REVIEW ARTICLE

ELECTROENCEPHALOGRAPHY IN ANESTHESIOLOGY

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In the past decade, many new drugs and new instruments have been made available to the anesthesiologist. One of the most widely applied devices associated with these advances has been the electroencephalograph. Since the literature regarding this application now has grown to several hundred articles in many languages, it appears advisable to attempt an assessment of the usefulness of electroencephalography in the clinical practice of anesthesiology.

The occurrence of electrical potentials in the brains of animals was first noted by Caton,[1] in 1875. The effects of chloroform anesthesia on brain waves were noted by von Marxow,[2] in 1890. In 1929, Hans Berger, of Jena, the "father of electroencephalography," demonstrated that the electrical potentials of the human brain could be recorded from electrodes placed on the surface of the head. There followed a series of investigations in this new field. Included among these was his demonstration of the effect of chloroform anesthesia on the brain potentials of humans, in 1933.[3] Early investigators [4, 5, 6] studied the correlation between the effects of anesthesia on the electroencephalogram and certain reflex states, but it was not until Gibbs, Gibbs and Lennox [7] published their work in 1937 that any suggestion was made that the method might be applied during anesthesia. They stated as follows: "A practical application of these observations might be the use of the electroencephalogram as a measure of the depth of anesthesia during surgical operations. The anesthetist and surgeon could have before them on tape or screen a continuous record of the electric activity of both heart and brain."

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Rubin and Freeman,[8, 9] in 1940 and 1941, reported changes associated with the use of light planes of cyclopropane anesthesia. Brazier and Finesinger,[10] in 1945, studied barbiturates and noted differences in cortical activity associated with the size of the dose. Courtin,[11] in 1950, and later, Kiersey [12] and Possati and Hunter,[13] all working with two of us (Bickford and Faulconer), classified the electroencephalographic changes produced by ether,[11] thiopental [12] and cyclopropane [13] under surgical conditions. The effects of other agents have been studied since by various authors.

MECHANISM OF ELECTROENCEPHALOGRAPHIC CHANGES

While the mechanism underlying the normal electrical activity of the cortex is little understood, recent evidence suggests that the rhythms represent fluctuating potentials produced from dendrites.[14] Hence, it appears that sequential changes in the electroencephalographic pattern described in relationship to anesthetic agents probably arise from chemical action primarily in this region of the neuron. However, it is also clear that anesthetic agents may have a depressive effect on the spike discharge from the neuron cell body as it is recorded by the micro-electrode technique.[14] However, these spike potentials probably do not contribute to the electroencephalogram and are presently of no practical significance in anesthesiology because of unsolved technical difficulties of single-unit recording in man.

From the clinical standpoint, one of the more fortunate effects of anesthetic agents on the brain is their tendency to limit individual variation in wave patterns seen in the normal electroencephalogram, so that a relatively characteristic series of changes is produced by any one agent. If this ironing out of individual variation were not a feature of the anesthetic state, variability of pattern at any one level

clearly would preclude practical use of the technique in monitoring depth of anesthesia.

As moderate to deep stages of anesthesia are reached, a further simplifying tendency becomes apparent with the disappearance of local differences in cortical electrical activity. Thus, at the stage of "burst suppression," the entire brain may appear to discharge as a unit, this synchrony of activity being maintained at cortical and subcortical structures.[15] These observations require the existence of some synchronizing system relating electrical activity in different cortical and subcortical regions. In fact, the studies of Swank [16] have shown the existence of such a network by the use of techniques allowing isolation of cerebral lobes. Much recent work has tended to implicate the reticular activating system as a network responsible for control of cortical rhythms. This system, consisting for the most part of short multisynaptic elements, has been shown by French, Verzeano and Magoun [17] to be sensitive to blocking by anesthetic agents. It remains uncertain as to whether other diffuse neuronal integrating systems such as that described by Forbes and Morison [18] play a significant role in synchronization during deeper levels of anesthesia.

There remains a problem of the relationship of rhythms seen in the lighter stages of anesthesia to those of sleep. From the electroencephalographic standpoint, the two states apparently are separable, as the normal rhythms of sleep are not commonly seen during induction of anesthesia; however, during recovery from anesthesia, transition between the two states may be present that is electrically recognizable. Thus, it appears likely that the anesthetic agent is not acting via systems responsible for the sleep state.

Studies of Specific Anesthetic Agents

In the following classifications of electroencephalographic changes, a general basic pattern can be constructed (fig. 1). Early in the variations from normal comes an increase in frequency to 20 to 30 cycles per second. As consciousness is lost, this pattern of small rapid waves is replaced by a large (50 to 300 microvolts) slow wave (1 to 5 cycles per second) that increases in amplitude as it slows. The wave may become irregular in form and repetition time, and it may have secondary faster waves superimposed as the level of anesthesia deepens. The amplitude next begins to decrease, and periods of relative cortical inactivity (the so-called burst suppression) may appear until the depression finally results in the entire loss of cortical activity and a flat or formless tracing.

Nitrous Oxide. Beecher and McDonough,[4] in 1939, included nitrous oxide in their investigation of the effects of 17 anesthetic agents on the electroencephalogram of the cat. While depth classification was not attempted, this constitutes the first record of the effects of the drug on brain potentials. Faulconer, Pender and Bickford,[19] in 1949, studied the effects of nitrous oxide at increased pressures without hypoxia in humans and noted distinct changes in the electroencephalogram. As consciousness was lost, the waking frequencies, which had decreased in amplitude during induction, were replaced by slow waves (2 to 4 per second) of progressively greater amplitude. Deepening the anesthesia increased the amplitude of the slow waves to 40 to 70 microvolts; thereafter, fluctuations in amplitude occurred that could not be correlated with clinical estimates of the depth of anesthesia. Burst suppression was not evident. In 1952, Faulconer [20] showed that a concentration of nitrous oxide in excess of 10 mg. per 100 ml. of blood reduced the amount of ether needed to reach a given electroencephalographic level of anesthesia.

Pearcy, Knott and Bjurstrom [21] observed wave forms of 5 to 7 cycles per second with administration of 70 per cent nitrous oxide and

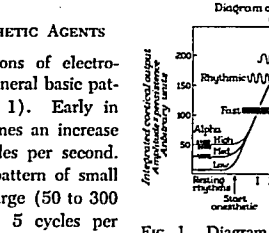

FIG. 1. Diagram of average changes in the electroencephalographic pattern during anesthesia.

noted their modification by supplementary opiates.

