Minimum Alveolar Anesthetic Concentration:
A Standard of Anesthetic Potency

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The minimum alveolar concentration of anesthetic (MAC) necessary to prevent movement in response to a painful stimulus was relatively constant in dogs anesthetized with halothane. MAC varied over a two-fold range with the intensity of the stimulus, but appeared to reach an upper limit beyond which a further increase in intensity did not increase MAC. For the same stimulus MAC was constant from dog to dog. MAC was unaffected by duration of anesthesia, unaltered by hypocarbia or hypercarbia, by phenylephrine-induced hypertension or by mild hypoxia (Pa_{O_2} 30 to 60 mm. of mercury). Hemorrhagic hypotension or marked acute metabolic acidosis reduced MAC by 10 to 20 per cent. Severe hypoxia (Pa_{O_2} less than 30 mm. of mercury) reduced MAC by 25 to 50 per cent.

MAC appears to be a useful standard by which all inhalation anesthetics may be compared.

IN 1963 Merkel and Eger described a technique for the determination in dogs of the minimum alveolar concentration of anesthetic (MAC) required to prevent gross muscular movement in response to a painful stimulus.[1] The alveolar concentration ** was chosen as the most readily measured index of brain anesthetic tension. The dogs were anesthetized with a small dose of thiopental and anesthesia was maintained thereafter with either halothane or halopropane. The concentration required to produce unresponsiveness was found to be fairly constant in any one dog regardless of duration of anesthesia. This apparent reproducibility led us to believe that MAC might be useful as a standard of anesthetic potency. Potency may be defined as the reciprocal of MAC, or potency equals 1/MAC. Thus, nitrous oxide would be less potent than cyclopropane, and cyclopropane less potent than halothane. A standard such as MAC would allow a comparison of respiratory or circulatory (or other) effects produced by equipotent doses of two or more anesthetics. However, before general use for this purpose, we must know the limits of reproducibility of MAC and whether it is affected by such things as intensity of the painful stimulus, duration of anesthesia, hypocarbia, hypercarbia, hypotension, hypertension, hypoxia, or metabolic acidosis. We have attempted to answer the above questions in this study.

Methods and Results

The technique previously described was altered slightly in that thiopental was not used. Anesthesia was induced and maintained with oxygen plus the gas to be studied (usually halothane). This change was made after discovery that an induction dose of thiopental (150 to 200 mg.) reduced MAC by 5 to 20 per cent for 2 to 4 hours. Rusy *et al.*,[2] similarly found that the anesthetic effect of 225 mg. of thiopental on cyclopropane requirement in dogs was apparent 45 minutes or longer after injection. At least in dogs, thiopental may have a more than evanescent

** In this and the succeeding papers concerning MAC, we will use alveolar concentration (volumes per cent) rather than partial pressure. However, concentration will always be described relative to a pressure of one atmosphere (760 mm. of mercury). For those who would prefer partial pressure, our figures may be converted to atmospheres pressure simply by moving the decimal point two places to the left.

effect. After induction an endotracheal tube was inserted, usually without succinylcholine, and a temperature probe placed in the esophagus. A peripheral vein was cannulated and an infusion of 5 per cent dextrose and water begun and continued throughout the procedure. An artery was cannulated and pressure monitored with a Statham transducer and direct writing polygraph. In the previous study the stimulus had been applied for 5 to 10 seconds and then withdrawn. However, we found that a negative response at 10 seconds might become positive if the stimulus were continued for 30 seconds. As a result, the stimulus was applied for at least 30 to 40 seconds, usually for a minute. A positive response was a gross purposeful muscular movement, usually of the head (jerking or twisting) or extremities (running or clawing). Coughing, swallowing, or chewing were not included as positive responses. The alveolar concentration was held constant for at least 15 minutes before stimulation. Assuming a cerebral blood flow of 50 ml./100 g./minute[3] and a brain/blood partition coefficient of 2.5,[4] a 15-minute interval allowed for 3 time constants or at least 95 per cent equilibration between arterial and brain tensions for halothane.[5] For all other anesthetics the 15-minute equilibration time allowed for an even closer approach to equilibration since the brain/blood partition coefficients are all less than that for halothane. MAC was taken to be the concentration midway between the highest concentration allowing and the lowest concentration preventing a positive response. For example, if no response were obtained at 1.00 per cent halothane the concentration was lowered to 0.80 per cent and the stimulus re-applied. If movement then occurred MAC was said to be 0.90 per cent (a maximum possible error in the true MAC of about 10 per cent).

