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Anterior Shift of the Dominant EEG Rhythm during Anesthesia in the Java Monkey:

Correlation with Anesthetic Potency

John H. Tinker, M.D., Frank W. Sharbrough, M.D.,† John D. Michenfelder, M.D.‡*

EEG amplitude dominance in awake man is posterior. During EEG monitoring in patients, the authors observed the abrupt appearance of anterior amplitude dominance during induction of anesthesia with halothane, enflurane, or thiopental. This EEG change is coincident with loss of eyelid reflex and loss of ability to respond to command. This EEG change was studied with several anesthetics in five Java monkeys to determine alveolar anesthetic concentrations at which it occurred and to observe the effects of various stimuli on it. EEG recordings were obtained after equilibration at each level with increasing concentrations of halothane, enflurane or isoflurane in oxygen and each agent again in 30 per cent N_2O, in separate experiments in the same animals. EEG amplitude dominance became anterior in each animal with each anesthetic and combination at concentrations less than MAC, which was also determined in the same experiments. At lower concentrations, stimulation at equilibrated anesthetic concentrations resulted in abrupt EEG return to posterior amplitude dominance. The end-tidal anesthetic concentration at which persistence of anterior EEG dominance was seen after stimulation was approximately 0.4 MAC for each anesthetic and combination tested. This is interpreted as support for physical solution–lipid solubility theories of anesthetic action. In addition, an EEG change common to various anesthetics may increase the clinical usefulness of EEG monitoring. It is speculated that this EEG change may signal loss of awareness. If so, observance of sustained anterior EEG amplitude dominance may provide assurance of obliteration of awareness during anesthesia. (Key words: Brain, electroencephalography; Monitoring, electroencephalography; Anesthesia, monitoring depth.)

ELECTROENCEPHALOGRAPHY was first suggested in 1937 as a possible method of monitoring the "level" of anesthesia in man.[1] An extensive literature has accumulated, beginning with correlations of EEG activity with clinical signs of anesthetic depth,[1–5] or blood levels of anesthetic,[6–8] and, more recently, extending to computerized frequency range analyses of complex waveforms.[9–13] Emphasis has been on frequency alterations and on qualitative differences among agents.[14] Necessarily subjective clinical estimates of depth are difficult to correlate with EEG patterns. Further, such studies have often ignored the fact that EEG patterns observed during anesthesia may be dependent not only upon anesthetic concentration but also upon level of stimulus, though EEG alteration with stimulus becomes progressively less marked at concentrations greater than 1 MAC. The clinical usefulness of the EEG in anesthetic practice has been thus limited by emphasis on differences between anesthetics, by emphasis on complex frequency analysis, and by lack of recognition of the importance of level of stimulus at clinically useful concentrations.

Our purpose in the present study was to attempt to identify and quantitate an EEG change that might be common to many, if not all, anesthetics. Early investigations of the effects of barbiturates on the EEG revealed abrupt alterations in EEG frequency and amplitude, with the change in rhythmic activity first appearing in the frontal region, followed by posterior spread.[15] Recently,[16] appearance in frontal areas of amplitude dominant rhythmic activity has been seen during halothane anesthesia. During continuous EEG monitoring of more than 500 patients undergoing carotid endarterectomy with various anesthetic techniques, including halothane, enflurane, and nitrous oxide–narcotic, we have repeatedly observed that at approximately the point at which loss of response to command occurs, amplitude dominant rhythmic activity rather abruptly appears in the frontal area. This appearance of frontal amplitude dominant activity occurs at anesthetic levels below MAC. As anesthesia deepens, amplitude increases, and frequency decreases, in accordance with well-described EEG characteristics with individual agents.[16,17] Frontal amplitude dominance, however, remains, though it is less pronounced.

Operating room observations are limited both by lack of control over stimulus level and by difficulty in achieving equilibrated incremental anesthetic concentrations. To examine this EEG change under more controlled circumstances, this study was carried out using the Java monkey (*Macaca fascicularis*), an animal that has a waking posterior amplitude dominant EEG pattern similar to that of man. The study was carried out at quantitated, incrementally increased levels of anesthesia, with controlled stimuli, to determine 1) whether the appearance of a frontally dominant EEG pattern was consistent with different agents and combinations, and 2) whether the anesthetic concentration at

* Assistant Professor of Anesthesiology.
† Assistant Professor of Neurology.
‡ Professor of Anesthesiology.

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Address reprint requests to Dr. Tinker.

which this pattern appeared could be correlated, at a given stimulus level, with MAC determined in the same animal.

