Review Article

Neurophysiologic Effects of General Anesthetics:

I. The Electroencephalogram and Sensory Evoked Responses in Man

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General anesthetics can profoundly alter electrical activity of the human brain. As the concentration of a specific agent is increased, recordings from scalp electrodes undergo a predictable series of changes. This article will demonstrate that the structures of anesthetics are systematically related to their effects on extracranial records of the human electroencephalogram (EEG) and sensory evoked responses (SER's). A second part of the review, to be published in the July issue, will examine central neural events responsible for these effects. Analysis of neuroelectric reactions to general anesthetics should help elucidate some mechanisms by which chemical compounds affect the brain. In turn, this should aid in more intelligent design of various types of neurotropic drugs, including anesthetics.

Some preliminary remarks are needed in order to relate neuroelectric recordings to clinical experiences with anesthetics. The earliest observations of general anesthesia established its essential clinical features. Pkmlney's and Snow's first papers on diethyl ether reported that its administration quickly produced confusion, then excitement and unconsciousness, and finally quiescence and loss of reaction to surgical stimulation. More ether was necessary to obtund responses to more intense stimuli. Subsequently, many compounds have been used as general anesthetics. They all produce the same series of effects. Snow's findings, therefore, still suggest a definition of general anesthesia suitable for all these drugs: unconsciousness accompanied by lack of unwanted somatic or autonomic reactions to surgical stimuli. We shall use this definition.

Snow took another important step when he determined minimum inspired concentrations at which different agents produce general anesthesia. Eger and his colleagues later put this procedure on a sounder basis when they introduced MAC, substituting alveolar for inspired concentrations. MAC is the minimum alveolar concentration which prevents movement in response to a standard skin incision. It is an ED50. This important critical concentration aids in comparing the neurophysiologic effects of different drugs, both within and between species. Our particular definition of general anesthesia suggests at least two other critical concentrations, also ED50's, of similar utility. One would be the concentration which causes unconsciousness (CUNC). A criterion for unconsciousness is failure of the patient to respond to a familiar stimulus, the calling of his name. Another critical value which our definition of general anesthesia suggests would be the concentration of maximum efficacy (CME). The CME prevents reactions to the severest surgical stimuli such as mesenteric traction or forceful rectal dilation. Still higher concentrations of anesthetic would only aggravate side-effects. Clinicians have rough estimates of these two critical concentrations for various anesthetics. Stoelting, Longnecker, and Eger recently determined "MAC awake," the concentration at which a patient first regains consciousness. MAC awake should be near CUNC. The various critical concentrations, CUNC, MAC, CME, and MAC awake, are not points on a dose-response curve. The behavioral alterations which define them do not fall on a linear scale. These concentrations

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instead are ED₉₀'s at which a general anesthetic elicits clinically important events in patients. The question of how these events relate to neuroelectric changes induced by general anesthetics now arises.

Barbiturates

An additional advantage of MAC is that it permits calculation of a therapeutic index for anesthetics. The index is derived by dividing MAC for a drug into the concentration which first yields unmanageable side-effects. Under current clinical practices, cyclopropane, for example, would have a therapeutic index between 6 and 7. In contrast, barbiturates would have a therapeutic index (based on arterial concentrations) somewhat below 2. This relatively low index combined with slow metabolism and excretion makes a barbiturate by itself a poor clinical anesthetic. Nonetheless, barbiturates have received more neurophysiologic study in both man and animals than any other anesthetic drugs. The ease of handling the drugs may partly explain this fact. In any event, the information available on these agents establishes them as a natural starting point for examining neurophysiologic effects of anesthetics. All barbiturates used clinically apparently yield identical neuroelectric phenomena. The drugs differ among themselves in potency and duration of action. Thus, we shall treat oxybarbiturates and thiobarbiturates as one class. As with all agents which we discuss, we first describe effects on the electroencephalogram and then effects on sensory evoked responses.

Electroencephalogram. The earliest electroencephalographers tested the effects of barbiturates in man.⁸⁻⁹ This work eventually led to recognition of the sequential effects shown in figure 1. These records come from a study done in our laboratory.

The first changes induced by barbiturates in the EEG are 20−30-Hz waves¹⁰⁻¹⁶ (see fig. 1A). We label this pattern the “initial rapid response” to barbiturates. It begins frontally, where it is most prominent, and spreads toward the occipit.¹⁶⁻²¹ Its dominant frequency drops to about 15 Hz.¹⁷⁻¹⁹ Next, 5−12-Hz waves superimpose themselves on the fast activity, often in spindle-shaped bursts.¹⁵⁻¹⁶,²² These “barbiturate spindles” probably were what Berger originally reported as unusual groups of alpha waves. Loss of consciousness occurs just as the initial rapid response yields to slower 5−12-Hz oscillations.¹¹,¹²,¹⁷,²⁰,²² Spindle bursts of 5−12-Hz waves become prominent (fig. 1B) and in turn decline as the EEG develops large polymorphic waves of 1−3 Hz.¹¹,¹²,¹⁵,¹⁶,²⁰,²⁴ (fig. 1C). Rapid injection of barbiturate can produce this slow-wave configuration without engendering more than a few traces of its predecessor.²² When polymorphic slow activity becomes dominant, the patient tolerates skin incision. The minimum arterial concentration (MAC) for a barbiturate to produce general anesthesia thus lies in the range which yields slow waves.