Courtin [22] demonstrated that the addition of 60 to 70 per cent nitrous oxide to the inspired gas slowed the frequency and increased the amplitude in the electroencephalographic pattern of humans under light trichloroethylene anesthesia.

Ethylene. Beecher and McDonough [4] reported that ethylene was similar to other volatile anesthetic agents in its effect on the electroencephalogram of the cat during both "light" and "deep" phases of the experiments. In their studies, "deep" referred only to that level which barely suppressed the flexion reflex. Attempts at classification of depth were not made.

Diethyl Ether. Courtin and co-workers [11, 23] were the first to demonstrate the usefulness of electroencephalographic changes in the operating room. They classified the results of administration of ether into seven distinct "electroencephalographic levels of anesthesia," which were reproducible and reasonably constant from one patient to another. These levels (fig. 2) are described below as they occur during deepening ether anesthesia. Their standard leads were bipolar and fronto-occipital.

LEVEL I (Flat). Alpha waves disappear as consciousness is lost. Low-amplitude (30 microvolts) fast discharges (20 to 30 cycles per second) occasionally are seen in the otherwise flat tracing. The duration of this stage is about 7 minutes with the usual induction of ether anesthesia.

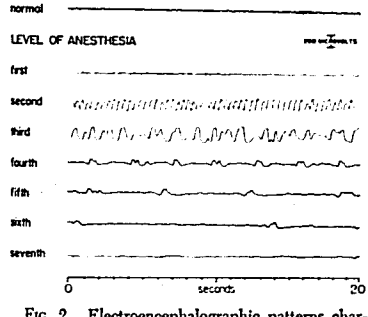

FIG. 2. Electroencephalographic patterns characteristic of successive electroencephalographic levels of anesthesia. (Reproduced with permission of the authors from Courtin and associates.[11])

LEVEL II (Rhythmic). This stage is marked by the sudden appearance of slow waves (average 2 to 8 cycles per second) of high amplitude (200 to 300 microvolts), with pronounced rhythm and lack of interference. The duration is about 60 seconds.

LEVEL III (Complex). Rhythmicity is abruptly lost and a complex of slow waves with superimposed faster waves appears. The amplitude is less than that in level II. Suppression does not appear.

LEVEL IV (Slight Suppression). The burst suppression that characterizes deeper levels of anesthesia appears, with no suppression lasting longer than 3 seconds. The waves are 2 to 4 cycles per second, with an average amplitude of 150 microvolts. During the suppression, the activity is less than 20 microvolts.

LEVEL V (Moderate Suppression). The periods of suppression last 3 to 10 seconds, and the intervening waves are usually single and of smaller amplitude than those of level IV.

LEVEL VI (Severe Suppression). Periods of activity do not occur more frequently than once every 10 seconds and there is no tendency toward regularity. The amplitude is about 70 microvolts.

LEVEL VII (Complete Suppression). Measurable waves are absent and the activity does not exceed 20 microvolts.

Intermediate patterns are seen, most frequently between levels I and II. Recovery patterns closely mirror the tracings obtained during induction until light planes of anesthesia are reached, after which emergence varies with the duration of anesthesia. Emergence from longer periods of anesthesia often is associated with return of low-amplitude waves of 8 to 13 cycles per second prior to return of responsiveness to pain or voice. Sleep rhythm also may appear.

Courtin [23] observed that abdominal relaxation was excellent in level V, moderate in level IV and inadequate or absent in level III. Level III was required for quiet during incision of the skin.

Faulconer [20] investigated the concentrations of ether in arterial blood at various electroencephalographic levels of anesthesia in hu-

mans and found an almost linear correlation between the mean concentration and the electroencephalographic levels as just defined. This confirmed the value of the electroencephalogram in the quantitative assessment of at least one consistent effect of the drug.

Artusio,[24] and Bellville and Artusio,[25] subdivided the classic stage I (Guedel) of ether anesthesia to include a state of analgesia and described for it an electroencephalographic pattern with an amplitude of 30 to 40 microvolts and a dominant frequency of 20 to 24 cycles per second. This focuses clinical interest on the level I depicted by Courtin. At this level, patients are said to be free of pain and responsive to the spoken voice. Bellville and Artusio postulated that this represents a block between thalamus and cortex, which suppresses the perception of pain without significantly depressing the recticular activating system. The mean concentration of ether in the blood for this analgesic state was 11.3 mg. per 100 ml. Further depth of anesthesia produced loss of consciousness and the appearance of slow waves.

Clowes and co-workers [26] also studied ether anesthesia in dogs and humans and found six levels of activity that were of the same order as those described by Courtin.[11] Measurement of ether in the blood confirmed the work of Faulconer.[20]

Cyclopropane. Beecher and McDonough [4] included cyclopropane in their survey of anesthetic effects on animal cortical potentials. However, as already noted, a depth classification was not presented.

Rubin and Freeman [8, 9] studied the effects of cyclopropane on the human electroencephalogram in 1940. They observed a decrease in frequency and an increase in amplitude as alpha activity was lost; high-amplitude waves of great regularity at 3 cycles per second appeared. Their patients then were permitted to emerge from anesthesia. These changes apparently represented superficial levels of anesthesia and were not associated with the surgical procedure.

Possati, Faulconer and Bickford,[13] in 1953, published their observations on cyclopropane anesthesia for surgical procedures. Electroencephalographic patterns were correlated with blood levels of the drug. They defined six levels of activity, the first five of which are much like those of ether except that the amplitude tended to be less than that for ether (fig. 3). Little activity was present in level VI, the tracing appearing to be an almost flat line. Again, an almost linear relationship existed between the mean concentration of gas in the blood and the classified sequence of electroencephalographic changes. This supported the validity of the method in assessing the degree of activity of the anesthetic agent.

Davis and co-workers [27] showed that the effect of cyclopropane is more pronounced at the level of the reticular activating system in the midbrain that it is on the thalamic evoked response.

Chloroform. Beecher and McDonough [4] also included chloroform in the series of drugs studied for their effects on the cat electroencephalogram in 1939.

Pearcy and associates [28] studied the correlation of the electroencephalographic changes in the dog with the concentration of chloroform in the blood. Six distinct and reproducible levels were defined as follows (fig. 4):

LEVEL I. Shortly after the start of administration, waves of slower frequency and higher amplitude appear against the fast, low-amplitude, background activity.