Methods

Seven to ten days prior to the study, each of the five Java monkeys was anesthetized with halothane, the scalp incised, and screw-type stainless steel electrodes were implanted through the calvarium into the epidural space. The electrodes were designed to accommodate a 25-gauge needle, which subsequently could be passed percutaneously by palpation. The electrodes were positioned in the anterior-to-posterior pattern shown in figure 1. These transcalvarial electrodes, used repeatedly, provided consistent EEG recordings.

Each animal was studied on six separate occasions, with at least ten days between exposures. The anesthetics tested were halothane, enflurane, and isoflurane in oxygen and again with 30 per cent nitrous oxide in oxygen. No premedicant was used. Alveolar anesthetic concentrations were approximated by determining end-tidal concentrations with a calibrated Beckman LB-2 analyzer, sampling via a small-bore polyethylene tube inserted through the endotracheal tube to the carina.

Immediately after administration of pancuronium (0.04 mg/kg, im), intubation of the trachea, and establishment of mechanical ventilation, the animals were exposed to the first increment of anesthetic (approximately 0.25 per cent halothane and isoflurane, 0.4 per cent enflurane). Needle electrodes were placed and EEG recording begun. At least 15 minutes were allowed for equilibration at each end-tidal anesthetic concentration. Ventilation was adjusted to maintain end-tidal P_{CO_2} at 37 ± 2 mm Hg. Four channels of EEG activity were then recorded in a quiet room for two minutes with

TABLE 1. Comparison of Anesthetic Concentrations at Which Frontal Dominance Occurred with MAC*

Agent	EEG Shift Concentration in Per Cent V/V after Electrical Stimulation of Tail†	MAC (Per Cent V/V)†	Shift Concentration / MAC Ratio
Halothane	0.48 ± 0.05	1.15 ± 0.09	0.42
Enflurane	0.70 ± 0.06	1.84 ± 0.07	0.38
Isoflurane	0.47 ± 0.02	1.28 ± 0.08	0.37
Halothane + 30 per cent N_2O	0.33 ± 0.04	0.75 ± 0.06	0.44
Enflurane + 30 per cent N_2O	0.54 ± 0.04	1.46 ± 0.03	0.37
Isoflurane + 30 per cent N_2O	0.48 ± 0.04	1.46 ± 0.03	0.44

* The same five animals were studied with each agent and combination.
† ±standard error of the mean.

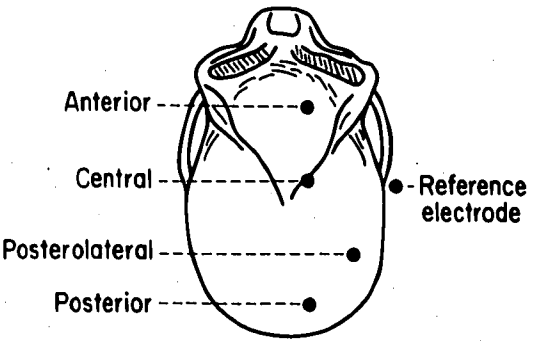

FIG. 1. Locations of electrodes.

the animals' eyes closed. The eyes were then opened for 15 seconds, followed by a 5-second electrical stimulus applied to the tail with a Block-Aid monitor, then a 10-second period with the eyes still open. After the series of stimuli, another two-minute recording was made with the eyes closed and the series repeated. The electrocardiogram was recorded on an additional channel to permit identification of EKG artifact in the EEG. End-tidal P_{CO_2} was checked at each anesthetic level with a Severinghaus electrode calibrated for gas samples.

A Grass model 78-B recorder, with 7-P5-11 amplifiers, was used with 30 mm/sec paper speed for EEG recording, with each electrode calibrated at 5 μV/mm. The reference electrode was placed subcutaneously in front of the right (ipsilateral) ear.

Neuromuscular blockade with the initial dose of pancuronium was generally sufficient for the entire study, with occasional requirement for an additional dose (0.02 mg/kg, im) to prevent movement artifact.

