addition to reporting its neurophysiologic effects, have observed cardiac arrhythmias occurring in the electroencephalogram after one or several arousal reactions have occurred. We, too, have observed arrhythmias to occur in patients 45 to 90 seconds after an arousal reaction, and agree with others that this may be related to stimulation of the central autonomic nervous system itself or liberation of endogenous catecholamines.[11] The clinical significance of these arrhythmias needs to be defined.

The respiratory pattern changes following arousal reported herein have not been prominent in animal studies because the animals under study are usually paralyzed, and ventilation is automatically controlled with a ventilator; therefore, the associated respiratory effects have gone largely unrecognized. However, Kaada *et al.* did describe movement and apparent lightened anesthesia in some of their unrestrained animals.[10] We believe monitoring respiration in spontaneously ventilating patients may provide a clue as to when to look for electroencephalographic arousal. We do not have data on the specific event that elicited each electroencephalographic arousal detected in our study. We noticed that when the change in power-spectrum analysis was observed during the course of anesthesia it was usually associated with a surgical maneuver, such as pulling on the mesentery or peritoneum, that might induce painful stimuli in conscious patients. However, in this study there was no way of documenting the surgical maneuver, if any, that elicited an arousal response.

There has been discussion of the possibility that arousal and recall do occur during anesthesia.[12] Some these papers have been directed at re-examining the use of very light levels of anesthesia,[13] and few have been concerned with the possibility that even during stages of established MAC 1 anesthesia arousal might occur.[14] We have observed electroencephalographic arousal does occur during light halothane, methoxyflurane and balanced anesthesia. These data were analyzed retrospectively so that unfortunately we have no follow-up on the incidence of recall in these patients, but the evidence presented in this paper suggests that stimuli could bring about an arousal so that phenomena such as those described by Levinson might be accounted for.[15] A recent paper discounted the ability to recognize arousal,[16] but with electroencephalographic power-spectrum analysis, arousal can be recognized.

One wonders whether reports of recall during anesthesia are in any way related to the electroencephalographic arousal reaction we have reported. It is conceivable that a sustained arousal reaction from MAC 1 or MAC 2 anesthesia, such as that shown in figure 2, might be associated with recall rather than recall's being related simply to too light a level of anesthesia. If the former is a valid hypothesis, it behooves us to investigate means of blocking such an arousal reaction.

Arousal is manifest by desynchronization in the electroencephalogram, or slowing of the dominant frequency, and an increase in amplitude of the waveform can and does occur during light halothane–nitrous oxide or narcotic–nitrous oxide anesthesia in man. It is usually accompanied by irregular respirations in spontaneously ventilating patients, and may be followed by cardiac arrythmias.

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