At still higher concentrations, the EEG displays periods of suppression (fig. 1D). Each such period terminates with a “burst” of renewed activity which contains high-frequency components. The burst gradually subsides as it leads into the next episode of suppression. This combination of alternating phases of high-amplitude and low-amplitude periods has been called “burst suppression” or “suppression burst.” Some authors use these terms to designate only the low-amplitude periods. Often the terms are used to indicate an effect believed common to all anesthetics. Careful examination shows, however, that each of the two phases of a “burst suppression” may differ in configuration among anesthetics. The so-called “bursts” for some agents actually consist of a few slow waves; for others the “bursts” begin with sudden, sharp oscillations. Recording at higher gains shows that some anesthetics produce rhythmic, slow waves during “suppression.” We will reserve the term “suppression” for the periods of relatively low activity and will designate periods of activity between suppressions as “intersuppression activity.” Thus, barbiturates produce suppressions and cause intersuppression activity which starts at about 8 Hz and decelerates to 2−6 Hz.¹²,¹³,¹⁵,¹⁶ Suppressions due to barbiturates become prolonged as concentration rises. At dangerously high concentrations, intersuppression activity is lower in amplitude and in dominant frequencies. The CME for barbiturates used alone apparently lies in the range of concentrations producing lengthy suppressions and dangerous side-effects.
Fig. 1. Electroencephalographic effects of intravenous administration of thiopental in unpremedicated man (Subject 1-1). Records for each condition were taken from three bipolar pairs of electrodes designated at the right of the control tracing. A, rapid activity at onset of administration. B, spindles of 7–10 Hz. C, slow waves. D, suppressions and intersuppression “bursts.” See text for discussion.

Sensory Evoked Responses. Evoked responses to transient external stimuli are generally too small to be recorded with scalp electrodes from man by conventional methods of amplification and display. Dawson’s introduction of automatic averaging techniques surmounted this problem. In essence, averaging extracts a recurrent signal (the evoked re-
NEUROPHYSIOLOGIC EFFECTS OF ANESTHESIA

Fig. 2. Effects of intravenous administration of thiopental on somatic evoked responses in man (Subjects 2-1, 2-2, and 2-3). Each record was taken over a 3-minute period following drug injection. The next injection was then given. The cumulative dose in mg/kg for each subject appears above the record. See text for further description. Adapted from Abrahamian, Allison, Goff, et al.25 (Reprinted by permission from Anesthesiology.)

Response to repeated stimuli) from ongoing spontaneous “noise” (such as the EEG) which otherwise masks the signal. Average evoked responses provide new neurophysiologic measures for comparing effects of different anesthetics in man and animals.

Somatosensory average evoked responses to tactile or electrocutaneous stimuli in unanesthetized man contain two types of potentials, “specific” and “nonspecific.” Specific responses have short latencies, are largest at extracranial loci overlying the contralateral post-Rolandic sensory cortex, and reflect activity generated in that region.26 The first brief positive (upward) wave in the control record for Subject 2-1 in figure 2 is a specific response. Nonspecific parts of average somatic evoked responses in man are diffusely and bilaterally distributed and exceed specific potentials in latency. In the control record for Subject 2-1, the second positive wave and all succeeding activity are nonspecific.

Figure 2 shows that a barbiturate progressively diminishes the nonspecific part of the human somatic SER.27 Low doses of drug may transiently enhance nonspecific waves.27, 28 Barbiturates, however, clearly do not reduce early specific somatosensory potentials 27–30 even at concentrations which cause short electromyographic suppressions. The records from Subject 2-1 illustrate the resistance of specific somatic evoked activity to barbiturates. Those from Subject 2-3 demonstrate that barbiturates may unmask small, early specific somatic responses.

This differential suppression by barbiturates of nonspecific components of SER’s is less pronounced in the human visual and auditory systems. Several investigations of human visual evoked responses show that doses of barbiturates close to the CUNC do not depress, but may enhance, early specific activity at occipital sites.21–22 Larger doses diminish these specific visual evoked responses.21–25 The potentials virtually disappear when the EEG contains long periods of suppression.25–27 Barbiturates, however, diminish the nonspecific visual responses more rapidly than specific visual potentials.24–27 Low doses are reported to increase nonspecific activity transiently.22 Ber-
gamaseo's results differ from those of other investigators. He claims that doses of barbiturates which cause slow-wave EEG's also facilitate longer latency components in human visual evoked potentials. His findings may be an artifact, due to averaging against a background of large, slow electroencephalographic activity. Applying the averaging process to a slow-wave EEG when the external stimuli are far below threshold can produce records which spuriously resemble slow, late evoked potentials.