EEG recordings were obtained according to the above protocol at successively increased anesthetic concentrations (0.15 to 0.30 vol per cent per increment), allowing at least 15 minutes for equilibration at each level. MAC was then determined in each study by continuing the incremental increases in end-tidal anesthetic concentration beyond the point at which the EEG change to frontal dominance persisted following the stimuli, adding tail clamping in the manner described by Eger *et al.*[18] to the above-described stimulus regimen at each end-tidal concentration. Slight movements (the animal remained partially paralyzed) were accepted as indications that alveolar anesthetic concentration was below MAC. When no movement occurred during tail clamping for one minute, neostigmine, 0.04 mg/kg, and atropine, 0.02 mg/kg, were given by single injection into a peripheral vein. After assurance of clinical reversal by cessation of tetanic fade (gastrocnemius muscle), the tail-clamp stimulus was repeated and further increments of anesthetic administered as necessary until no movement occurred during one minute of tail clamping. MAC was recorded as the average of the end-tidal concentrations of agent just above and below the point at

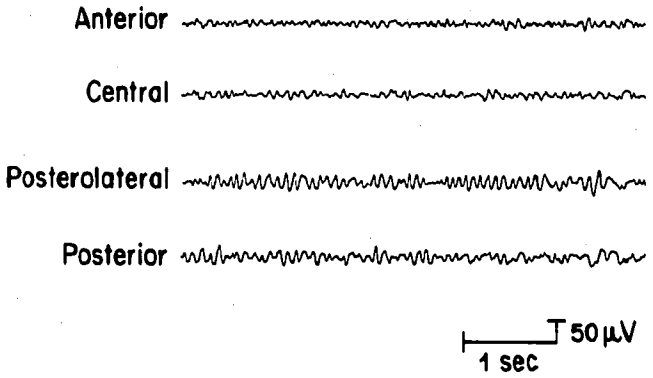

FIG. 2. Monkey "S." Enflurane, 0.39 per cent in oxygen, equilibrated. Eyes closed, unstimulated. Example of posterior amplitude dominance. Similar to alpha waking rhythm seen in man.

which movement in response to tail clamping was no longer observed.

The one-second period following the recorded artifact of the electrical tail stimulus on the EEG paper was chosen for subsequent EEG analysis because it best represented a reproducible and easily identifiable stimulus level. The recordings were first interpreted by visual inspection. Amplitude dominance occurring in either the frontal or central lead was considered anterior, and that occurring in either the posterolateral or posterior lead, posterior. Additionally, in order to minimize subjective bias each tracing was measured with vernier calipers during the one-second period following electrical tail stimulus for the single highest amplitude waveform in either of the two anterior leads, compared with that in either of the two posterior leads. Dominance was considered to be present when peak amplitude was greater by 0.2 mm (1.0 μV) or more by caliper measurement.

The average of the equilibrated end-tidal anesthetic concentrations just below and just above the point at which anterior dominance was sustained during the one-second period following application of the electrical stimulus to the tail was recorded as the "EEG shift concentration" (see table 1). This concentration was then compared with MAC determined in the same experiment.

In all experiments, stimuli in the absence of anesthesia were minimized as much as possible. In each study, the anesthetic was started immediately after establishment of mechanical ventilation. Half

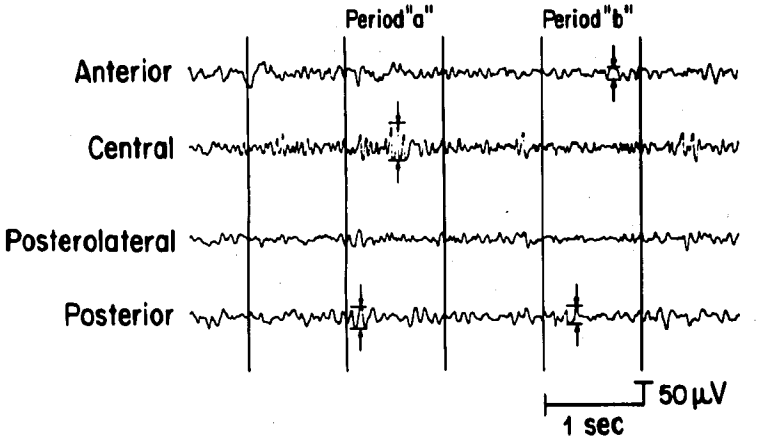

FIG. 3. Monkey "S." Enflurane, 0.61 per cent in oxygen, equilibrated. Eyes closed, unstimulated. Tracing divided into 1-second intervals. Peak amplitude occurred during period *a*—57.0 μV anterior–33.5 μV posterior—indicating period of anterior dominance. Period *b*, 20.5 μV anterior–28.0 μV posterior, indicates posterior dominance. Dominance continued to alternate at this concentration.