Alveolar gas analyses for halothane, fluroxene, and methoxyflurane were carried out with an infrared analyzer calibrated as previously described.[6, 7, 8] Halothane and methoxyflurane samples were drawn by suction through the analyzer at end-expiration from a nylon catheter inserted into and down the endotracheal tube. End-tidal samples were collected from a Rahn sampler[9] in the case of fluroxene.

Arterial blood gas analyses for P_{O_2}, P_{CO_2}, and pH were performed with appropriate electrodes.[10] Base excess was calculated from the Siggaard Andersen nomogram.[11] End-tidal P_{CO_2} was determined by infrared analysis. Esophageal temperature was maintained at 37.5 ± 1.0° C.

Relation Between Intensity of Stimulus and MAC. Three dogs were anesthetized with halothane, and MAC values for various stimuli determined in duplicate for each dog. The stimuli were: (1) Tail clamp—a 10-inch hemostat was clamped on the shaved tail about 2–4 inches from its base until the rachet caught. The tail was moved continuously with the hemostat for the duration of stimulation. The site of the tail clamp might or might not be varied. No apparent diminution in sensation occurred when the tail was repeatedly clamped at the same place. (2) Tail clamp in the presence of an increase in end-tidal P_{CO_2} of about 20 mm. of mercury. (3) Electrical stimulation of 10, 30, and 50 volts, 50 cycles per second, 10 milliseconds duration from a Grass stimulator through needle electrodes placed 2–3 inches apart in the cheek or in sensitive mucous membranes. (We found that more than 10 to 15 volts produced an extremely painful sensation when applied via needle electrodes placed into the skin of our own forearms.) (4) Manual movement of the endotracheal tube in its longitudinal axis. (5) A 20 cm. vertical incision into the flank. The first incision was placed posteriorly and each succeeding incision progressed cephalad about 2 cm. (6) Paw clamp—a 10-inch hemostat applied across the paw or to the web between the toes. (7) No stimulation other than the presence of the endotracheal tube and cut-down catheters.

The MAC values for these stimuli are given in table 1. An alveolar halothane concentration of 0.80 to 0.84 per cent (MAC for these stimuli) was required to abolish movement in response to the tail clamp with or without added carbon dioxide, or to electrical stimulation with 30 or 50 volts. Response to surgical incision or 10 volts electrical stimulation could be precluded with 0.66 to 0.69 per cent (MAC for these stimuli); 0.46 to 0.55 per cent (MAC for these stimuli) prevented spontaneous movement or response to endotracheal movement or paw clamp. The latter were the

TABLE 1.   MAC for Halothane
(Percentage halothane)

Stimulus	Dog 1	Dog 2	Dog 3	Mean
Tail clamp	0.89 (100)	0.85 (96)	0.68 (76)	0.81
Tail clamp, plus end-tidal CO₂ of 57 mm. Hg	0.92 (100)	0.89 (97)	0.60 (65)	0.80
10 volts	0.80 (100)	0.70 (88)	0.47 (59)	0.66
30 volts	0.98 (100)	0.82 (84)	0.68 (69)	0.83
50 volts	0.98 (100)	0.82 (84)	0.71 (73)	0.84
Endotracheal tube	0.89 (100)	0.52 (58)	0.35 (39)	0.55
Incision	0.80 (100)	0.52 (65)	0.76 (95)	0.69
Paw clamp	0.50 (100)	0.64 (128)	0.35 (70)	0.50
Spontaneous movement	0.50 (100)	0.52 (104)	0.35 (70)	0.46

The figure in brackets is 100 times the value for that dog divided by the same value for dog 1. For example, for 10 volts the bracketed number following the dog 2 datum was derived as 100 × .70/.80 = 88.

least effective stimuli. Note that the above mean values may represent considerable individual variations. Variation, as described by the bracketed values in table 1, appeared to increase as the intensity of stimulation decreased. Thus, variation was less for tail clamp or 50 volts than for endotracheal tube movement, paw clamp or spontaneous movement.

