# *Minimum Alveolar Concentrations of Methoxyflurane, Halothane, Ether and Cyclopropane in Man: Correlation with Theories of Anesthesia*

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The minimum anesthetic concentration (MAC) required in man to prevent a muscular response to a skin incision in 50 per cent of the subjects was determined for cyclopropane, halothane, diethyl ether and methoxyflurane in man. These were (volumes per cent at one atmosphere pressure): cyclopropane 9.2, halothane 0.765, diethyl ether 1.92 and methoxyflurane 0.16. We believe these values, along with the previously determined MAC's for fluroxene[5] (3.4 per cent) and nitrous oxide[4, 6] (101 per cent), represent equipotent doses of these agents and provide a useful standard when comparing the circulatory, respiratory or other physiologic effects of one anesthetic with those of another.

MAC as a measure of anesthetic potency correlates better with lipid solubility than with any other physical constant. This correlation should be considered when the primary site of anesthetic action within the brain is sought.

STUDIES of the comparative effects of anesthetics on respiration, circulation or other physiological parameters require that a standard of equipotency be established for the anesthetics studied. Until recently, no standard has been available either for laboratory animals or for man. Our laboratory has determined such values for methoxyflurane, halothane, ether, fluroxene, cyclopropane, nitrous oxide and xenon in the dog.[1] The standard of equipotency was the minimum alveolar concentration (MAC)[2] of anesthetic required to prevent gross muscular movement in response to a noxious stimulus. The stimulus was either application of a tail clamp, or 40 volts at 50 cycles per second, 10 milliseconds duration, given through needle electrodes placed subcutaneously. The MAC was unchanged by duration of anesthesia and varied only slightly between animals.[3]

We also have determined MAC in man for halothane,[4] and fluroxene[5] with and without nitrous oxide. After equilibration at a given alveolar concentration in any one patient, a surgical skin incision was made and the patient observed for gross movement. A group of such patients were studied at various concentrations for each agent. The concentration preventing movement in 50 per cent of patients was called MAC. MAC values obtained in these studies were: halothane 0.74 per cent, and fluroxene 3.4 per cent; while with nitrous oxide (65 per cent with halothane and 72 per cent with fluroxene) they were: halothane 0.28 per cent, fluroxene 0.8 per cent. If the effect of either of these anesthetics is additive with nitrous oxide, then a MAC for nitrous oxide of 101 per cent may be predicted.

Assuming that the narcotic action of anesthetics are additive,[6] we may determine MAC for nitrous oxide from the following equation: $C_{N_2O}/MAC_{N_2O} + C_H$ or $F/MAC_{H\text{ or }F} = 1$ where $C_{N_2O}$, $C_H$, $C_F$ equal concentrations of nitrous oxide, halothane or fluroxene which when administered together (nitrous oxide and either halothane or fluroxene) give the same anesthetic effect as $MAC_{N_2O}$, $MAC_H$ or $MAC_F$ alone. Using the above data and solving for $MAC_{N_2O}$ we obtain a mean value of 101 per cent.

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This report adds to the above data of MAC studies on man, data for three other commonly used anesthetics: methoxyflurane, ether and cyclopropane.

The determination of MAC for the very soluble anesthetics, ether and methoxyflurane, presents a problem in obtaining alveolar samples which accurately reflect arterial partial pressures. We recently found that a difference in partial pressure for nitrous oxide exists between alveolar gas and arterial blood.[7] The data suggest that this difference was brought about in large part by the difference in partial pressure between inspired and end-tidal gas. This is because there is a small but significant contamination of end-tidal with inspired gas which produces a difference between true alveolar gas (gas from alveoli that are adequately perfused) and that gas being sampled as alveolar gas (end-tidal) which is true alveolar gas plus gas from ventilated unperfused areas (anatomic plus physiologic dead space). The greater the inspired to true alveolar difference, the greater the effect of such contamination on the measured alveolar (end-tidal) concentration. Since methoxyflurane and ether are extremely soluble (blood-gas partition coefficients of 13.0[8] and 12.1,[9] respectively), the inspired to true alveolar difference is relatively large. During induction the inspired concentration may be 5 to 10 times as great as that in the alveolar. Under these circumstances, a 10 per cent contamination of alveolar gas with inspired gas produces an end-tidal partial pressure 50 to 100 per cent greater than that in the alveoli. In these studies we solved this problem by markedly reducing or eliminating the inspired to alveolar difference by prior saturation with the agent studied. We have also redetermined MAC for halothane (an agent of moderate solubility) after reducing the inspired to alveolar difference.