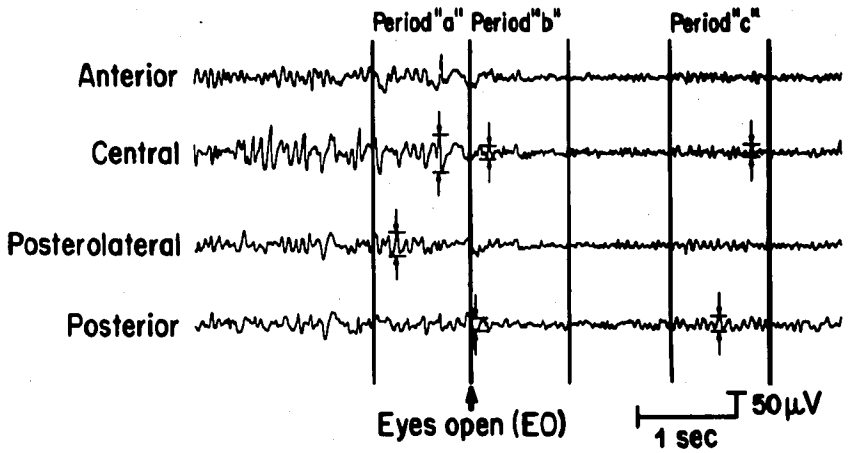

FIG. 4. Monkey "S." Enflurane, 0.80 per cent in oxygen, equilibrated. Anterior dominance persistent before stimulation. Period *a*, 57.5 μV anterior, 36.0 μV posterior. Eye opening (EO) returns pattern to posterior dominance in 2 seconds. Period *b*, 20.0 μV anterior, 18.5 μV posterior. Period c, 17.0 μV anterior, 21.5 μV posterior.

the experiments were performed with the animal initially breathing 30 per cent nitrous oxide. We assume that 30 per cent nitrous oxide and/or the first increment of volatile anesthetic (0.25 per cent for halothane and isoflurane, 0.4 per cent for enflurane) were analgetic. Needle scalp electrodes were always inserted through healed surgical scar tissue. No intravenous, intra-arterial or other invasive monitor was utilized. Tail clamping was not done until anterior dominant EEG rhythm was sustained following application of the electrical stimulus to the tail.

Results

In every animal and with each anesthetic and combination tested, persistence of frontal dominance after application of the electrical stimulus to the tail ("EEG shift") occurred at end-tidal anesthetic concentrations less than MAC. Frontal dominance was determined by both visual inspection and vernier caliper measurements as described. In five of the 30 experiments, persistence of frontal dominance was not obvious by visual inspection until a concentration increment one higher than that determined by caliper amplitude measurement was achieved. In the remaining 25 experiments, persistence of frontal dominance was found by both visual inspection and caliper measurement at the same anesthetic concentration. For purposes of comparison of EEG shift concentrations with MAC, caliper amplitude measurements only were used.

Frontal amplitude dominance persistent after application of the electrical stimulus to the tail occurred at 0.42 ± 0.02§ MAC for halothane, 0.38 ± 0.02§ MAC for enflurane, and 0.37 ± 0.02§ MAC for isoflurane, each agent in oxygen. Addition of 30 per cent nitrous oxide in separate experiments to these anesthetics reduced both MAC and the EEG shift concentration such that the ratios of the shift concentrations to MAC's remained essentially the same (0.37–0.44, range). Comparison of MAC's *vs.* EEG shift concentrations for all 30 experiments (six anesthetic combinations, five animals each) yielded a correlation coefficient $r = 0.88$, $P < 0.001$. By Student's t test for paired values, the ratios between EEG shift concentrations and MAC's remained relatively constant for all six anesthetic combinations tested, *i.e.*, no significant difference was found. Table 1 summarizes these findings.

Figures 2 through 6 document typical EEG recordings with increasing increments of agent (see legends). At lower concentrations, amplitude dominance is posterior, then alternates between posterior and anterior, becoming persistent anteriorly during the unstimulated period in figure 4. However, the anterior dominant rhythm can be seen in figure 4 to revert rapidly to posterior dominance upon opening the eyes, at the same equilibrated concentration.

§ Standard error.