We believe that in none of these or the subsequent studies did any dog suffer pain on application of these noxious stimuli. This belief is based on published [8, 12] and unpublished observations in man at similar depths of anesthesia. At alveolar concentrations insufficient to prevent movement in response to a noxious stimulus (surgical incision) there is apparently no memory of the event.

In a separate study with 4 dogs given fluroxene and another 4 given methoxyflurane,
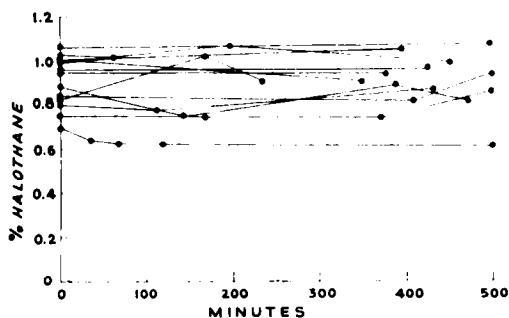

FIG. 1. Changes in halothane MAC with time. Time zero is the time of the first MAC determinations for each dog. Each graph represents MAC's of one dog during the course of one experiment.

an attempt was made to test the possible summation of two stimuli, tail clamp and 40 volts, applied together. Determinations were done in triplicate in each dog. In no dog did the combined stimuli require a higher alveolar concentration to suppress movement than did tail clamp alone.

Tail clamp appeared to be a maximal stimulus: that is, a further increase in stimulus as noted above did not increase MAC. For this reason, we chose tail clamp as the stimulus to be used in the remainder of our experiments. All succeeding MAC determinations were done in duplicate.

Reproducibility of MAC. Seven dogs were anesthetized with halothane for prolonged periods. MAC was determined at the beginning, at the end, and in several dogs at intervening times during the experiment. Concurrently, respiratory response to carbon dioxide was examined.[13] These animals were allowed to recover, and after at least two weeks were reanesthetized and MAC redetermined. The mean MAC was 0.90 ± 0.12 per cent halothane for all 7 dogs for all determinations (the values for each dog being weighted equally.). Deviaiton from the initially determined MAC during the course of any one study is illustrated in figure 1. Mean deviation of a MAC determination from the immediately previous determination was 0.07 ± 0.07 per cent halothane. Mean deviation between the first and second studies (different days) for the same dog was 0.07 ± 0.05 per cent.

Metabolic Acidosis. The effect of acute metabolic acidosis was studied as follows. Three dogs were anesthetized with halothane and MAC determinations made on each. Sixty to eighty milliequivalents of ammonium chloride were slowly infused. End-tidal P_{CO_2} was held constant despite increase in ventilation by causing rebreathing to occur. After completion of the acid infusion, MAC was again determined. The average MAC decreased from 0.90 per cent to 0.73 per cent while the *p*H had fallen from 7.38 to 7.20. Eighty to ninety milliequivalents of sodium bicarbonate were infused and MAC and *p*H redetermined. The mean MAC moved to 0.79 per cent while the *p*H averaged 7.40. The entire process was repeated for 2 of the

dogs. Results along with arterial P_{CO_2} are graphed in figure 2.