## Methods

The methods utilized in determining the MAC's for the agents studied varied sufficiently to warrant describing them separately.

*Methoxyflurane.* All patients were given premedication of 0.4 to 0.8 mg. of atropine. Anesthesia was induced with cyclopropane-oxygen in 17 surgical patients without cardiorespiratory disease. Methoxyflurane was added and cyclopropane was discontinued within 5

TABLE 1. Data Obtained in the Methoxyflurane MAC Determination

| Patient | Total Minutes Methoxyflurane* | Minutes At Test Concentration† | $F_E$‡ | $F_I$§ | $\frac{(F_I - F_E)}{F_E} 100$ | Movement | Temperature | Age |
|---|---|---|---|---|---|---|---|---|
| 1 | 44 | 9 | 0.095 | 0.085 | −11 | Yes | 36.4 | 38 |
| 2 | 113 | 15 | 0.11 | 0.095 | −14 | Yes | 35.4 | 52 |
| 3 | 96 | 21 | 0.115 | 0.11 | −4 | Yes | 35.9 | 32 |
| 4 | 92 | 11 | 0.13 | 0.08 | −39 | Yes | 36.2 | 31 |
| 5 | 203 | 16 | 0.14 | 0.12 | −14 | No | 36.9 | 40 |
| 6 | 91 | 21 | 0.14 | 0.26 | 86 | Yes | 36.2 | 40 |
| 7 | 141 | 21 | 0.15 | 0.10 | −33 | Yes | 36.0 | 37 |
| 8 | 82 | 17 | 0.16 | 0.24 | 50 | No | 35.2 | 47 |
| 9 | 132 | 19 | 0.16 | 0.27 | 69 | No | 36.4 | 27 |
| 10 | 47 | 13 | 0.17 | 0.22 | 29 | No | 37.0 | 24 |
| 11 | 70 | 15 | 0.17 | 0.28 | 65 | Yes | 36.1 | 41 |
| 12 | 115 | 15 | 0.18 | 0.17 | −6 | Yes | 35.6 | 36 |
| 13 | 105 | 15 | 0.19 | 0.28 | 48 | No | 37.0 | 25 |
| 14 | 68 | 15 | 0.20 | 0.42 | 110 | No | 35.8 | 48 |
| 15 | 211 | 31 | 0.22 | 0.23 | 5 | No | 37.2 | 26 |
| 16 | 108 | 29 | 0.23 | 0.40 | 74 | No | 35.5 | 49 |
| 17 | 77 | 16 | 0.27 | 0.57 | 110 | No | 36.2 | 41 |

* Total time of methoxyflurane administration prior to incision.
† Total time at the end-tidal concentration at time of incision.
‡ End-tidal methoxyflurane immediately prior to incision.
§ Inspired methoxyflurane immediately prior to incision.

TABLE 2. Data Obtained in the Diethyl Ether MAC Determination

| Patient | Total Minutes Ether* | Minutes At Test† Concentration† | $F_E$‡ | $F_I$§ | $\frac{(F_I - F_E)}{F_E}100$ | Movement | Temperature | Age | IV Ether |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 82 | 25 | 1.54 | 1.54 | 0 | Yes | 36.1 | 54 | No |
| 2 | 92 | 44 | 1.66 | 2.41 | +45 | Yes | 36.0 | 44 | No |
| 3 | 85 | 25 | 1.72 | 1.65 | −4 | Yes | 36.3 | 32 | No |
| 4 | 65 | 24 | 1.78 | 1.83 | +3 | Yes | — | 45 | No |
| 5 | 45 | 20 | 1.82 | 1.75 | −4 | No | 35.1 | 23 | Yes |
| 6 | 57 | 27 | 1.82 | 1.82 | 0 | Yes | 36.8 | 35 | Yes |
| 7 | 82 | 18 | 1.85 | 1.38 | −25 | Yes | 36.3 | 54 | No |
| 8 | 325 | 95 | 1.87 | 1.97 | +5 | Yes | 36.8 | 19 | No |
| 9 | 64 | 23 | 1.89 | 2.02 | +7 | No | 36.0 | 60 | No |
| 10 | 203 | 26 | 1.97 | 1.52 | −23 | No | 35.9 | 20 | No |
| 11 | 100 | 23 | 2.07 | 2.07 | 0 | Yes | 35.8 | 36 | Yes |
| 12 | 81 | 24 | 2.10 | 2.13 | +1 | No | 36.3 | 45 | Yes |
| 13 | 140 | 25 | 2.17 | 1.72 | −21 | No | 36.3 | 23 | No |
| 14 | 57 | 22 | 2.22 | 2.27 | +2 | No | 35.1 | 40 | Yes |
| 15 | 205 | 60 | 2.32 | 1.78 | −23 | No | 35.8 | 20 | No |
| 16 | 60 | 19 | 2.37 | 2.42 | +2 | No | 35.5 | 46 | Yes |
| 17 | 214 | 14 | 3.16 | 2.27 | −30 | No | 36.2 | 25 | No |