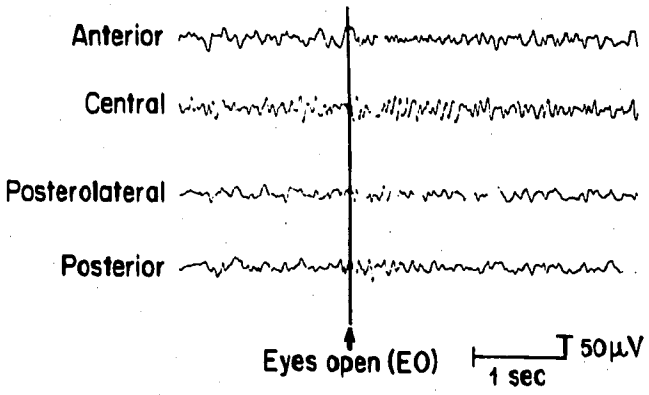

FIG. 5. Monkey "S." Enflurane, 1.02 per cent in oxygen, equilibrated. Anterior dominance persists after eye opening.

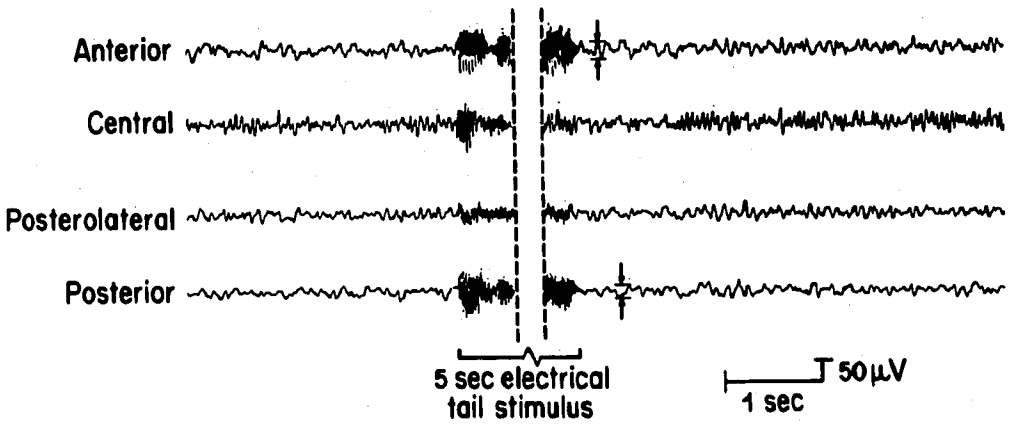

FIG. 6. Monkey "S." Enflurane, 1.02 per cent in oxygen, equilibrated. Anterior dominance persists after electrical stimulus applied to the tail. Values during the first second after application of the stimulus—anterior 25.5 μV, posterior 21.0 μV. The EEG change after application of the stimulus is considered to have occurred midway between 0.80 and 1.02 per cent enflurane in oxygen in this experiment.

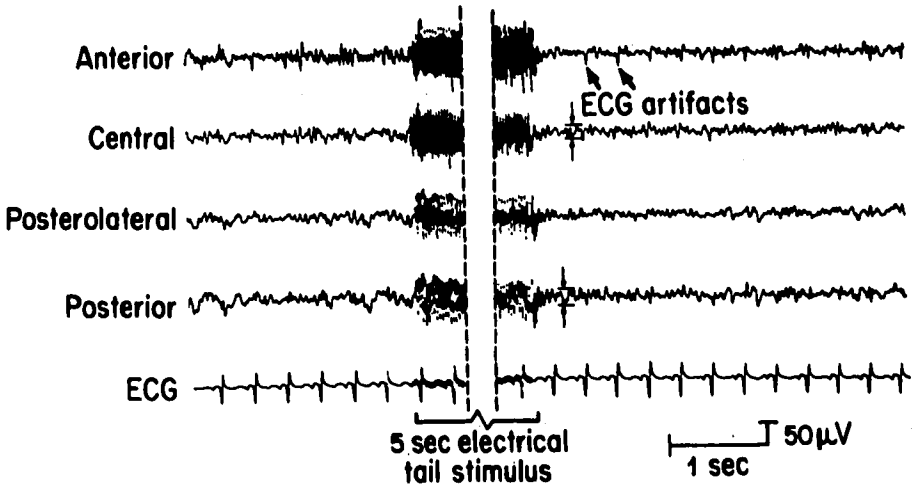

FIG. 7. Monkey "T." Isoflurane, 0.22 per cent, nitrous oxide, 30 per cent, and oxygen, equilibrated. Anterior amplitude dominance prior to application of the stimulus. Posterior dominance following stimulus. Values during the first second after application of the stimulus—anterior 19.0 μV, posterior 24.0 μV. ECG artifact evident.