The effects of barbiturates on early specific acoustic responses reported by Heath and Galbraith have not been studied. Barbiturates definitely alter average auditory SER's at the human vertex. These potentials begin too late to be a specific activity and too soon to be the K complex, the prolonged response which auditory stimulation evokes in a conventionally recorded EEG. Later parts of the auditory SER at the vertex overlap temporally with the K complex. Both the SER and the K complex are largest during the initial rapid EEG reaction. As barbiturates then change the EEG to a slow-wave pattern, earlier deflections vanish from the average extracranial auditory evoked response. Later ones, however, seem to increase. Two considerations suggest that this latter observation represents an artifact. First, averaging against a background of large slow waves is involved, and this can produce spurious results. Second, the K complex vanishes by the time the EEG contains spindles and some slow waves after barbiturates.

In summary, in man barbiturates block nonspecific average SER's to auditory, somatic, and visual stimuli. These nonspecific potentials may show temporary enhancement during the initial rapid reaction of the EEG. The drugs do not decrease specific somatic responses, and decrease specific visual responses more slowly than nonspecific potentials. Data on the effects of barbiturates on human specific auditory SER's are lacking.

**Inhalational Agents**

The remainder of this article concerns neurophysiologic effects of inhalational anesthetics in man. We do not discuss newer “dissociative” anesthetics or other intravenous drugs. After covering inhalational agents, we conclude with a table which relates chemical structure to neurophysiologic effects in man.

**Diethyl Ether**

_Electroencephalogram._ Next to barbiturates, diethyl ether (“ether”) probably has undergone

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### Fig. 4. Effects of different concentrations of diethyl ether on the human electroencephalogram. Each set of tracings is from a different subject. Frontocentral bipolar electrodes. See text for explanation.

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- **DIETHYL ETHER**

The most extensive neurophysiologic study. Early observations indicated that ether slowed the EEG. Early later work by Courtin et al. and Faulconer specified the successive stages of electroencephalographic change illustrated in figure 3. These studies generally involved use of nitrous oxide with ether. This combination first elicits a low-voltage fast pattern. Small bursts of 20-30 Hz activity appear as consciousness is lost. The second stage of action of nitrous oxide-ether produces waves said to lie between 2 and 8 Hz in frequency; illustrations show oscillations around 3 Hz. When Guedel's stage III, plane 1 is reached, the EEG contains complex slow waves of 1-3 Hz. Further increase in ether concentration elicits suppressions of lengthening duration. Unlike barbiturates, nitrous oxide-ether yields intersuppression activity consisting of a few slow waves of relatively small amplitude. Attainment of the CME entails suppressions of about 10 seconds or more. Arterial levels of
ether needed for a particular electroencephalographic pattern are higher when nitrous oxide is used only for induction than when it is used for induction and maintenance.41

In recent studies, we 42, 43 obtained results with ether alone which differ noticeably from the nitrous oxide-ether sequence of Courtin et al. Our volunteer subjects were stabilized at various mixed-expired concentrations of ether. Since stabilization required several hours of exposure for any particular concentration, only one or two levels could be studied in a single subject. Figure 4 shows control EEG's and effects of ether for various subjects. Although we could not study all concentrations in one individual, the findings form an orderly progression which agrees with several previous reports. At 1.46 per cent ether, Subject 4-1 barely responded to the sound of his name. His EEG showed small alpha activity mixed with low-voltage bursts of 20–30-Hz waves. Subject 4-2 was studied at a concentration of 1.74 per cent between CUNC and MAC. His EEG contained prominent bursts of 20–30-Hz activity riding on small 6–8-Hz waves. Several other investigators have reported this pattern.16, 22, 44 They too administered ether slowly and without nitrous oxide. The 20–30-
Hz activity apparently marked Guedel’s deeper stage 1.16 In line with our findings. Figure 4 next shows that a mixed-expired concentration approximately corresponding to MAC in Subject 4-3 yielded 6-Hz regular waves in the EEG, with a little superimposed rapid activity. Other workers also report regular waves between 4 and 12 Hz at Guedel’s stage III, plane 1.15, 16, 44, 45 As concentration of ether increases above MAC, the EEG gradually develops slower waves whose frequency may reach 1 Hz. Residual rapid activity vanishes. Figure 4 shows this progression. Previous reports also present comparable data.15, 16, 44-46 We avoided concentrations of ether which might have produced suppressions. Calculated blood levels of ether for subjects in figure 4 who gave slow polymorphic EEG’s are 1.6 to 1.8 times those reported by Fauleconer 41 for similar patterns. He used premedication, however, whereas we did not; and he used a completely different technique of anesthesia.

Rapid administration of high concentrations of ether quickly produces slow waves with few traces of the intervening stages just described.46 This mimics the effects of normally administered nitrous oxide-ether. Virtually no 20–30-Hz activity appears, rhythmic waves have frequencies around 2–3 Hz rather than 6–8 Hz, and polymorphic slow waves signal stage III, plane 1.