* Total time of ether administration.
† Total time at the end-tidal concentration at the time of incision.
‡ End-tidal ether immediately prior to incision.
§ Inspired ether immediately prior to incision.

to 10 minutes following induction. An inflow of 5 liters per minute of methoxyflurane-oxygen was continued thereafter. Succinylcholine was used in some cases to obtain muscle relaxation prior to tracheal intubation. In all cases the glottis and trachea were topically anesthetized with 2 ml. of 5 per cent cocaine.

End-expired gas samples were collected

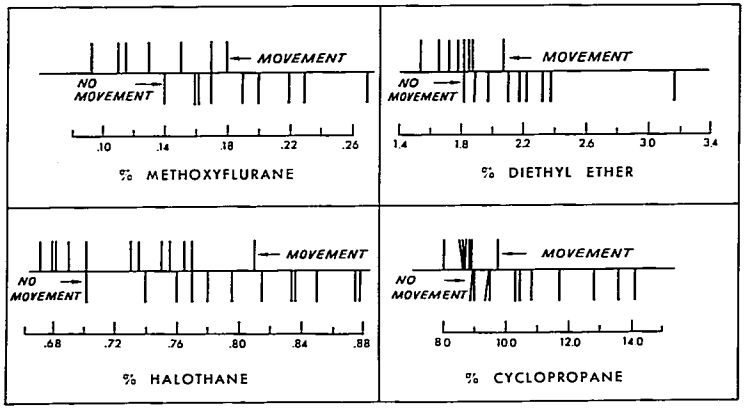


FIG. 1. The individual responses to a skin incision are plotted against the end-tidal ($F_E$) concentration at which the incision was made. A deflection above each horizontal line indicates movement while a deflection below the line indicates no movement. MAC was derived from these data (fig. 2).

through a nylon catheter passed to the tracheal end of the endotracheal tube. Methoxyflurane was analyzed with a Beckman LB1 infrared halothane analyzer. A calibration curve for the analyzer was prepared as previously described.[4] The analyzer was intermittently calibrated with a standard from a pressurized tank. Analysis was performed at ambient pressure and at zero flow through the analyzer. Esophageal or nasopharyngeal temperature was obtained for each patient. Anesthesia was progressively deepened until the end-tidal methoxyflurane equalled 0.3 to 0.7 per cent, usually about 0.45 per cent; this concentration was maintained for ½ to 3 hours. About 15 to 40 minutes prior to incision the end-tidal concentration was rapidly lowered to a value (test concentration) between 0.095 and 0.27 per cent and held at this value until the time of incision. With three exceptions the test concentration was held for at least 15 minutes, sufficient to allow for nearly complete equilibration of brain with the alveolar partial pressure of anesthetic.[5] Incomplete equilibration would mean that the alveolar concentration would underestimate that in the brain, since the cerebral concentration was being reduced from a higher value. As seen in table 1, prior equilibration at an elevated concentration produced an inspired to end-tidal difference at the time of incision that ranged from −39 to +110 per cent. On incision, the patient was observed for movement. The test concentrations of methoxyflurane spanned a range in which at the lower level all patients moved, and none at the higher. Similar ranges of concentrations were used in the studies on ether, halothane and cyclopropane.