Hypercarbia and Hypocarbia. In our initial study of the importance of stimuli, we found that elevation of end-tidal carbon dioxide to about 60 mm. of mercury had no discernible effect on MAC. To test the effect of decreased carbon dioxide, we determined MAC in 3 spontaneously breathing dogs anesthetized with halothane. Respiration was then controlled to achieve an end-tidal P_{CO_2} of about 10 mm. of mercury, where it was held while MAC was redetermined. Spontaneous respiration was resumed and MAC again determined. Concomitantly, in all 3 dogs arterial P_{CO_2} values were obtained, and in 2 dogs pH values were also measured (fig. 3). On going from a mean arterial P_{CO_2} of 42 mm. of mercury to 14 mm. of mercury, average MAC changed from 0.94 per cent halothane to 0.95 per cent. Similarly, on return of the mean P_{CO_2} to 41 mm. of mercury from 14 mm. of mercury, average MAC changed from 0.95 per cent to 0.91 per cent.

Hypoxia. Six dogs were anesthetized with halothane and oxygen and MAC values determined. Oxygen concentration in the circle system was decreased to various values, as measured with a Pauling meter, by adding nitrogen to the oxygen-halothane inflow, and MAC was redetermined. Concomitant arterial P_{O_2} determinations were made. As
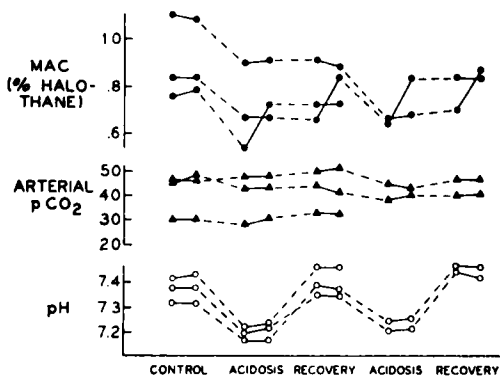

FIG. 3. Changes in halothane MAC with acute reduction in arterial P_{CO_2} by hyperventilation. Three dogs were tested, although arterial pH values were obtained in only 2.

seen in figure 4, MAC did not change appreciably until P_{O_2} fell below 30 mm. of mercury. In the 2 dogs tested below 30 mm.

FIG. 4. Change in halothane MAC with change in arterial P_{O_2}. The P_{O_2} values for the average control MAC are all at or above 400 mm. of mercury. These are connected by line and arrow to the succeeding values obtained under hypoxia. (Note that the lines do not indicate the path taken by MAC but only connect the two points observed.) Each set of points represents the values for one dog. Recovery values of MAC following hypoxia are not shown. Unlike the preceding and following graphs, the x-axis has a logarithmic scale.

FIG. 2. Effect on halothane MAC of acute changes in arterial pH by the infusion of ammonium chloride. The return to control pH values is achieved by infusion of sodium bicarbonate. Experimental results from 3 dogs are shown. In 2 dogs the process of acidosis and recovery was repeated.
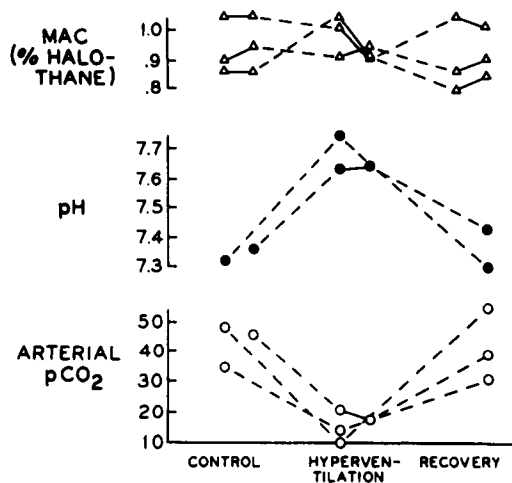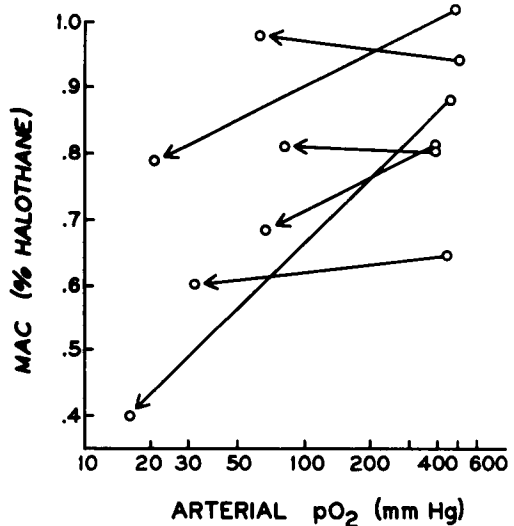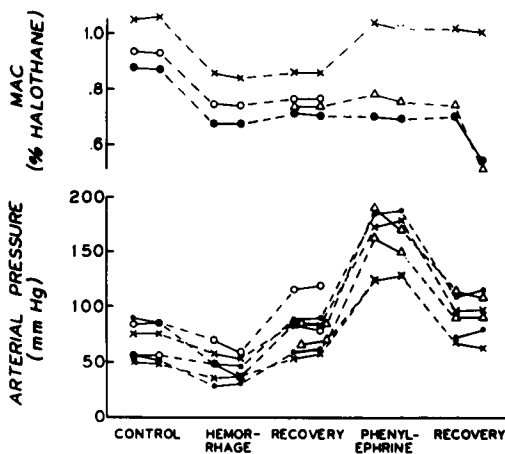
FIG. 5. Response of halothane MAC to hypotension produced by hemorrhage and to subsequent hypertension resulting from phenylephrine infusion. Results from 4 animals are shown. Two completed the series while one underwent hypotension but not hypertension, and another underwent hypertension but not hemorrhage.