Sensory Evoked Responses. Relatively little is known about effects of ether on human SER’s. Concentrations near CUNC can somewhat diminish average specific somatic evoked responses.42 Mixed-expired concentrations above MAC abolish these potentials,12 in marked contrast to lack of this effect with barbiturates. Domino and his colleagues 55, 47 report that ether also eliminates specific visual evoked responses in man. Barbiturates do this in perhaps a less pronounced fashion. Concentrations of ether around CUNC in man severely decrease or even abolish extracranial nonspecific somatic evoked potentials.12 Similarly, the drug blocks human nonspecific visual evoked activity.25, 47

Cyclopropane

Electroencephalogram. Existing reports on the initial effects of cyclopropane on the human EEG are contradictory. Some claim that this agent first induces low-voltage, fast electroencephalographic activity.16, 48 This pattern probably represents an arousal response to the smell of cyclopropane. More detailed studies with concentrations of drug below CUNC have revealed nothing but slowing, especially in frontal areas.15, 49 Figure 5 illustrates this result. Progressively increasing the concentration of cyclopropane beyond CUNC simply causes larger and slower waves in the EEG.22, 50–52 These large waves become remarkably regular and are largest frontally. Suppressions have been reported at very high concentrations 48 but probably require potentiation by barbiturates or perhaps by hypercarbia.52 Our subjects 56 at normocarbia did not show suppressions at concentrations above those reported to produce them.

Sensory Evoked Responses. Cyclopropane seems unusual in reducing specific somatic SER’s at concentrations below CUNC.43, 44, 55 Concentrations above CUNC completely abolish specific somatic potentials 36 and decrease or eliminate specific visual evoked activity in man.47, 56 The drug quickly suppresses non-
Cyclopropane

Fig. 5. Effects of cyclopropane on the electroencephalogram and somatic evoked responses (SER) of conscious (Subject 5-1) and unconscious (Subject 5-2) man. EEG: monopolar frontal. SER: averaged responses from monopolar recordings at the contralateral post-Rolandic scalp. Fast time base to the left of the vertical bar for evoked responses, slow time base to the right of the bar. Arrows indicate times in msec after stimulus (STIM).

Specific somatic and visual potentials as well, although some parts of visual nonspecific activity reportedly show transient enhancement at certain concentrations. Figure 5 illustrates effects on somatic SER’s.

Noble Gases

One study describes the effects of hyperbaric xenon on the human EEG. The data resemble those obtained with cyclopropane. The dominant frequency of the EEG drops as exposure progresses, until waves of 2–5 Hz are prominent. Some surgery is possible when this configuration appears. The authors report no suppressions. We have found no data on human SER’s during exposure to noble gases.

Nitrous Oxide

Electroencephalogram. Nitrous oxide at atmospheric pressure does not obtund responses...
to surgical stimulation in healthy patients. It therefore requires hyperbaric administration or combination with other drugs. Nitrous oxide by itself yields a characteristic dose-dependent sequence of changes in the EEG, which figure 6 partly illustrates. This figure comes from our studies. Concentrations as high as 30 per cent rarely alter the EEG, although some psychological functions may be disturbed. The first electroencephalographic change due to the drug is progressive loss of alpha rhythm. This is just starting at a concentration of 25 per cent in figure 6. Virtual disappearance of alpha waves signals attainment of the CUNC. The CUNC for Subject 6-1 exceeded 50 per cent. As alpha lessens, short episodes of fast activity enter the EEG, especially frontally and centrally. Finally, the EEG develops 4-5-Hz waves which grow larger and come to focus in temporal regions. Figure 6 illustrates fast waves embedded in 4-5-Hz activity at 75 per cent nitrous oxide. In other subjects given 80 per cent nitrous oxide with d-tubocurarine, we observed small 4-5-Hz waves without rapid activity. These EEG changes seem to mark the limit of effects of nitrous oxide alone at one atmosphere. Further slowing of the EEG may occur with hyperbaric administration. High concentrations of nitrous oxide at atmospheric conditions also may produce such slowing during hyperventilation, probably as a result of hypocapnia. Incising the dura or performing a neurotomy under these circumstances interrupts the slow waves and reinstates alpha and even faster activity.

Sensory Evoked Responses. Concentrations of nitrous oxide which exceed the CUNC in man decrease extracranial specific somatic evoked responses. Reports of effects on specific visual evoked potentials are inconsistent. The drug, however, abolishes nonspecific visual and somatic activity in man. At concentrations below CUNC, it reduces in a dose-related fashion virtually all nonspecific auditory evoked waves recorded at the vertex.

Fluroxene

Electroencephalogram. Besides diethyl ether, several other four-carbon ethers have been used as anesthetics: divinyl ether, ethyl vinyl ether, and trifluoroethyl vinyl ether or fluroxene. The results resemble those for diethyl ether up to a point.

Fluroxene combined with nitrous oxide produces an electroencephalographic sequence similar to that for nitrous oxide-ether. During initial 15-25-Hz activity, unconsciousness occurs. Regular oscillations then enter into combination with the fast activity. The regular waves start at 6-8 Hz and gradually decrease to 3-5 Hz as their amplitude slowly increases. Surgery is possible when the dominant frequency is below 6 Hz. Further increases in concentration of fluroxene elicit 2-4-Hz polymorphic waves which gradually become even slower.