At the next increment, figure 5, frontal dominance persists after eye opening, and in figure 6, after application of the electrical stimulus to the tail.

With a different anesthetic combination, the spatial shift of amplitude dominance is again demonstrated in figures 7 through 10. This example is presented to point out that the EEG change is observed despite the presence of ECG artifact. In figure 10, with the concentration of volatile agent equilibrated near MAC, the EEG pattern is still quite dependent upon stimulus level, *i.e.*, the stimulus results in considerable frequency change but frontal amplitude dominance persists.

Discussion

EEG studies concerned with determination of anesthetic "depth" have tended to describe and emphasize the spectrum of qualitative pattern differences between varying concentrations of different agents, resulting in a confusing and sometimes contradictory literature.[17] Further, from a practical standpoint, interest in ascertaining "depth" of anesthesia is largely concerned with obtaining assurance of obliteration of awareness, particularly during administration of low concentrations of agent in conjunction with neuromuscular blockade. The appearance of high-voltage fast rhythmic EEG activity associated with barbiturates was first described by Cohn and Katzenelbogen[19] in 1942, with the further demonstration by Brazier and Finesinger[15] in 1945 that this altered activity started frontally. Sustained frontal EEG dominance during anesthesia with halothane has been mentioned[16] but not studied in animals or man. Similar shifts have been seen in certain comatose states.[20] In patients undergoing carotid endarterectomy, we have observed this shift during anesthesia with halothane (fig. 11), enflurane, nitrous oxide–narcotic, and thiopental. The onset of this EEG change appears to relate temporally to loss of response to simple commands. Whether such a shift is common to the anesthetic state, regardless of anesthetic, is unknown; nor is it known whether

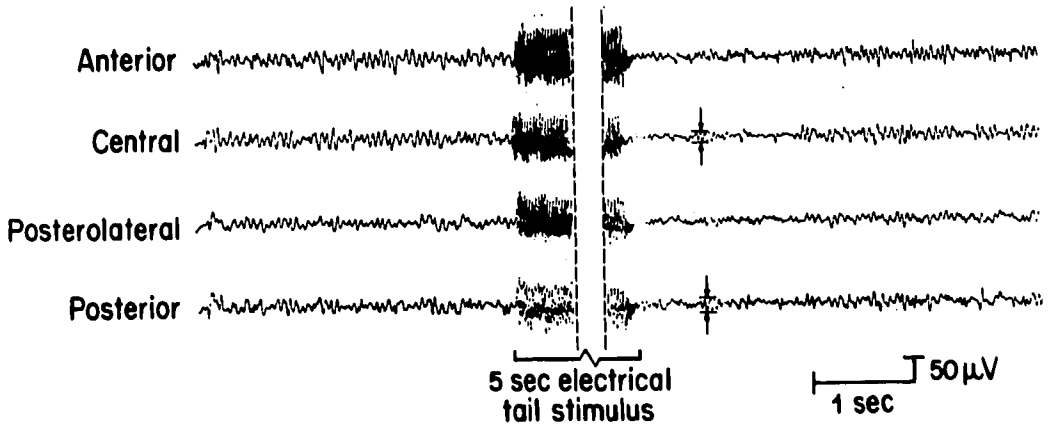

FIG. 8. Monkey "T." Isoflurane, 0.38 per cent, nitrous oxide, 30 per cent, and oxygen, equilibrated. Anterior dominance prior to application of the stimulus. Posterior dominance during the first two seconds following stimulus. Values: anterior 15.5 μV, posterior 18.0 μV. Note the rapid return to anterior dominance after application of the stimulus, suggesting that the concentration is near the level of persistence of anterior dominance.