*Diethyl Ether.* Preparation of the patient was that as described for methoxyflurane; 17 patients were studied. As with methoxyflurane, anesthesia was initially held at a deep level (4 to 5 per cent end-tidal ether) for ½ to 3 hours (table 2). This was reduced to the test concentration (1.5 to 3.2 per cent) 14 to 95 minutes prior to incision. Analysis was done with a Beckman LB1 infrared ether analyzer. Those subjects with an inspired concentration higher than the end-tidal were given intravenous ether (5 volumes per cent in 5 per cent dextrose in water) at a rate sufficient to allow the inspired concentration to be reduced to the end-tidal concentration.

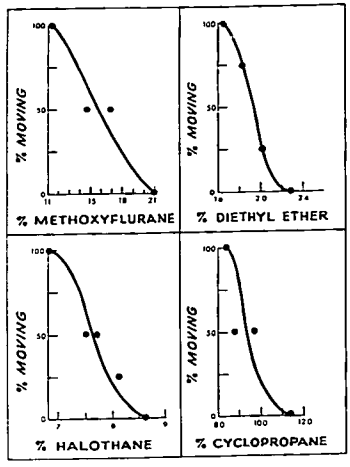


FIG. 2. This figure illustrates the manner in which MAC was determined. Starting with the lowest concentration (fig. 1), subjects were taken in groups of four and the percentage of patients within each group that moved were plotted on the vertical axis against the mean end-tidal concentration of the group of four on the horizontal axis. MAC is represented as the point where a line connecting the individual points passes through the 50 per cent point.

*Halothane.* The procedure was that for methoxyflurane except that anesthesia was induced in 24 patients with halothane and succinylcholine was not usually necessary to facilitate intubation. Anesthesia was usually held above 1.2 per cent for ½ or more hours and reduced to between 0.67 and 0.88 per cent. The test concentrations were held for 14 to 60 minutes prior to incision.

*Cyclopropane.* The lungs of 18 patients were preoxygenated for a minimum of 5 minutes with 10 liters per minute inflows into a circle system. Oxygen percentage in the inspiratory limb of the circle was monitored with a Beckman Model D oxygen analyzer. When cyclopropane was begun, the oxygen percentage within the circle exceeded 99 per cent. During induction, the total flow of cy-

cyclopropane and oxygen exceeded 4 liters per minute. Succinylcholine, 40 mg. was given, the glottis and trachea anesthetized with 2 ml. of 5 per cent cocaine, and the trachea intubated. Following intubation, inflow continued at 3 liters per minute or greater. Inspired cyclopropane concentration was derived indirectly by subtraction of inspired oxygen percentage from that obtained with pure oxygen. Alveolar cyclopropane concentration was calculated as the inspired cyclopropane concentration, diluted by water vapor (that is, inspired cyclopropane concentration times 0.94). It was assumed that at the time of incision, the uptake of cyclopropane was negligible,[10] and counterbalanced in part by a respiratory quotient of less than one. Inspired cyclopropane concentration was held constant at a predetermined level for a minimum of 10 minutes prior to incision.

## Results

The data obtained for methoxyflurane, ether and halothane are given in tables 1, 2 and 3 and graphically plotted in figure 1; the data are summarized in table 4. The summary data for cyclopropane are also contained in this table along with similar summary data obtained in previous studies for fluroxene[5] and nitrous oxide.[4, 5] Data on xenon are also included.[6] For each anesthetic, there was a concentration range within which patients both moved and did not move (cross-over range) (tables 1, 2 and 3 and figure 1). For methoxyflurane, this range extended from 0.14 to 0.18 per cent, for ether from 1.82 to 2.07 per cent, for halothane from 0.705 to 0.81 per cent, and for cyclopropane from 9.0 to 9.8 per cent.