Other authors have reported similar data for patients given nitrous oxide for induction of anesthesia and then exposed to fluroxene upon cessation of nitrous oxide flow. Under these circumstances, high concentrations of fluroxene caused brief suppressions. We have recently examined effects of stable end-tidal concentrations of fluroxene alone in volunteers at normocarbia. Our findings show that concentrations below CUNC slowly decrease the frequency and amplitude of alpha waves. Intermittent 15-20-Hz waves appear; these grow in amplitude and duration as concentration exceeds the CUNC (1.4-1.5 per cent end-tidal fluroxene in our studies). At concentrations around MAC (3.50-3.87 per cent end-tidal fluroxene in our studies), the EEG is predominantly 20-25 Hz with some very small 4-Hz waves. Adding nitrous oxide eliminates the rapid oscillations and amplifies the 4-Hz waves. So far, the sequence is much like that for ether. At concentrations as high as 6.90 per cent end-tidal fluroxene in oxygen, however, the EEG is still dominated by 10-12-Hz activity. We have not observed the slow polymorphic waves produced by ether. This finding suggests that residual nitrous oxide in the closed systems used by other investigators influenced their results. We shall report our findings elsewhere in more detail.

Sensory Evoked Responses. We have discovered no previous reports on SER's in patients exposed to fluroxene. We have obtained such data on somatic responses, however, from our volunteers. The results resemble those for ether. Low concentrations of fluroxene vir-
Nitrous Oxide

**CONTROL**

**25%**

**50%**

**70%**

50 μV

1 sec

**Fig. 6.** Effects of 25, 50, and 70 per cent nitrous oxide on the EEG of Subject 6-1. Monopolar lead over somatosensory hand area, referred to the nares. Description in text.

...tually eliminate nonspecific activity, but seem to leave some early specific potentials. Flu-oxene around MAC abolishes the entire somatic evoked response.

**METHOXYFLURANE**

**Electroencephalogram.** Methoxyflurane is one of a series of halogenated methyl ethyl ether anesthetics. Inhalation of low concentrations of methoxyflurane by premedicated subjects produces a low-voltage fast EEG. This quickly converts to a pattern of 15–25-Hz waves of moderately large amplitude. After the CUNC is reached, the EEG slows somewhat, but still displays 12–16-Hz activity when surgery is possible. Further increases in concentration may introduce some small, slow activity of about 1–4 Hz. Far larger 10–15-Hz oscillations, however, still remain. We have made similar observations on two volunteers at end-tidal methoxyflurane concentrations of 0.19 and 0.23 per cent. Other reports on electroencephalographic effects of methoxyflurane mention slow waves and even suppressions at higher concentrations of drug. The latter studies, however, involved premedication, nitrous oxide, thiopental induction, or rapid induction with methoxyflurane which could produce hypotension. Thus, methoxyflurane by itself seems mainly to yield persistent EEG activity in the 10–16-Hz range at MAC and above.

**Sensory Evoked Responses.** Concentrations of methoxyflurane below the CUNC leave average specific somatic evoked responses essentially intact. These concentrations depress nonspecific somatic potentials. Concentrations at MAC and above are reported sometimes to increase and sometimes to decrease later, nonspecific human visual evoked activity.

**ISOFLURANE AND ENFLURANE**

Two other halogenated methyl ethyl ethers, isoflurane or Forane (CF₃CHClOCHF₂) and enflurane or ÊETHANE (CHFCICF₂OCF₂H), have recently been introduced as general anesthetics. The compounds are structural isomers with different arrangements of halogens on the ethyl group. To a degree, the drugs have similar neurophysiologic effects in man.
Electroencephalogram. We recently studied the effects of various concentrations of isoflurane on the human EEG in volunteers. The results confirm another report. Figure 7 shows EEG patterns obtained at different concentrations of isoflurane in a hypoxic subject. Normocarbia yielded this sequence of effects at similar concentrations in other subjects. Low concentrations of isoflurane produce 15–30-Hz activity, especially in frontal areas. Then the EEG develops small 2–4-Hz waves with 14-Hz activity. Figure 7 does not show either of these initial stages, during which consciousness is lost. Attainment of MAC produces 4–8-Hz large waves which dominate the EEG. As concentration increases further, the EEG becomes slower and then develops suppressions. The suppressions may be quite long and may contain only 8–10-μV activity. The bouts of intersuppression activity lack any frank slow-wave and spike formations, which we found with enflurane. Hypocarbia does not lengthen the duration of suppression due to isoflurane.