Hg halothane, MAC fell by 0.25 and 0.5 per cent. Below 20 mm. Hg blood pressure and ventilation became unstable and one dog (not shown) died soon after a P_{O_2} of 20.3 mm. of mercury was obtained. Recovery MAC values are not shown, although when P_{O_2} values greater than 30 to 60 mm. of mercury were maintained, no change was seen. However, when the arterial P_{O_2} was less than 30 mm of mercury, a reduction in MAC of 0.1 to 0.2 per cent halothane from the initial control MAC values (prehypoxia MAC) was found on recovery.

Hypotension and Hypertension. The influence of hemorrhagic hypotension and of phenylephrine-induced hypertension were next studied. Three dogs were anesthetized with halothane and MAC determined. Each dog was heparinized and bled until the diastolic pressure had fallen to two-thirds to one-half of its initial value. It was maintained thereafter at this level while MAC was again measured. This required the loss (total) of 900, 550, and 875 ml. of blood in the 3 dogs. After MAC determinations in the hypotensive state, the shed blood was reinfused and the animal given sodium bicarbonate to correct the 2 to 6 mEq. base deficit that had developed. After a 15-minute recovery period MAC was re-

examined. A phenylephrine infusion was then administered at a rate sufficient to hold the diastolic pressure at twice the control value. This resulted in the prompt death of one of the animals. MAC was determined again in the remaining 2 animals, after which the phenylephrine infusion was stopped, the arterial pressure returned to slightly above control values, and MAC again determined. The results obtained are described by figure 5. A fourth dog was added to the study after the death of the dog given phenylephrine. His control values are added in the first "recovery" column. He was then treated with phenylephrine and allowed to recover while appropriate MAC determinations were made. These data are added in the phenylephrine and second recovery column.

Average MAC decreased following hemorrhage, from 0.96 per cent halothane to 0.76 per cent. On recovery, mean MAC remained essentially unchanged at 0.77 per cent. Mean MAC value preceding the phenylephrine drip was 0.77 per cent halothane. This rose slightly with the blood pressure rise to 0.83 per cent. On recovery it returned to 0.76 per cent.

Discussion

The most striking finding in these studies is the stability of MAC. For example, different dogs have relatively the same MAC for halothane (0.90 ± 0.12 per cent). Similar observations have been made in man.[12] This is contrary to the general clinical impression that there is a wide range of susceptibility to an anesthetic agent. These two observations are not necessarily in conflict. The patient who has a large cardiac output or a diminished alveolar minute volume will take up a greater proportion of the inhaled anesthetic than the patient whose ventilation is supplemented or whose cardiovascular system is less vigorous. The latter patient requires less halothane than the former to maintain the same alveolar concentration.[14] There is then a difference in the amount required from the anesthetic machine, although anesthetic partial pressure in lungs (and brain) may be identical.