TABLE 3. Data Obtained in the Halothane MAC Determination

| Patient | Total Minutes Halothane* | Minutes At Test Concentration† | $F_E$‡ | $F_I$§ | $\frac{(F_I - F_E)}{F_E} 100$ | Movement | Temperature | Age |
|---|---|---|---|---|---|---|---|---|
| 1 | 43 | 25 | 0.67 | 0.83 | +24 | Yes | 36.1 | 54 |
| 2 | 42 | 22 | 0.68 | 0.79 | +16 | Yes | | 35 |
| 3 | 57 | 39 | 0.68 | 0.73 | +7 | Yes | 36.0 | 37 |
| 4 | 45 | 20 | 0.69 | 0.35 | +23 | Yes | 36.0 | 40 |
| 5 | 48 | 26 | 0.705 | 0.83 | +18 | No | 35.8 | 48 |
| 6 | 60 | 17 | 0.705 | 0.82 | +16 | Yes | 35.8 | 38 |
| 7 | 38 | 31 | 0.73 | 0.84 | +15 | Yes | 36.0 | 38 |
| 8 | 32 | 14 | 0.735 | 0.80 | +9 | Yes | 36.5 | 35 |
| 9 | 55 | 41 | 0.74 | 0.785 | +6 | No | 36.0 | 33 |
| 10 | 57 | 13 | 0.75 | 0.86 | +15 | Yes | 36.4 | 53 |
| 11 | 63 | 60 | 0.755 | — | — | Yes | 35.8 | 37 |
| 12 | 36 | 16 | 0.76 | 0.86 | +13 | No | 36.5 | 34 |
| 13 | 37 | 21 | 0.765 | 0.96 | +25 | Yes | 36.3 | 40 |
| 14 | 58 | 27 | 0.77 | 0.845 | +10 | No | 35.5 | 52 |
| 15 | 65 | 42 | 0.77 | 0.855 | +11 | Yes | 35.5 | 50 |
| 16 | 60 | 20 | 0.78 | 0.845 | +8 | No | 36.5 | 47 |
| 17 | 85 | 25 | 0.795 | 0.90 | +12 | No | 35.4 | 50 |
| 18 | 53 | 17 | 0.81 | 0.91 | +12 | Yes | 36.9 | 42 |
| 19 | 46 | 26 | 0.815 | 0.93 | +14 | No | 36.2 | 35 |
| 20 | 45 | 25 | 0.834 | 0.905 | +8 | No | 35.9 | 52 |
| 21 | 42 | 21 | 0.835 | 0.88 | +5 | No | 36.9 | 41 |
| 22 | 65 | 38 | 0.850 | 0.91 | +7 | No | 36.2 | 31 |
| 23 | 62 | 36 | 0.875 | 0.99 | +13 | No | 36.7 | 36 |
| 24 | 42 | 27 | 0.88 | 0.92 | +5 | No | 35.4 | 51 |

* Total time of halothane administration prior to incision.
† Total time at the end-tidal concentration at time of incision.
‡ End-tidal halothane immediately prior to incision.
§ Inspired halothane immediately prior to incision.

TABLE 4. Summary of Data For MAC Values in Man

| Agent | Patients | Age* | Equilibrium Time at MAC | MAC |
|---|---|---|---|---|
| Methoxyflurane | 17 | 38±9 | 18±6 | 0.16 |
| Halothane | 24 | 42±7 | 27±11 | 0.77 |
| Ether | 17 | 37±14 | 31±19 | 1.92 |
| Fluroxene | 12 | 44±16 | 13±1 | 3.4 |
| Cyclopropane | 19 | 44±15 | 18±5 | 9.2 |
| Nitrous oxide | 30 | 43±15 | | 101.0 |
| Xenon† | | | | 71.0 |

* ± One standard deviation.
† See reference 6.

## Discussion

In previous studies on MAC, we assumed that alveolar concentration accurately reflected partial pressure of anesthetic in brain. Holaday's work with methoxyflurane suggested this to be an incorrect assumption in the case of soluble agents.[11] They found differences between the end-tidal and the arterial anesthetic partial pressure. These also were associated with a high inspired to end-tidal methoxyflurane difference. A probable cause for the difference is contamination of the alveolar gas sample with inspired gas. This could occur as the result of ventilation of under-perfused (or hypo-perfused) areas of lung from which no (or reduced) uptake of anesthetic occurs. The partial pressure from these under-perfused areas would approach that of inspired gas, and when mixed with gas from perfused alveoli, would falsely elevate the end-tidal sample. We have reduced this difficulty by reducing or eliminating the inspired to alveolar methoxyflurane difference as explained in the introduction. The mean inspired to end-tidal difference is +31 per cent (table 1). If as much as 10 per cent of alveoli were unperfused, the true alveolar gas (that from ventilated perfused alveoli) would be elevated only 3.1 per cent (that is 0.31 times 10). The mean difference of 31 per cent is much less than the inspired to end-tidal difference seen on induction which may exceed 500 to 1,000 per cent.[12] By exposing the patient to higher alveolar tensions of methoxyflurane (2 × MAC) before equilibration at the test level, we decreased uptake from perfused alveoli, and therefore decreased inspired to alveolar and hence arterial difference. If this difference is eliminated, then contamination of the alveolar sample with inspired gas does not alter the reading obtained and that reading is then representative of the arterial anesthetic partial pressure. The problem of contamination is considerably less for ether because of the lower solubility of ether in tissues.[13] The problem is still less for halothane with a blood/gas partition coefficient ⅛ that of ether.[12]