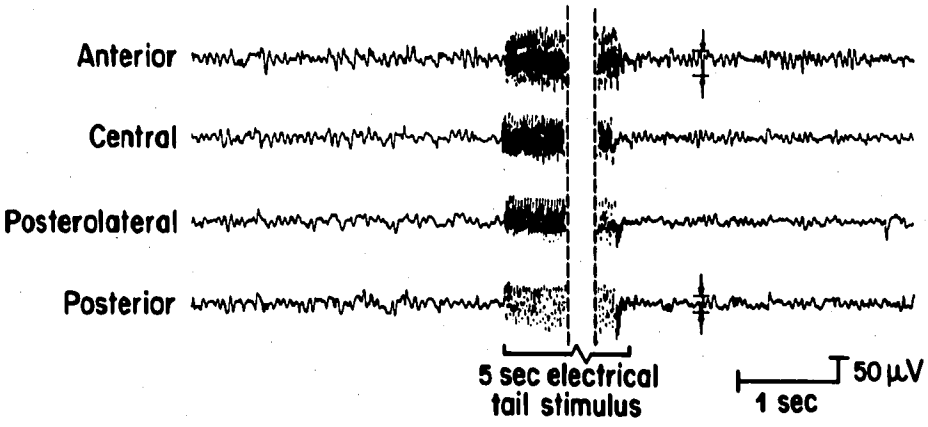

FIG. 9. Monkey "T." Isoflurane, 0.54 per cent, nitrous oxide, 30 per cent, and oxygen, equilibrated. Anterior dominance now persists following application of the stimulus. Values during the first second: anterior 36.0 μV, posterior 23.5 μV. The EEG change is considered to have occurred midway between 0.38 and 0.54 per cent enflurane in 30 per cent nitrous oxide.

the occurrence of a shift relates to a specific anesthetic depth. We have therefore attempted to study and to quantify this EEG change, which is easily identifiable, is common at least to the agents tested, and appears to be related to a relatively constant anesthetic depth.

Specifically, the present study has shown that in subhuman primates 1) there is an anterior shift of the amplitude dominant EEG rhythm as alveolar concentration of an anesthetic is increased; 2) this EEG change and the EEG pattern in general are dependent upon level of stimulus, at least at alveolar concentrations below 1 MAC; 3) the ratio between the concentration at which anterior amplitude dominance persists after a given stimulus and MAC appears to be relatively constant for the anesthetics and combinations tested.

Potential criticisms of this study include the following. End-tidal gas sampling might not accurately reflect arterial concentration. We believe that this question has been thoroughly and satisfactorily addressed by Eger *et al.*[21] Our manual method of analysis of EEG recordings might have allowed bias. We attempted to avoid this by 1) not recording on the tracing the actual anesthetic concentration, only code numbers; 2) varying the increments by which alveolar anesthetic concentrations were increased; 3) measuring amplitude with vernier calipers. Our MAC values for the Java monkey are somewhat higher than those reported for man or dogs. No other MAC studies in this species have been published.¶ We have no explanation for this other than to speculate that clamping the prehensile tail of these monkeys may represent a more intense stimulus than applying the clamp to the canine tail.

In support of our contention that the onset of an anterior dominant EEG pattern relates to a cerebral functional anesthetic end-point are the following reported studies. Stoelting *et al.*[22] recorded alveolar anesthetic concentration during awakening from inhalation anesthesia. They reported "MAC-awake" values of 50–60 per cent of MAC for various anesthetics. Our results agree. Shapiro *et al.***

¶ Eger EI II: Personal communication.

** Shapiro HM, Greenberg JN, Reivich MD, et al: Local cerebral glucose uptake in awake and anesthetized states. Abstract annual meeting of the American Society of Anesthesiologists, October 1975, pp 173–174

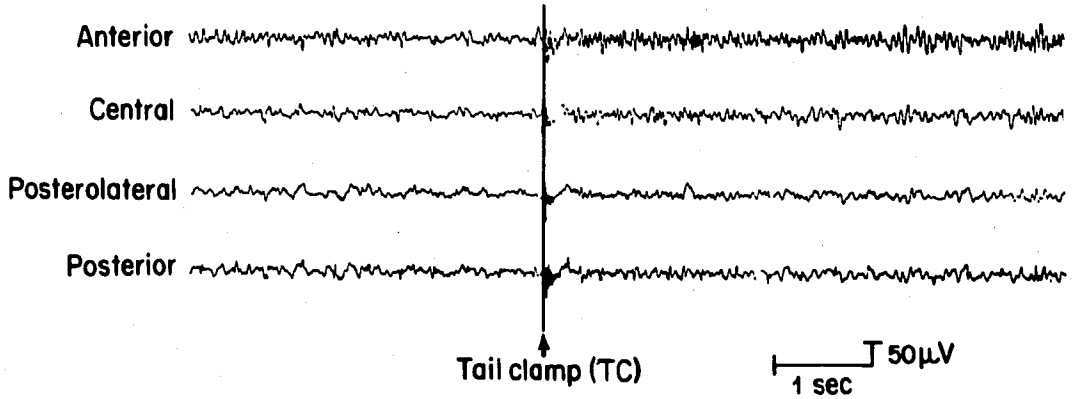

FIG. 10. Monkey "T." Isoflurane, 0.94 per cent, nitrous oxide, 30 per cent, and oxygen, equilibrated. Application of the tail clamp results in alteration of the pattern, with increased frequencies in all leads, but anterior amplitude dominance persists. MAC was determined to be 1.02 per cent in this experiment. This is evidence that even near MAC, EEG is still affected by both anesthetic concentration and stimulus level.