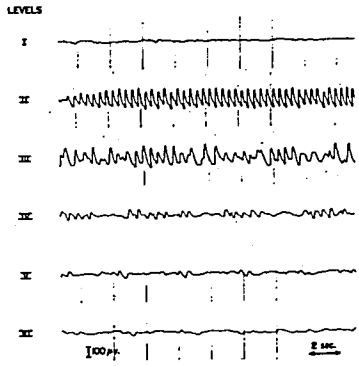

FIG. 3. Electroencephalographic levels of cyclopropane anesthesia in humans. (Reproduced with permission of the authors and the publisher from Possati and co-workers.[13])

LEVEL II. The low-voltage, fast activity returns.

LEVEL III. Frequencies in the "beta range" suddenly appear, with activity in the range of 20 to 30 cycles per second.

LEVEL IV. Slow high-voltage waves of the delta type appear as this level begins and increase in prominence, organization and voltage as the level progresses.

LEVEL V. The sudden end of the waves of 20 to 30 cycles per second initiates this level, leaving the slow waves dominant. A variable and irregular amount of activity in the theta range is present.

LEVEL VI. The amplitude of the slow delta waves decreases. Fewer theta waves are present than in level V.

Pearcy's group did not find burst suppression despite the terminal flattening of the tracings. Surgical anesthesia as confirmed by appropriate concentrations of chloroform in the blood was accompanied by the patterns described for levels II, III and IV.

Certain comparisons were made between patterns seen during surgical anesthesia with chloroform in dogs and those seen during ether analgesia and early in the administration of thiopental in humans. Because of possible species differences, conclusions were not drawn.

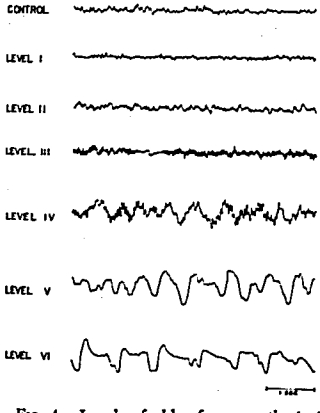

FIG. 4. Levels of chloroform anesthesia in the dog. (Reproduced with permission of the authors and the publisher from Pearcy and co-workers.[28])

Barbiturates. Derbyshire and co-workers,[6] in 1936, studied the action of pentobarbital (Nembutal) on the cerebral action potentials and the evoked reflex responses of the cat.

Gibbs, Gibbs and Lennox,[7] in the following year, described continuous multilead tracings in man before and during the administration of phenobarbital, pentobarbital, hexobarbital (Evipal) and sodium bromide. An effect was not apparent unless drowsiness or sleep occurred. With phenobarbital, large waves of 14 cycles per second appeared with sleep. They produced "surgical anesthesia" by the intravenous injection of pentobarbital and hexobarbital. Their tracings showed a change to fast activity prior to unconsciousness that faded as slow waves of 1 to 2 cycles per second appeared after consciousness was lost. Burst suppression was seen as narcosis deepened. A great similarity exists between their tracings and those later described for thiopental by Kiersey, Bickford and Faulconer.[12]

Beecher and McDonough[4] also included hexobarbital and pentobarbital in their aforementioned study on the cat. They noted the similarity to sleep patterns under the conditions of their experiments.

Brazier and Finesinger,[10] in 1945, described the effects of amobarbital (Amytal), thiopental and pentobarbital in small doses on humans. The initial change was the appearance of "high-voltage, fast activity," which decreased with the appearance of delta waves as the dose became larger.

Finesinger and associates[29] subsequently investigated levels of consciousness and electroencephalographic effects induced by thiopental. High-voltage, fast activity appeared with early hypnosis and euphoria and showed an abrupt transition to slow waves with scarce fast activity as consciousness was lost.

Courtin's group[11, 23] found that induction with thiopental had a specific effect on the tracings of early ether anesthesia. Slow waves of low amplitude with superimposed faster frequencies appeared in place of ether level I in the induction sequence and delayed the time of appearance of ether level II.

In 1951, Kiersey, Bickford and Faulconer[12] reported the first systematic study of electro-

encephalographic changes produced by thiopental in the operating room and classified their findings for practical use into the following five levels (fig. 5):

LEVEL I (Fast). High-amplitude (75 to 80 microvolts) fast waves (10 to 30 cycles per second) of spiky appearance vary with fast waves of somewhat less amplitude.

LEVEL II (Complex). Slower wave forms of irregular contour and random occurrence appear. The frequency varies widely and may be as low as 2 cycles per second, with an amplitude up to 150 microvolts. Superimposed on and between these slow waves are spiky waves of irregular amplitude with frequencies of about 10 cycles per second.

LEVEL III. Recognizable suppression occurs but is less than 3 seconds in duration. Bursts that frequently have two phases separate the quiet periods. The first phase, of about 1-second duration, has a frequency of about 10 cycles per second. A second phase of two or more slow waves (about 2 cycles per second) then tails off into the next suppression.

LEVEL IV. This is marked by suppression phases lasting 3 to 10 seconds, with activity as in level III but of slightly less amplitude.

LEVEL V. There is no activity more frequent than once each 10 seconds. The amplitude lessens and may decrease to less than 25 microvolts.

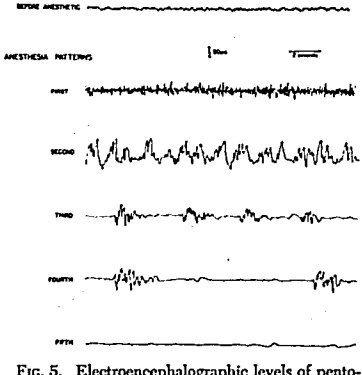

FIG. 5. Electroencephalographic levels of pentothal anesthesia in humans. (Reproduced with permission of the authors and the publisher from Kiersey and associates.[12])

Shimazono and co-workers[30] reported studies on barbiturates in 1953 and found an early increase in and later absence of fast activity in the electroencephalographic tracing as anesthesia deepened.

Bickford's group,[15] working with depth electrography in humans, found that barbiturates caused burst suppression also in the deeper regions of the brain. They noted that fast activity was more abundant in the frontal zones, less in the pontine area and absent in the occipitoparietal regions.

Wyke[31] made the interesting observation that the increased cortical activity associated with light levels of barbiturate anesthesia in the cat frequently was associated with convulsive motor phenomena. These convulsions disappeared with increased depth of anesthesia and occurred in animals even in the absence of hypoxia, hypercarbia, hyperthermia or hypoglycemia. He thought that the convulsions seen during anesthesia may be caused by extremely light anesthesia and the resultant cortical stimulation and may tend to occur in patients with convulsive tendencies. He referred to the accepted practice of using light sedation with barbiturates to unmask convulsive tendencies for diagnostic electroencephalography.