The importance of contamination of alveolar with inspired gas may be seen from a comparison of MAC obtained with and without elimination of the inspired to alveolar difference (table 5). The reduction in MAC achieved by eliminating the inspired end-tidal difference is greatest with methoxyflurane, intermediate with ether, and negligible for halothane. These data also argue against the possibility that these decreases in MAC result simply from the effect of prolonged and/or deep anesthesia. If the latter were the case, then one would expect the percentage decrease to be the same for all three anesthetics.

The problem of end-tidal contamination in the case of cyclopropane is minimal, since cyclopropane is a relatively insoluble anesthetic. As Seehzer *et al.*[10] have shown, the inspired and end-tidal cyclopropane concentrations rapidly approach each other in man.

The values of MAC obtained agree in general with previous reports that attempt to relate depth with anesthetic concentrations. Differences between our results and those of others[14-18] may be due to the technique of analysis, or to the end point sought.

TABLE 5. Possible Error in MAC Resulting From the Contamination of Alveolar with Inspired Gas

| Anesthetic | Methoxyflurene | Ether | Halothane |
|---|---|---|---|
| MAC without elimination of the $F_E$ to $F_I$ difference ($MAC_1$) | 0.25 | 2.6 | 0.74 |
| MAC with the elimination of the difference ($MAC_2$) | 0.16 | 1.92 | 0.77 |
| $(MAC_1-MAC_2)/MAC_1$ (*i.e.*, per cent error due to the difference.) | +56 | +30 | −4 |

Previous investigators have measured the inspired partial pressure rather than the alveolar partial pressure. The partial pressures may be similar in the case of relatively insoluble anesthetics, but dissimilar for soluble anesthetics, such as ether or methoxyflurane.

The MAC for cyclopropane of 9.2 per cent closely approximates the values obtained by others. For example, concentrations of 7.4 per cent,[14] and 7.1 to 14.2 per cent,[15] were found during light cyclopropane anesthesia in man.* However, in both studies, patients were premedicated with morphine and scopolamine, each of which may reduce the anesthetic requirement. Munson (unpublished data) using a procedure identical to ours, has redetermined MAC for cyclopropane and found it to be 9.75 per cent. The MAC for man is far less than for that in dog, 17.5 per cent,[1] a general pattern in which all human values are less than those observed in dogs. In part, this may be due to the difference in stimulus used. In dogs, the tail clamp is used, whereas skin incision is used in man. In dogs, skin incision appears to be a less intense stimulus.

The MAC value for ether of 1.92 per cent compares with a figure of 1.82 per cent reported by Faulconer during EEG level I ether anesthesia in man.[16] Haggard[17] reported that 3 to 4 per cent inspired concentrations of ether were required for anesthesia in dogs. Ebersole and Artusio found a blood ether concentration of 32 mgm per cent (1 per cent alveolar concentration) during "ether analgesia."[19] The difference between their value and ours may be attributed to a) ether analgesia is a lighter level of anesthesia than MAC, b) thiopental, which will decrease MAC,[1] was used for induction.[20]

The MAC for methoxyflurane of 0.16 per cent is considerably higher than that suggested by Holaday *et al.* for man,[11] where an arterial partial pressure of 0.66 mm. of mercury (0.087 per cent) was sufficient for light surgical anesthesia. However, many of their subjects were induced with thiopental and/or were concomitantly anesthetized with nitrous oxide, which would considerably reduce the requirement for methoxyflurane.[4, 5] A MAC of 0.23 per cent has been found in dogs [4]; as with cyclopropane, the human methoxyflurane MAC is less than the dog MAC.

The extrapolated figure of 101 per cent for the nitrous oxide MAC is in good agreement with Faulconer[15] and with Bert,[21] who produced light surgical anesthesia in man with partial pressures of 750 mm. of mercury in a hyperbaric chamber.

A relationship between anesthetic potency and lipid solubility as defined by the oil/gas partition coefficient, has been suggested by several authors.[22, 23] This relationship has been tabulated in the fourth column of table 6. The product of the oil/gas partition coefficient times MAC varies from a low of 109 for cyclopropane to a high of 172 for halothane. This represents a difference of 58 per cent, and is remarkably small considering the 630-

* The values reported are often given in terms of milligrams per cent in blood. We have converted these to volumes per cent by the use of the appropriate solubility coefficients and the gas laws.