During studies reported elsewhere, we recorded EEG’s at various concentrations of enflurane. Figure 8 shows a sequence of typical tracings from a volunteer. The data agree with findings by Bart et al. Enflurane first induces rapid activity in the EEG. Consciousness disappears while this activity is prominent. Further increase in concentration of the drug brings out large 7–12-Hz waves. In this phase, the patient tolerates an incision (MAC is about 1.7 per cent). At higher concentrations, the EEG contains slower frequencies and the rapid 15–25-Hz waves dwindle. Just as these low frequencies begin to dominate the EEG, suppressions suddenly appear. They are interrupted by dramatic epileptoid bursts. The bursts may contain spike-and-dome complexes. Other authors have reported a similar sequence, which differs markedly at this point from that for isoflurane. The pattern of suppressions and epileptoid bursts has another unusual feature, unlike results with isoflurane. Decreasing the arterial carbon dioxide tension increases the length of suppressions, decreases the duration of bursts, but increases their amplitude and main frequency components. Increased carbon dioxide tension with anesthetics other than enflurane usually promotes the same electroencephalographic changes caused by increased concentrations of these drugs. The changes include lengthened suppressions. The striking difference between enflurane and other
Fig. 8. Effects of alternating concentrations of ethrane and carbon dioxide on SER and EEG. Left column: early and late evoked responses from C2P and M8A.47 5 μV, 100-Hz calibration signal from computer is shown at the bottom. Right column: segments of EEG's from which corresponding SER's were derived. The small spikes on the solid lines beneath each pair of EEG's indicate stimuli. Ethrane concentrations, carbon dioxide tensions, and cumulative dTe dosages are as indicated (reprinted by permission from Journal of Applied Physiology).
anesthetics in response to altered Pa\textsubscript{CO\textsubscript{2}} suggests that enflurane produces some dose-dependent central nervous system irritability. Lebowitz, Blitt and Dillon\cite{96} have reported this phenomenon in patients with temporal- lobe epilepsy.

**Sensory Evoked Responses.** Studies on human somatic evoked responses further confirm the similarities of and differences between the actions of isoflurane and enflurane. Isoflurane (fig. 7) and enflurane\cite{47, 42} rapidly decrease nonspecific averaged evoked activity to electrocortaneous stimuli in man. At concentrations between CUNC and MAC, either agent may diminish specific somatosensory SER's. As figure 7 shows, high concentrations of isoflurane still leave visible an early post-Rolandic focal negativity. Recordings in neurosurgical patients\cite{28} under local anesthesia suggest that the negativity signals activity in thalamocortical fibers entering the post-Rolandic cortex from the ventrobasal thalamus. High concentrations of enflurane introduce an abnormally large, early post-Rolandic response whose latency exceeds that of a normal specific SER. Hypocarbic potentiates these unusual evoked responses (see fig. 8) but does not alter the early negativity, which survives isoflurane. With high levels of enflurane, long-latency diffusely distributed waves follow the abnormally large early activity and also increase during hypocarbic.

**Trichloroethylene**

Trichloroethylene first produces rapid electroencephalographic activity,\cite{16, 87-93} which may persist through CUNC and MAC. Four-Hz to 7-Hz waves occur at increased concentrations and convert to slow arhythmic patterns with addition of nitrous oxide.\cite{87-90} No data on effects of trichloroethylene on human SER's exist.

**Halothane**

At first glance, the literature on neurophysiologic effects of halothane seems chaotic. Some authors describe electroencephalographic patterns which others fail to mention. The confusion disappears when results with halothane alone are separated from results with nitrous oxide and halothane. The identical problem arose concerning effects of ether and fluoxetine. We treat in detail observations with halothane alone and comment only briefly on the results of adding nitrous oxide.

**Electroencephalogram.** The first EEG reaction to halothane is activity in the 10–20-Hz range.\cite{45, 50-58} This pattern persists through loss of consciousness. Around MAC, the dominant frequencies in the EEG are between 10 and 15 HZ.\cite{91, 92, 94-98, 99, 99} One report\cite{97} even mentions 20-Hz spindles. Halopropene apparently gives similar results.\cite{100} Increasing the concentration of halothane well beyond MAC reportedly slows the EEG into the 1–3-Hz range, and may even provoke suppressions.\cite{51-94, 96-99, 101} These effects, however, may reflect decreased cerebral blood flow secondary to hypotension or hypocarbic.\cite{91} Similarly, slow waves due to rapid induction with high concentrations of halothane\cite{52} also may spring from hypotension or high initial brain concentrations.

Halothane combined with nitrous oxide gives a somewhat different dose-dependent sequence of electroencephalographic patterns. Loss of consciousness occurs when the EEG contains 12–15-Hz activity.\cite{92, 102} At concentrations below MAC, noxious stimuli can desynchronize 8–12-Hz rhythmic waves.\cite{91, 89} Surgical incisions are not tolerated until some 6–8-Hz waves have appeared.\cite{102, 103} A progressively slower EEG then accompanies higher concentrations of halothane and involves frequencies as low as 2 Hz.\cite{2, 39, 102, 104, 105}

**Sensory Evoked Responses.** The effects of halothane on human sensory ER's have received limited attention. Available data demonstrate little effect on specific visual evoked potentials but slow decreases in nonspecific activity.\cite{32, 47, 50}