Trifluoroethylvinyl Ether (Fluoromar). Brechner and Dornette[32] classified the electroencephalogram associated with use of trifluoroethylvinyl ether in man after induction of anesthesia with nitrous oxide. Because of the decreased blood pressure associated with deeper levels of anesthesia produced by trifluoroethylvinyl ether, their patients were maintained for long periods in light anesthesia. Consequently, these workers did not determine whether burst suppression occurred in "deeper" anesthesia and they did not carry the doses to the stage in which cortical electric suppression was produced. Their classification follows (fig. 6):

FIRST PATTERN. The resting alpha rhythm is replaced by faster activity of 15 to 25 cycles per second, with a decrease in voltage from control values of 25 to 50 microvolts to levels of 25 microvolts or less.

SECOND PATTERN. Waves of slower frequency (4 to 6 cycles per second) and low voltage (up to 50 microvolts) appear as

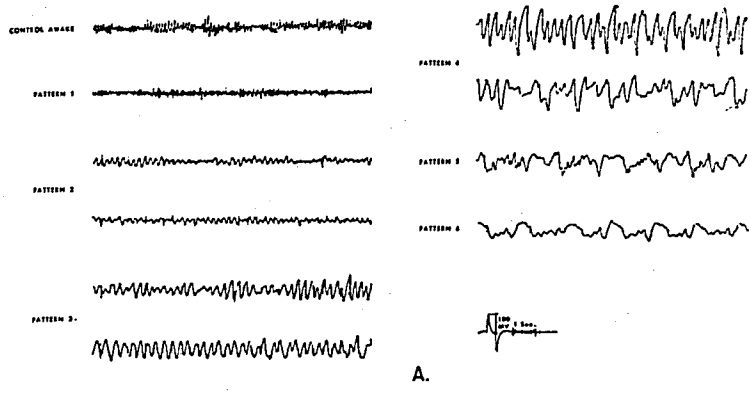

FIG. 6. Electroencephalographic patterns during nitrous oxide-Fluoromar anesthesia in humans. (Reproduced with permission of the authors and the publisher from Brechner and Dornette.[32])

spindles lasting 6 to 8 seconds superimposed on the fast activity of the previous level. As the level becomes well established, the pattern becomes regular and symmetric, and the spindling disappears.

THIRD PATTERN. The fast background activity ceases, and the dominant waves increase in voltage and slow in frequency. Transition patterns show notching and spindling, but the well-established pattern is that of regular waves of 3 to 5 cycles per second and an amplitude of 75 to 125 microvolts.

FOURTH PATTERN. This pattern shows irregular large slow waves (100 to 300 microvolts, and 2 to 4 cycles per second), with no tendency to repeat themselves.

FIFTH PATTERN. The dominant forms are fairly regular, slow, high-voltage waves of long duration. They appear at a rate of one every 1 to 2 seconds, with a spread of about 1 second. Their voltage varies from 100 to 175 microvolts. Superimposed on and between these slow waves are faster ones of 3 to 5 cycles per second and an amplitude of 25 to 75 microvolts.

SIXTH PATTERN. The dominant slow-wave frequency decreases to one every 2 seconds. The superimposed waves of 3 to 5 cycles per second decrease to 25 to 50 microvolts and appear only between the dominant waves.

Fluothane. Gain and Paletz[33] published their observations on electroencephalography in humans during anesthesia produced by use of 1,1,1-trifluoro-2,2-Bromochlorethane (Fluothane). They identified seven changes in pattern from induction to complete cortical suppression. Severe physiologic changes were associated with level IV and beyond; however, they reported good operative conditions with level III or less if ventilation is assured. These levels are as follows (fig. 7):

LEVEL I. The pattern obtained while the patient is awake changes to fast, low-voltage waves (15 to 20 cycles per second, and amplitude of 10 to 25 microvolts).

LEVEL II. Slow waves of 3 to 6 cycles per second and an amplitude of 50 microvolts appear; the fast, low-voltage activity is superimposed.

LEVEL III. Slow waves are 4 cycles per second, with an amplitude of 50 to 100 microvolts; the fast activity is disappearing.

LEVEL IV. The fast activity has disappeared. Only slow waves remain, with an amplitude of 100 to 300 microvolts and a frequency of 2 to 3 cycles per second. Many are notched and irregular.

LEVEL V. The slow waves now have a frequency of 1 cycle per second and an amplitude of 100 to 200 microvolts; between them

appear smaller and faster waves, with an amplitude of 25 to 50 microvolts and a frequency of 6 to 8 cycles per second.

LEVEL VI. The slow-wave frequency is 1 cycle per 2 or 3 seconds. The superimposed and interposed waves of 6 to 8 cycles per second have a reduced amplitude of about 25 microvolts. The first burst suppression appears.

LEVEL VII. There is now no cortical electric activity for an extended period; complete absence of any wave form is noted.

An interesting similarity is present between this description and that of Brechner and Dornette concerning the effects of trifluoroethylvinyl ether.

Trichloroethylene. Gibbs, Gibbs and Lennox [7] mentioned trichloroethylene in their 1937 investigation as an agent that had no effect on the electroencephalogram. It was used in minute doses in one experiment only. Beecher and McDonough [4] classed its effects with those of the other volatile agents they studied. Little note of this agent was made until the publication of Courtin,[22] in 1955, describing the administration of trichloroethylene and nitrous oxide. He noted the following three electroencephalographic levels of anesthesia and showed that the presence of nitrous oxide affects the tracing (fig. 8):

LEVEL I (Fast). The amplitude of the tracing as compared to that of the awake patient is diminished and its frequency is increased. Clinically, this represents increasing analgesia followed by unconsciousness.

LEVEL II (Rhythmic). The tracing shows rhythmic large slow waves, with an amplitude of 100 to 200 microvolts and a frequency of 3 to 5 cycles per second. If nitrous oxide is discontinued, this pattern tends to revert toward that of the level I tracing.

LEVEL III (Complex). Rhythmicity is lost, the frequency remains low and the amplitude is high.