TABLE 6. Correlation of Human MAC Values with Lipid Solubility and with Vapor Pressure

| Agent | MAC | Oil/Gas Partition Coefficient | O/G (37° C.) ×MAC | Vapor Pressure (37°/C.) | V.P./MAC |
|---|---|---|---|---|---|
| Methoxyflurane | 0.16 | 970 | 155 | 56 | 350 |
| Halothane | 0.77 | 224 | 172 | 480 | 623 |
| Ether | 1.92 | 65 | 125 | 820 | 427 |
| Fluroxene | 3.4 | 47.7 | 162 | 600 | 176 |
| Cyclopropane | 9.2 | 11.8 | 109 | 7,450 | 809 |
| Nitrous oxide | 101 | 1.4 | 141 | 59,300 | 588 |
| Xenon* | 71 | 1.9 | 135 | 60,800† | 867 |

(O/G is the Oil/Gas Partition Coefficient)
* See reference 6.
† Extrapolated figure.

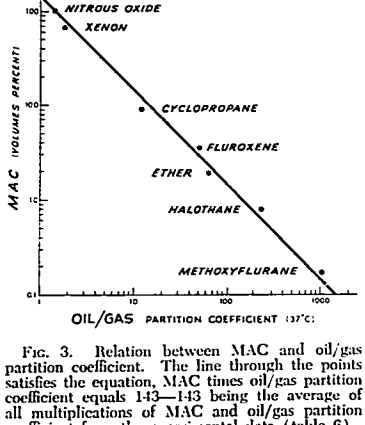


FIG. 3. Relation between MAC and oil/gas partition coefficient. The line through the points satisfies the equation, MAC times oil/gas partition coefficient equals 143—143 being the average of all multiplications of MAC and oil/gas partition coefficient from the experimental data (table 6).

fold range of anesthetic concentrations from which these products were derived. This relationship between MAC and lipid solubility is illustrated in figure 3.

A number of other physical properties of anesthetic agents have been related to anesthetic potency. Among these are vapor pressure,[24] molecular weight,[25] van der Waals forces,[26] and the dissociation pressure of hydrate crystals.[27, 28] Of these, the relationship between anesthetic potency and vapor pressure is the most consistent. The relationship is such that vapor pressure divided by MAC yields a relative constant. However, as seen in the last column in table 6, the minimum figure obtained is 176, and the maximum is 867. The latter figure is 392 per cent greater than the former. Compare this with the 58 per cent difference seen with the oil/gas and MAC relation. This does not prove that anesthetics exert their effect in the lipid phase of the brain. However, the remarkable correlation between lipid solubility and potency must not be overlooked when the precise mechanism of anesthetic action is sought.

MAC is indicative of only one aspect of anesthetic potency, *i.e.*, abolishing response to a surgical incision in 50 per cent of patients. Because of the manner in which MAC is determined, any one patient may or may not respond at anesthetic concentration higher or lower than MAC. MAC in a group of patients might be altered by variations in physical status, temperature, metabolic status or age.

The primary importance of MAC is in the establishment of what we believe are equipotent dose of anesthetic agents. With these doses, comparative studies may be made of the circulatory,[29, 30] respiratory,[31, 32] metabolic or other effects of anesthetics. Thus, the effect of 0.16 per cent methoxyflurane may be compared with the effect of 1.92 per cent ether on cardiac output. Similarly, 0.32 per cent methoxyflurane might be compared with 3.84 per cent ether, each of these being equipotent or equal multiples of equipotent anesthetic dose.

## Summary

The minimum alveolar concentration (MAC) required in man to prevent a gross muscular response to a surgical incision has been determined for cyclopropane, halothane, diethyl ether and methoxyflurane. These were: cyclopropane 9.2 per cent, halothane 0.765 per cent, diethyl ether 1.92 per cent, and methoxyflurane 0.16 per cent. These values, along with previously determined MAC's for nitrous oxide (101 per cent)[4, 5] and fluroxene (3.4 per cent),[5] provide a useful standard for comparison of anesthetic depth. A good correlation exists between MAC for an anesthetic and the anesthetic lipid solubility.

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