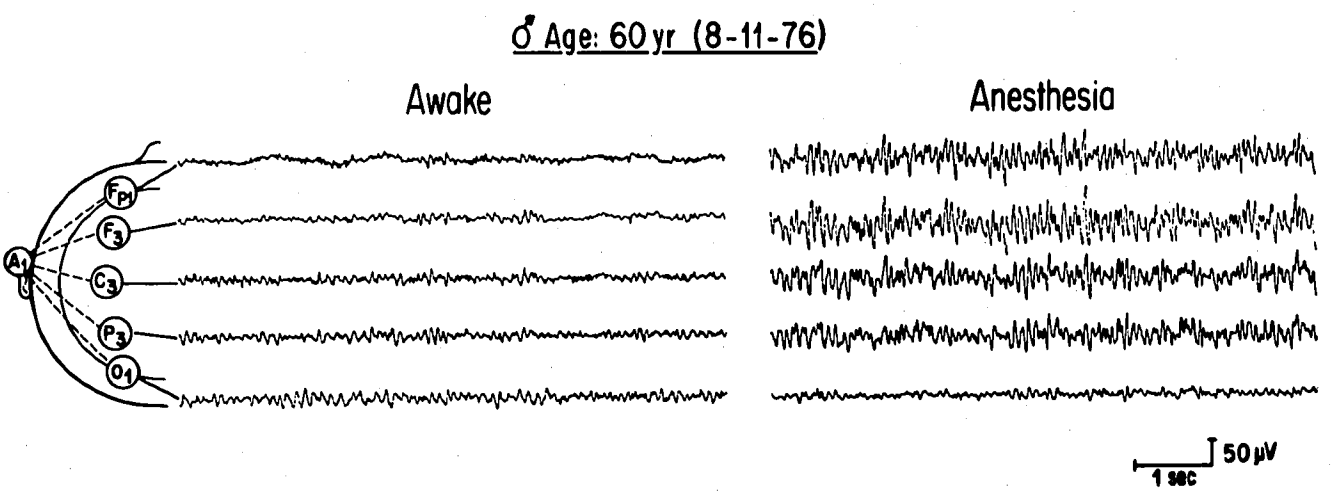

FIG. 11. EEG recording from a patient during carotid endartedectomy, comparing the waking EEG with that two hours after induction of anesthesia during operation. Halothane, 0.5 per cent, nitrous oxide 30 per cent. Anterior amplitude dominance during anesthesia is demonstrated.

reported depression of monkey cerebral cortical glucose uptake to be greater posteriorly than anteriorly at 1 MAC halothane. This may correlate with loss of EEG posterior dominant activity. Stullken *et al.*[23] have recently reported a nonlinear decrease in canine cerebral oxygen consumption between zero and 1 MAC halothane, with the majority of the decrease seen during the period when the EEG changed to sustained high-voltage activity. It should be noted that frontal EEG dominance is not observed in dogs or cats with halothane, enflurane, isoflurane, or thiopental.[23] This species difference may be related to the anatomic frontal lobe development seen in primates.

Whether a "dose–response" curve exists for "anesthesia" has been extensively discussed.[17,24,25] The pharmacologic definition of a dose–response curve cannot be satisfied because end points of observation have differed (*e.g.*, movement in response to painful stimulus, eye opening on command, EEG changes). Nonetheless, comparisons of MAC,[26] MAC-awake,[22] and the concentrations at which the EEG changed (reported herein) with oil:gas solubility ratios yield similar correlations. This indicates that, though perhaps they are not points on the same dose–response curve, the use of MAC fractions in comparisons of different agents is valid. These observations also provide support for the lipid-solubility concepts as a basis for the mode of action of inhalational anesthetics.

We cannot state from this study that onset of EEG anterior dominance is a reflection of the point at which awareness is lost. Administration of 1 MAC of a volatile anesthetic is generally accepted to be more than sufficient to prevent awareness.[18] Future studies may indicate whether the presence of anterior amplitude dominant EEG activity, sustained after stimulation, may be useful in providing assurance of obliteration of awareness. If so, this will enable administration of lower anesthetic concentrations, thereby minimizing physiologic trespass and the possibility of toxicity.

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