Patients who are premedicated with atropine and pentobarbital tolerate operation well in level II. Tachypnea and arrhythmias are seen in level II if the patient is not premedicated, are rare if premedication is used, and are severe in all patients in level III. The technique that Courtin described permits maintenance of anesthesia at level II for prolonged operations. Apparently adverse effects of trichloroethylene on the respiratory and cardiovascular systems have precluded searching for patterns of burst suppression at deeper levels of anesthesia.

MISCELLANEOUS ANESTHETIC AGENTS

Amylene hydrate and *tribromoethanol* given separately were found by Beecher and McDonough [4] to modify the cortical potentials of cats, and Derbyshire and associates [6] noted that "Avertin" was distinct from ether in its action on the cerebral action potentials of cats.

Beecher and McDonough [4] classified *divinyl ether* (Vinethene) with other volatile anesthetic agents, and Davis and co-workers [34] noted that Vinethene had a greater effect on the midbrain reticular activating system than it did on the thalamus. Classification of levels in man is not available.

Ethyl chloride was studied by Ujiie,[35] who noted decreased frequency and increased amplitude as the electroencephalographic level of anesthesia deepened. He found the electroencephalogram to be an adequate indicator of the depth of narcosis produced by ethyl chloride. The agent was included in Beecher and McDonough's [4] study without classification of the level.

Procaine hydrochloride (Novocaine) obliterates the rapid activity of the cerebellum when applied topically, as described by Swank and Brendler.[36] *Lidocaine* (Xylocaine) administered intravenously has been shown by Ottoson [37] to reduce the cortical after-discharge following electroconvulsive therapy. He quoted evidence that grand mal and Jacksonian seizures could be arrested by the intravenous injection of lidocaine.

Effects of *xenon* on the electroencephalogram were reported by Morris, Knott and Pittinger [38] and by Pittinger and co-workers [39] at normal [38] and increased [39] pressures. These investigators were unable to catalogue "levels" even at increased pressures and the production of profound clinical anesthesia. Patterns of burst suppression and total suppression were not seen even at maximal concentrations.

The effects of *hydroxydione* (Viadryl), a steroid anesthetic agent, were examined electroencephalographically by Scott and Gordon.[40] Sleep and surgical anesthesia were produced

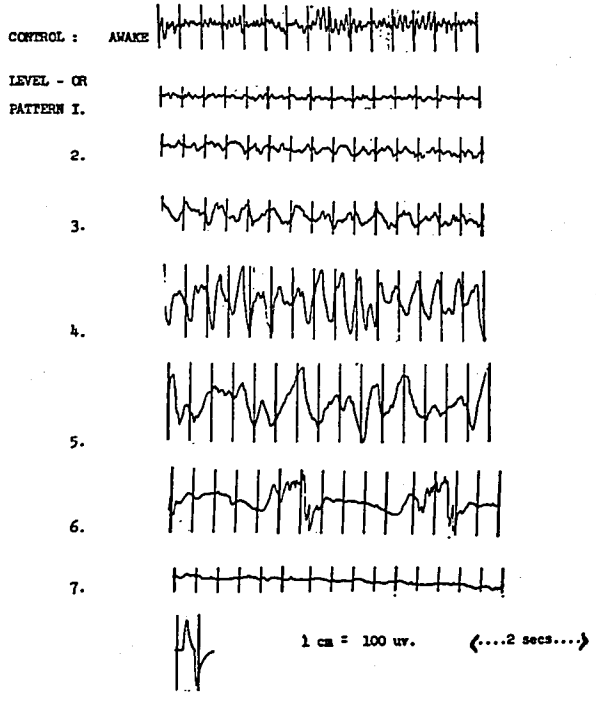

FIG. 7. Electroencephalographic levels of fluothane anesthesia in humans. (Reproduced with permission of the authors and the publisher from Gain and Paletz.[33])

without evidence of suppression of alpha activity. Slow waves (4 to 5 cycles per second) of increased amplitude appeared after induction and disappeared after 15 to 20 minutes. Thereafter, the tracing reverted to waking patterns despite the fact that the patients were asleep and relaxed with use of hydroxydione and 75 per cent nitrous oxide in oxygen. Boyan, Howland and Bellville [41] studied the electroencephalograms of 20 patients who were anesthetized with hydroxydione and found four distinct patterns as anesthesia deepened (fig. 9). The first level increased in amplitude (20 to 60 microvolts) and frequency (10 to 24 cycles per second) over resting activity, but its onset was delayed to 4 or 5 minutes after intravenous administration of the drug was begun. The second level was typified by a compound pattern with a basic frequency of 8 to 12 cycles per second and an amplitude of 60 to 100 microvolts; superimposed low fast activity produced a "spiky" effect. The third level showed burst suppression of several seconds' duration. The fourth level had widely spaced bursts of activity of less than 20 microvolts in an otherwise almost flat tracing. They noted movement of the patient in response to painful stimulation even at level IV of anesthesia produced by hydroxydione and oxygen.

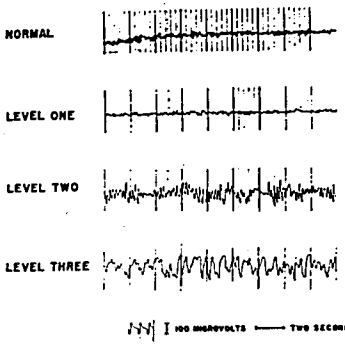

FIG. 8. Electroencephalographic levels of nitrous oxide-trichloroethylene anesthesia in humans. (Reproduced with permission of the author and the publisher from Courtin.[22])

EFFECTS OF OTHER DRUGS

Gibbs and associates,[7] in 1937, investigated numerous drugs to determine their effect on the electroencephalogram and found that *epinephrine* (Adrenalin), *amphetamine* (Benzedrine), *caffeine with sodium benzoate, ergotamine tartrate, histamine, vasopressin* (Pitressin), *sodium nitrite* and *strychnine* were without detectable cortical influence in the awake patient. Epinephrine had no effect on the electroencephalogram in 18 awake patients studied by Gottschalk.[42]

Cass [43] used two groups of subjects narcotized with barbiturate to evaluate *bemegride* (Megimide) and found that this drug would revert the electroencephalogram affected by barbiturates to lighter patterns of narcosis. By itself, bemegride has the effect of a convulsant on the tracing of the awake patient. This can be blocked readily by small doses of barbiturate. Bemegride was not so effective in lessening the degree of narcosis if given after chloralose or ether.