Differences in apparent anesthetic requirement among patients also may be partially

explained by variation in the stimulus presented. In our study an extremely painful stimulus such as tail clamp or electrical stimulation (table 1) consistently required a higher alveolar halothane concentration for suppression of movement than did surgical incision. Surgical incision in turn was a more severe stimulus than paw clamp. It should be noted, however, that the difference in alveolar concentrations required is relatively small and that, as far as we can tell, increasing the stimulus beyond a certain point (tail clamp) does not increase MAC. For the same stimulus (surgical incision) MAC appears to be essentially the same in both dog and man.[12]

The finding that in the same dog there is little variation in MAC with time (fig. 1) again appears to be at variance with the clinical observation that patients require less and less agent as the anesthetic progresses. Again, these two observations are not in conflict because uptake at a constant alveolar concentration decreases with time, and hence the amount of anesthetic required from the machine similarly must decrease.[6, 7] The anesthetic dose (MAC) remains constant while the amount of anesthetic administered decreases.

It is also possible that MAC might decrease with time in the presence of vascular shunts through the lungs or abnormalities in ventilation/perfusion ratios. Shunts through the lungs would produce an alveolar to arterial anesthetic tension gradient.[15] The alveolar concentration would not then be representative of arterial or brain anesthetic partial pressure until the gradient disappeared. This would occur after tissues had equilibrated with the alveolar anesthetic partial pressure. Since equilibration occurs with time this effect would be minimized in our studies, since the first MAC determination was made at least one and one-half and usually two hours following induction. Our data from dogs, however, are not at variance with similar data from man where a shorter interval between induction and MAC determination (usually less than one-half hour) was taken. For example, our mean MAC for surgical incision in dogs was 0.69 per cent halothane, whereas Saidman and Eger found a MAC of 0.74 per cent for the same stimulus in man.[12]

Acute metabolic acidosis produced by ammonium chloride appeared to cause a small but consistent decrease in MAC (fig. 2). Return of arterial pH to control levels or above by infusion of sodium bicarbonate resulted in little change in MAC. We might speculate that the reason for the small decrease with onset of acidosis is not to be found in the decrease in pH but rather in the presence of a relatively high blood ammonia concentration. The central depressant effect of opiates is usually increased in the presence of liver failure and elevated blood ammonia levels. Under these circumstances, coma may follow the injection of a normal dose of opiate.[16] Similarly, if ammonia adds to the effect of halothane, MAC should be reduced following ammonium chloride infusion. This thought is supported by the finding that following the initial decrease, MAC in two of the five experiments rose to control levels while the animals were still acidotic (metabolic elimination of ammonia?) and also by the finding that reversal of the acidosis did not alter MAC. Further support comes from the data showing that neither respiratory acidosis (table 1) nor alkalosis (fig. 3) affected MAC.

The lack of effect of changes in P_{CO_2} on anesthetic depth disagrees both with the findings that anesthetic effect increases with hypercarbia[17, 18, 19] and with the clinical impression that hyperventilation decreases anesthetic requirement.[20, 21] The disagreement with clinical impression again may be more apparent than real, since hyperventilation at a constant inspired concentration raises the alveolar halothane concentration.[14] Thus, clinically, anesthesia does deepen when ventilation is changed from spontaneous to controlled if the inspired concentration is held constant. However, it does so only because of the increased alveolar concentration of halothane, and not the decrease in P_{CO_2}.