**Chloroform**

Although rarely used today for anesthesia, chloroform produces instructive neurophysiologic effects. Berger\cite{106} originally reported that chloroform abolished alpha activity in man. Results from later investigations suggest that this agent may act like halothane. Efuni and Tsibulyak\cite{90} state that chloroform administration first produces 20–25-Hz activity, during which loss of consciousness occurs. Thomas et al.\cite{107} did not observe these fast waves, but their recording apparatus apparently filtered out high frequencies. According to Efuni and Tsibulyak, surgery is possible when the EEG
shows a mixture of 15-Hz waves and small slow activity. The slow components might be absent with gradual drug administration. Thomas et al. report small 7-10-Hz waves when an incision is tolerated. Beyond concentrations corresponding to MAC, chloroform progressively and gradually slows the EEG, until arrhythmic waves occur. Suppressions about one second in duration appear at dangerous concentrations involving severe hypotension. As with halothane, reduced brain blood flow may underlie slow waves due to chloroform. We have found no data on effects of chloroform on human S.E.R.'s.

"Depth" of Anesthesia, Neuroelectric Activity, and Drug Structure

The electroencephalogram initially attracted attention from anesthesiologists as a possible measure of depth of anesthesia. As Snow had originally remarked, higher doses of anesthetic are necessary to prevent reactions to more intense surgical stimuli. This fact has suggested that different states of anesthesia fall along a continuum of "depth," with "deeper anesthesia" eliminating reactions to stronger stimuli. The anesthesiologist then needed to know when the patient had reached a depth of anesthesia commensurate with the impending stimulus. Individual differences in anesthetic requirements precluded quantitative judgments based only on direct measurement of concentration. Guedel 105 and Gillespie 109 finally solved the problem for diethyl ether. They showed that different constellations of somatic and autonomic signs marked different clinical levels (stages and planes) of anesthesia in a wide variety of patients.

Not long after development of Guedel's system, other anesthetics were introduced. Guedel 110 himself noted that his system was not quite appropriate for cyclopropane. As still other agents which did not fit his scheme appeared, determination of depth of anesthesia developed serious inconsistencies. An apparent escape from this dilemma arose with Berger's discovery of the human electroencephalogram. During his investigations, Berger found that barbiturates 8 and chloroform 108 changed the configuration of the EEG. Intensive study of the electroencephalographic effects of general anesthetics began around 1950. Within a decade, Martin, Faulconer, and Bickford 111 proposed in an important review in this journal that all general anesthetics yield a basically similar dose-dependent sequence of six different electroencephalographic patterns. Their position suggested that extracranial neuroelectric recordings might provide a general method of estimating depths of anesthesia for different agents and different patients. Faulconer and Bickford 112 cautioned, however, that some anesthetics did not produce every electroencephalographic pattern in the basic sequence. They also pointed out that a particular pattern did not necessarily signal the same clinical state for different drugs. Thus, the EEG fell short of affording the desired uniform measure of anesthetic depth. The introduction of muscle relaxants into clinical anesthesiology largely mooted the problem of measuring depth of anesthesia. Use of these agents with relatively low concentrations of general anesthetics eliminates somatic reactions to surgical stimuli. This technique leaves autonomic reflexes as unimportant effects of surgical stimulation. Patients can be maintained at modest concentrations of anesthetic between CUNC and MAC. There is a risk of being unable to judge whether consciousness is regained during surgery.

Modern practice thus has greatly lessened concern with estimating depth of anesthesia. It has not, however, eliminated the fundamental question of whether different agents have similar or different neurophysiologic effects. Our studies of volunteers, along with other data, now suggest that drug structure does systematically influence neuroelectric effects of anesthetics in man. Table 1 summarizes our views by arranging inhalational anesthetics according to electroencephalographic effects and chemical structure. Successive rows of the table contain agents which produce increasing signs of central nervous system irritability. The columns of the table represent different chemical groups.

The two top entries in table 1, xenon and cyclopropane, progressively slow the EEG as concentration is increased to CUNC, MAC, and beyond. The next row of the table contains only nitrous oxide, which appears as an inorganic agent below xenon. At CUNC nitrous oxide produces a low-voltage irregular electroencephalographic pattern. As concentration increases, episodes of 15-20-Hz activity appear and then dwindle. Achievement of
TABLE 1. Inhalational Agents Arranged by Structure and Neuroelectric Effects in Man

<table>
<thead>
<tr>
<th>Chemical Group</th>
<th>Inorganic Agents</th>
<th>Hydrocarbons</th>
<th>Four-carbon Ethers</th>
<th>Three-carbon Ethers</th>
<th>Halogenated Hydrocarbons</th>
<th>Increasing CNS Irritability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xenon Xe</td>
<td>Cyclopropane CH₃H₂CH₂</td>
<td>Diethyl ether CH₃CH₂OCH₂CH₃</td>
<td>Fluoroxene CF₃CH₂OCF₂CH₂</td>
<td>Methoxyflurane CH₂OCF₂CH₂</td>
<td>Trichloroethylene CHCl₃Cl₂</td>
</tr>
</tbody>
</table>

MAC requires hyperbaric conditions and produces 4-Hz activity. In the next row and in a new column is diethyl ether, which elicits a mixture of alpha and small 20–30-Hz waves at the CUNC. At MAC there are 6-Hz waves with some superimposed 20-Hz oscillations. Further increase in concentration slows the EEG.