The effects of *muscle relaxants* on the brain were first clarified by Smith and co-workers,[44] in 1947. An adult male volunteer was curarized, ventilated and allowed to recover. The electroencephalogram showed no change with curarization or administration of *neostigmine*, and the subject was awake throughout the study. Kiersey, Bickford and Faulconer [12] found that curare had no effect on the levels of thiopental if hypoxia and hypercarbia were avoided. Pirsch and McCrum [45] found that *erythroidine* had no effect on the electroencephalogram of ventilated cats. Davis and co-workers [34] could find no changes in the electroencephalogram of the cat from *curare, gallamine triethiodide* (Flaxedil), *decamethonium* (Syncurine) or *succinylcholine* that could not be attributed to hypotension, hypoxia or hypothermia.

Shea, Davidson and Davis [46] reported a technique of prolonged respiratory paralysis with curare plus controlled respiration with oxygen

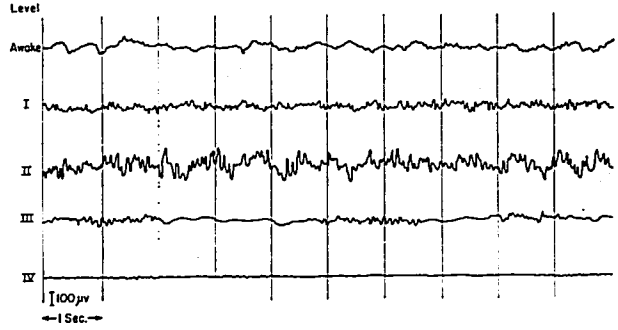

FIG. 9. Electroencephalographic patterns of hydroxydione anesthesia in humans. (Reproduced with permission of the authors and the publisher from Boyan and associates.[41])

after induction of anesthesia with 500 to 750 mg. of thiopental and minimal succinylcholine for intubation of the trachea. They noted recurrence of alpha activity unsuppressed by visual stimulation as long as curarization was "complete." The similarity of the tracing to that seen in hypnosis and hysterical blindness was discussed. These authors speculated on the presence of afferent sensory blockade with curare. Neostigmine in doses sufficient to overcome curarization produced return of the normal effects of visual stimulation on alpha rhythm. They reported no evidence of patient discomfort.

The use of *opiates* with nitrous oxide and thiopental is a widespread practice. Mazzia, Poznak and Artusio [47] found that *alphaprodine* (Nisentil) did not affect the servoanesthetic dose of thiopental when a 60-mg. dose given intravenously was added to stabilized thiopental anesthesia. Wikler [48] noted that large doses of morphine in persons who formerly had been addicted to its use produced slowing of the electroencephalographic waves while increasing their amplitude. These doses were administered slowly and were not associated with quantitative changes in consciousness. Pearcy, Knott and Bjurstrom,[21] using a vertex-ear lobe bipolar pickup rather than the usual fronto-occipital lead, found that intermittent doses of up to 300 mg. of *meperidine* (Demerol) imposed an irregular mixture of electrical activity of 5 to 30 cycles per second on the normal pattern of 5 to 7 cycles per second induced by a mixture of 70 per cent nitrous oxide and 30 per cent oxygen in man. As meperidine was injected more rapidly, the faster frequencies began to disappear and larger waves as slow as 1 cycle per second occurred. When meperidine was given first, the addition of nitrous oxide produced a sudden onset of slow waves rather than the usual, more gradual slowing of frequency.

Antagonists to opiates have been observed clinically to relieve the medullary depression caused by opiates but not necessarily to restore consciousness. Pearcy, Knott and Bjurstrom [21] stated that administration of *levallorphan* (Lorfan) to patients anesthetized by a combination of meperidine and nitrous oxide caused further slowing of frequencies in the electroencephalogram.

Carbon Dioxide

Rubin and Freeman [6, 9] noted that accumulation of carbon dioxide hastened the onset of deeper levels of cyclopropane anesthesia and made the slow rhythms more pronounced and regular.

In 1943, Brazier [49] reviewed the effects of changes in the amount of carbon dioxide in the blood on the electroencephalogram. She concluded that a decrease in the carbon dioxide tension, such as that resulting from voluntary hyperventilation in man, results in high-voltage, slow waves that are a function of the decrease in carbon dioxide and not of anoxia secondary to vasoconstriction. However, other workers have shown that hyperventilation with oxygen produced less alteration in brain potentials than did hyperventilation with air and that the waves produced by hyperventilation could be obliterated by having the subject inhale amyl nitrite in small quantities, which produces vasodilatation. Brazier noted that increase in the carbon dioxide tension of arterial blood increased the average frequency of brain potentials, and that inhalation of a mixture of 10 per cent carbon dioxide in oxygen decreased the voltage of the slow waves produced by hyperventilation and also those seen in petit mal. This does not occur when oxygen is used alone.

Clowes and co-workers [26] studied 8 patients stabilized at level III of ether anesthesia who were subjected to accumulation of carbon dioxide. They reported that progressive hypercapnia increased the depth of anesthesia as measured on the electroencephalogram in a predictable and reproducible manner, while the concentration of ether in the blood remained unchanged. This did not hold true, however, for levels I and II of ether anesthesia.

Ujiie [35] noted that evidence of an increase in carbon dioxide can be particularly well seen in the electroencephalogram. Holmberg [50] found that inhalation of 4.5 per cent carbon dioxide prevented the changes in frequency usually resulting from breathing 6.5 per cent oxygen in nitrogen. The conclusion was that these changes are hypocapneic and not anoxic.

Anoxia

The effect of inadequate cerebral oxygenation on the electroencephalogram has been

widely commented upon. Heymans and associates,[51] in 1937, found that circulatory arrest of more than five minutes' duration deprived their animals of certain higher centers needed for survival. In the following year, Lennox, Gibbs and Gibbs [52] studied the electroencephalogram of patients who had carotid-sinus syncope or orthostatic hypotension. They noted that consciousness was suddenly lost and high-voltage, slow waves appeared after 6 to 8 seconds of circulatory arrest. Shortly thereafter, the slow activity became progressively slower and lost amplitude until the record flattened completely. The sequence reversed itself as circulatory adequacy was restored.

Iwama [53] reported on patients who breathed 6 to 11 volumes per cent oxygen for 5 to 7 minutes. During the most severe lack of oxygen, small fast activity appeared within 60 seconds and was replaced in 2 to 3 minutes by slow large waves. Recovery was in reverse order, but normal patterns did not recur for a considerable time.

Ten Cate and Horsten [54] studied graded arterial occlusion in cats and dogs and found that total disappearance of electrical activity of the brain depended on occlusion of all arteries supplying that organ.