At the other extreme, carbon dioxide itself has an anesthetic effect if given in sufficient concentration.[18, 19] But these concentrations, which exceed 25 per cent, are far beyond those we have tested or those which are found clinically. It may be that MAC is too crude a test to reveal the effect of a change of 3 or 4 per cent carbon dioxide while the more sensitive test described by McAleavy et al.[17] could make such a discrimination. This may

be stated mathematically if we assume that the anesthetic effects of two gases are additive, so that

$$\frac{P_A}{P_{OA}} + \frac{P_B}{P_{OB}} = 1$$

where P_A and P_B are the respective partial pressures of anesthetics A and B which, when administered together, give the same anesthetic effect as P_{OA} or P_{OB}. P_{OA} and P_{OB} are the respective minimum partial pressures of A and B necessary to achieve anesthesia when used alone. From this we can see that the reduction in P_A relative to P_{OA} may be small and within the range of experimental error if P_B/P_{OB} itself is small.

MAC variations with hypoxia (fig. 4) indicate that changes in arterial P_{O_2} above 30 mm. of mercury (roughly an oxygen saturation of 50 per cent) have no effect, while below this tension there is a decrease in MAC. This decrease may be the result of pathological changes since MAC in these animals failed to return to control levels. The one death which occurred at an arterial P_{O_2} of 20 mm. of mercury also indicates that damage can result at this low partial pressure. It is only near the extreme limit of tolerable hypoxia that MAC is decreased.

Hypotension due to hemorrhage decreased halothane MAC from 0.96 per cent to 0.76 per cent. As with the changes accompanying profound hypoxia, MAC did not return to normal with return to control arterial pressures (fig. 5). Again, this may indicate the presence of pathological changes. Hypertension did not appreciably alter MAC (fig. 5).

MAC is constant and reproducible under a wide variety of circumstances. It allows a correlation between anesthetic dose and depth and as opposed to similar correlations of dose with EEG or changes in the cardiovascular or muscle systems, it is a technique that can be applied to all inhalation anesthetics in the same fashion.[9] It therefore provides a useful means for making comparisons of anesthetic potency.

The MAC measurement does have limitations. Since only two measurements are involved, alveolar anesthetic concentration and the presence (or absence) of gross movement,

it ignores other important responses to the stimulus imposed. Thus, at or above MAC although there is no movement, there are other responses to the imposed stimulus. Ventilation is increased with a concomitant fall in arterial P_{CO_2}. Arterial pressure may fall or rise and pulse rate increase. The dog may show signs of increased central nervous system activity such as chewing, coughing, or swallowing. None of these are considered in the present MAC concept.

The interpretation of our results may also be limited by two other factors. Although the acute stresses used (hypoxia, hypocarbia and hypercarbia, acidosis, alkalosis, hypotension and hypertension) produced minimal changes in MAC, we cannot assume that were these stresses chronic the same would be true. Also, we have tested only one anesthetic, halothane, for the effect of these stresses, and therefore have not proved that the same minimal changes would be found with other agents.

Summary

We have determined the minimum alveolar concentration (MAC) of halothane in dogs required to prevent movement in response to a painful stimulus. The concentration required varies within a moderate range depending on the severity of the stimulus. For any one stimulus the concentration range is small (±10–20 per cent). There appears to be an upper limit of stimulation beyond which the anesthetic requirement (alveolar concentration required to suppress movement) is not increased. Factors such as duration of anesthesia, differences in dogs, hypo- or hypercarbia, hypoxia to 60 mm. of mercury P_{O_2}, acute metabolic alkalosis, or hypertension induced with phenylephrine have little or no effect on MAC. Hypoxia below 30 mm. of mercury P_{O_2}, acute metabolic acidosis induced with ammonium chloride, and acute hemorrhagic hypotension all produce decreases of roughly 10 to 50 per cent of the initial MAC.

MAC appears to be a useful means for the determination of anesthetic potency.

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CORTICOSTEROIDS AND ETHER In rats no change in blood counts or plasma corticosteroid levels occurred during first 2 minutes of ether anesthesia. From 2 to 24 minutes the average plasma corticosteroid level increased fourfold. From 24 to 96 minutes of anesthesia the corticosteroid level increased slowly. (*Cann, M. C., and others: Effect of Ether Anesthesia on Plasma Corticosteroids and Hematologic Responses, Canad. J. Physiol. 43: 463 (May) 1965.*)