The rapid activity seen around CUNC with ether is much more evident with fluoroxyne and the remaining agents in the table. Fluoroxene resembles ether in causing 5–5-Hz waves mixed with 20-Hz waves at concentrations near MAC. It is chemically related to ether. Trichloroethylene lies in the same row with fluoroxene but in a new column. These two halogenated agents have similar electroencephalographic effects. The three anesthetics in the next row, methoxyflurane, halothane (below the two-carbon trichloroethylene), and chloroform, all cause 10–16-Hz activity at concentrations near MAC. The anesthetics listed so far do not easily cause suppressions and fast intersuppression activity.† This contrasts with the effects of isoflurane and enfurane. These drugs occupy the last two rows of the table and fall below methoxyflurane as halogenated methyl ethyl ethers. Isoflurane and enfurane cause prominent rapid activity at CUNC. Isoflurane produces 4–6-Hz and enfurane 7–13-Hz waves at concentrations around MAC. Both agents yield suppressions at higher concentrations. The intersuppression activity contains high-frequency components for isoflurane and becomes epileptiform for enfurane.

The arrangement of drugs in table 1 also accords with their effect on sensory evoked responses. All inhalational agents which have been tested decrease late parts of SER’s at relatively low concentrations. Cyclopropane eliminates early specific evoked activity most efficiently. The other drugs become progressively less effective, going down the table. In fact, enfurane assumes new properties: at concentrations of this agent above MAC, somatic stimuli produce an abnormally large, delayed, and prolonged specific response. This response is followed by large diffusely distributed evoked activity. No other agent studied has this peculiar effect.

† Seizures have been reported in humans with both divinyl and diethyl ether. Although few data regarding effects of divinyl ether on the EEG are available, this drug should lie just above or below diethyl ether in the column of four-carbon ethers. Two recent studies with animals support this prediction. Mori et al. found generalized seizure activity in the brains of cats with diethyl ether. The arterial concentration of ether measured in just one of these animals was around 275 mg/100 ml when seizures occurred. Joas et al. reported generalized seizures in dogs at 2.7 MAC diethyl ether. They also recorded generalized seizure activity with divinyl ether at 3.0 MAC. Six ethers arranged by Joas et al. according to MAC multiples which produced seizure activity are: divinyl ether, 3.0; diethyl ether, 2.7; fluoroxene, 2.0; methoxyflurane, 3.0; isoflurane, 2.0–2.5; enfurane, 1.5. These data fit nicely with our arrangement of table 1. No seizure activity was reported for cyclopropane, halothane, or chloroform at 2.5 MAC. Hypotension may have limited the doses of the latter two drugs.
Another feature of the table is the grouping of unhalogenated compounds in the first three rows and halogenated compounds in the remaining rows. Within the halogenated group, the one- and two-carbon hydrocarbons, trichloroethylene, halothane, and chloroform, cluster into a common region of the table. For the three halogenated methyl ethyl ethers in the column headed by methoxyfluorane, basicity of the ether oxygen decreases going down the column.

The classification of anesthetics in table 1 clearly differs from the conclusions of Martin, Faulconer, and Bickford. The table also implies that neuroelectric recordings could not in any case provide a simple uniform measure of anesthetic depth. Furthermore, it suggests that different anesthetic agents have somewhat different actions in the central nervous system. These actions should vary with drug structure, in accordance with table 1. They also should explain the findings from scalp electrodes during general anesthesia in man. Testing of these implications requires systematic examination of dose-dependent effects of different anesthetics on neuroelectric activity recorded in various regions of the central nervous system. The second part of our review undertakes this examination.

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References
7. Stoelting RK, Longnecker DE, Eger EI II: Minimum alveolar concentrations in man on awakening from methoxyflurane, halothane, ether and fluoroxyne anesthesia: MAC awake. Anesthesiology 33:5–9, 1970

Downloaded From: http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931551/
49. Findeis JC, Kien JA, Hulse KOW, et al: Power spectral density of the electro-


52. Rubin MA, Freeman H: Brain potential changes and skin temperature during cyclopropane anesthesia. Anesth Analg (Cleve) 20:45-49, 1941


64. Sadove MS, Yarbrough CG, Becka DR: Electrocencephalographic sleep patterns in general anesthesia. Ill Med J 7:7-9, 1961


76. Fujiwara Y: Clinical studies on the blood concentration of methoxyflurane used as an anesthesia. 2. Relationship of the concentration of methoxyflurane in blood, EEG and the depth of anesthesia. Jap J Anesthesiol 16:34-44, 1967


102. Gain EA, Paletz SG: An attempt to correlate the clinical signs of fluothane anesthesia with the electroencephalographic levels. Can Anaesth Soc J 4:289–294, 1957