Clowes and associates [26] investigated anoxia in anesthetized dogs and found no effect on the electroencephalogram until the hemoglobin of arterial blood reached 40 per cent saturation with oxygen. Arduini and Arduini [55] found that the reticular formation exhibited pronounced sensitivity to lack of oxygen, its electrical potentials disappearing much sooner than those of other regions of the brain.

Luft and Noell [56] produced acute anoxia in conscious adults by decompression. They showed that the onset of electric changes came about 15 seconds after exposure and that the electrical activity disappeared in as little as 3½ seconds more.

Bellville, Artusio and Glenn [57] reported one instance in which slow waves appeared 3 seconds after accidental torsion of the great vessels during cardiac manipulation. Bellville and Howland [58] described an initial transient increase in frequency and amplitude of the electroencephalographic waves after sudden complete hypoxia. This change was followed in 1 or 2 seconds by slow waves of increasing amplitude. The amplitude then decreased to a flat tracing after about 20 seconds of cortical circulatory arrest.

Following "anoxic accidents," Grönqvist and co-workers [59] reported the appearance in some cases of a "file pattern" of sharp, fast, low-amplitude waves superimposed on an otherwise almost flat electroencephalogram. They suggested that this picture was of grave prognostic significance. When considerable electric activity returned fairly promptly after an episode of hypoxia, the outlook was more favorable.

Theye, Patrick and Kirklin [60] commented on the electroencephalographic changes seen during extracorporeal circulation. When the baseline tracing was at level I of ether anesthesia, they noted 26 instances in which waves of 1 to 2 cycles per second and 100 to 300-microvolt amplitude appeared. These changes were the result of alterations in cerebral perfusion; the changes in 13 instances were caused by cerebral venous congestion due to obstruction of the superior vena cava, in another 12 they were due to a reduction of cardiac output and in one they were caused by interruption of perfusion. While transient similar changes can be seen at the start of perfusion, their appearance at any other time indicates abnormal cerebral perfusion and requires prompt and vigorous treatment.

Thus, the electroencephalogram is a sensitive index of cerebral anemia. Anoxic anoxia or stagnant anoxia will produce first an increase in rate and amplitude of the waves, followed by pronounced slowing, a great increase in amplitude and finally a decline in amplitude and rate to a flat tracing. These changes have been reported by Owens and co-workers [61] to be useful in the analysis of the effectiveness of pump-oxygenators for extracorporeal circulation.

Premedication

Gibbs, Gibbs and Lennox [7] gave scopolamine or atropine in doses of 1/100 to 1/50 grain intravenously to humans and noted first a decrease in voltage of all waves, after which bursts of regular, high-voltage waves with a frequency of 10 cycles per second were seen. The bursts came frequently at about 10-second intervals, lasting 1 to 3 seconds. The patients

remained awake. These authors found that the intravenous administration of morphine in doses of ¼ grain produced effects similar to those of atropine in three patients. Sedative doses of barbiturates were without electroencephalographic effect.

Wikler [48] found that analgesic doses of morphine, methadone and meperidine usually have no significant effect on the electroencephalogram of resting humans.

Taylor's group [62] studied the effects of various drugs on the concentration of ether in the arterial blood needed to produce anesthesia of electroencephalographic level IV in 52 patients. They found no significant reduction in the requirement for ether with ethinamate or a mixture of levorphan and levallorphan as premedication. Chlorpromazine, morphine or meperidine used for premedication significantly decreased the amount of ether in the blood needed to obtain level IV. Atropine alone was used as premedication in a control group.

Shagass [63] found no evidence of electroencephalographic change following intravenous administration of chlorpromazine (25 mg.) to 11 persons. The fast activity induced by intravenous injection of amobarbital also was not altered significantly by chlorpromazine. Andermann,[64] however, studied chlorpromazine, mepazine, reserpine and benactyzine and found that psychotic patients with scarce alpha activity had a more stable alpha rhythm after use of these drugs. This change was greatest in the temporal region, and he sought to associate it with changes in behavior attributable to the drugs.

Mazzia, Poznak and Artusio [47] were not able to measure any changes in the servomotor dose of thiopental when alphaprodine, levallorphan or chlorpromazine was added to the stabilized system. However, they did note clinical changes indicating increase in the depth of anesthesia.

Blood Sugar

Toman and Davis,[65] in 1949, listed many investigators who found that hypoglycemia causes a decrease in alpha activity that is reversible with ingestion of carbohydrates. Insulin coma produces an abrupt appearance of large slow waves as consciousness is lost. Hyperglycemia may protect against the discharges of petit mal but has no effect on the normal electroencephalogram. Wikler [48] noted that severe hypoglycemia may abolish cortical activity. The Arduinis [55] found this sensitivity to hypoglycemia most pronounced in the reticular system.

Hypotension

Changes in the electroencephalogram characteristic of hypoxia may accompany inadequate cerebral perfusion.[60, 61, 66, 67] Drug-induced vasodilatation to facilitate adequate perfusion of peripheral tissues has been a widely used technique and is often accompanied by hypotension. Van Bergen and co-workers [68] described the physiologic changes associated with hypotension produced in humans by hexamethonium. They demonstrated depression of the high-voltage, fast activity as arterial pressure declined; cortical activity ceased at levels of arterial pressure of about 50 mm. of mercury. The use of a vasopressor drug returned systolic pressure and cortical electric activity toward normal. They thought that the depression of activity resulted from inadequate cerebral perfusion and advised against the use of Fowler's position with the hypotensive technique.

Schallek and Walz,[69] using dogs to study hypotension produced by trimethaphan camphorsulfonate (Arfonad), found that decreasing the systolic pressure 10 mm. of mercury per minute permitted the animals to be maintained at a pressure of 40 mm. Hg for an hour without electroencephalographic effect. Rapid decreases in pressure, however, produced depression and slow waves that led to flattening of the record when the decrease was severe. They suggested that there may be a critical rate of vascular compensation.

Bellville and Artusio,[70] using a servoanesthesia mechanism with cyclopropane, were unable to demonstrate a reduction in anesthetic requirement associated with use of trimethaphan camphorsulfonate.

Hypothermia

Nims, Marshall and Nielsen,[71] in 1941, reported that direct freezing of small portions of the cortex obliterated cortical potentials from the frozen zone and severely disturbed

the patterns obtained from adjacent regions that were cooled to a lesser degree.

Koella and Ballin [72] found that "dial bursts" from the cortex of the cat decreased in frequency and amplitude and were less frequent in occurrence as temperature decreased. Background activity also diminished. Warming reversed this. At about 28 to 30 C., they noted typical "breaks" in the temperature curves.

Yoshii and colleagues [73] found a linear relationship between decline in background activity and decrease in temperature in cats and dogs anesthetized with barbiturates and subjected to hypothermia. Evoked thalamic potentials slowed somewhat with cooling to 28 C., and then declined to almost complete absence at 16 to 24 C.

A similar change in electrical activity in the brains of dogs was noted by de Castro,[74] who studied and classified five electroencephalographic patterns during administration of progressively increasing concentrations of ether as measured in arterial blood. These patterns were determined first at normal body temperature and again at 30 C. She described a progressive decrease in potential in a drug-paralyzed, unanesthetized dog during cooling to 30 C. The changes were reversed on warming.

Bok and Shadé [75] reported an interesting observation on the inverse relationship between changes in frequency and amplitude during cortical depression induced by drugs and by decreased temperatures. They found a decrease in frequency and an increase in amplitude of cortical waves in the rat as the temperature was lowered to about 30 C. Below this, the frequency remained constant and the amplitude decreased. If this relationship is set up as a quotient, one notes progressive divergence from normothermia to 30 C., then a return to "normal" as the temperature continues to decrease. The original relationship is re-established shortly before the animal dies from the effects of cold. They applied this amplitude-frequency quotient to prognosticate survival during arterial occlusion at hypothermic levels and concluded that the decrease in amplitude which begins after occlusion for varying lengths of time is the point at which the probability of survival begins to lessen. They also suggested that the critical level for hypothermia is that point at which the amplitude begins to decrease, and that cooling should not be continued beyond this point.

Servoanesthesia

Noting that the total output of electric energy of the cortex decreases as anesthesia deepens, Bickford [76] developed a device that stores energy to a set point and then releases it to activate a mechanism that delivers a single calibrated dose of drug to the patient. The mechanism then begins to store energy again until a sufficient amount accumulates to activate the dosimeter again. Thus, the more energy available, the more frequent will be the doses; then, as the level of anesthesia is deepened, the energy is reduced and the interval between doses is prolonged. As the interval lengthens, the patient is able to store, metabolize and excrete the anesthetic agent; thus, the level of narcosis lessens, the output of energy increases, and the interval between doses shortens. With this system, it is possible for a set level of electrical depression to be maintained.

Verzeano,[77] Soltero and associates,[78] Kiersey and co-workers,[79] Bellville's group [80] and Wyke [81] have all described such systems or commented upon their effectiveness. Thiopental, ether and cyclopropane have been administered by this technique.

Because of the substantial technical difficulty in its application, this method has not enjoyed widespread use in the operating room. In the laboratory, however, because it can maintain given levels of anesthesia satisfactorily, it may be useful in the evaluation of the effect of other drugs on anesthetic requirements.[70] It also may serve to control anesthesia as a variable when this is of importance in the interpretation of experimental data.

Itokawa and co-workers [81] constructed a meter system that reports momentary changes in an index specific for the anesthetic agent in use. This permits the anesthesiologist to adjust the dose based on the meter index of electroencephalographic change. They considered this a superior type of servomechanism in that the human element is still a part of the circuit.

Comments on Instrumentation

While this article on the application of electroencephalographic techniques in anesthesiology cannot deal with the complex field of instrumentation, it is necessary to note that many difficulties remain in the technique of recording the electroencephalogram in the operating room. The great amount of amplification needed to make brain potentials large enough to be recorded makes the technique liable to artifact, both from interference generated by other apparatus in the operating room and from biologic sources of potential, including such factors as movements of eyes and muscles. However, advances in instrumentation now allow the anesthesiologist to obtain satisfactory recordings under average conditions encountered in the operating room if reasonable attention is given to technical detail.

Some consideration of technique and instrumentation is also necessary when a comparison is made of reports from different laboratories. It should be remembered that the pattern obtained under any specific circumstance is related in some degree to the placement of the electrodes used for sampling and to the frequency response of the recording instrument. The former is more important in light anesthesia, in which some local differences in electrical activity between various parts of the scalp may still remain. Restriction of the frequency response of the amplifier sometimes has been used to remove faster frequencies from the record with a view to simplifying the electroencephalographic tracing and making the more significant patterns easily recognizable. These factors should receive adequate consideration before it is concluded that essential differences exist between the reports from different laboratories.

Evaluation

The foregoing body of information indicates that the electroencephalogram is of value in estimating the degree of cortical electrical alteration associated with the action of anesthetic drugs, lack of oxygen, decrease in temperature and accumulation of carbon dioxide. It is a rapid and sensitive indicator of inadequate perfusion of the brain with blood. A great virtue of the method lies in the fact that the responses are objective and, in most instances, subject to some degree of quantitation. Thus, a dose-response relationship has been established for most of the commonly used anesthetic drugs. Little doubt exists that these relationships are real. Their consistency has been shown to be of approximately the same order as that found in relating clinical estimates of depth of anesthesia to the dose of drugs.[82] The big question, of course, remains unanswered; namely, do the electroencephalographic patterns defined in the several classifications presented constitute a valid measure of depth of anesthesia? We believe this question unanswerable until a precise definition of "depth of anesthesia" is made. A comparison of the electroencephalographic and conventional signs has been published recently by Galla, Rocco and Vandam.[83]

In a broad sense, the electroencephalogram alone is no more valid a criterion of "depth" than is the manifest change in pattern of any single physiologic system, such as the oculomotor, the respiratory or the cardiovascular system. We must conclude that electroencephalography is a valuable tool in certain specific applications but that it is no more than a tool in the hands of the clinical anesthesiologist. Its value must be assessed in relationship to other circumstances peculiar to the moment.

In our opinion electroencephalography may make an important contribution to anesthesiology in its application for the following special purposes and other similar purposes:

1. The maintenance of a steady state in laboratory investigations in which variations in depth of anesthesia are undesirable.
2. The early detection of inadequate cerebral perfusion during whole-body perfusion with extracorporeal circulation.
3. Instruction in anesthesiology and the clinical evaluation of new anesthetic agents.
4. The assessment of damage and recovery after severe anoxic accidents during anesthesia or cardiac arrest.
5. The detection of critical changes in amplitude of cortical potentials during hypothermia.
6. The maintenance of a steady state of anesthesia in the operating room when all other signs of anesthesia are unavailable.

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