Determination and Applications of MAC

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Summary

Although the first published report of ether administration, by Bigelow, in 1847, does contain a description of an apparent overdose, the major concern of early anesthetists was how to administer sufficient quantities of the drug. John Snow's description of how some anesthetists ascertained “depth” of anesthesia is of interest:

The practice, I believe, is occasionally resorted to, of pricking the patient to ascertain whether he is insensible; there is no harm in it, but I consider that it would be inconclusive where it furnished only a negative result; and I never adopt it, as I constantly observe that there may be insensibility to a slight lesion—as a suture in the skin, for instance—at a time when a greater wound would cause signs of pain.

This pioneering anesthetist had concluded in 1858 that trial stimuli might be submaximal, and that blunting of the responses to such stimuli was related to anesthetic depth. With the introduction of a second anesthetic, namely chloroform, comparisons as to “potency” were inevitable. Snow reported that chloroform was about six times more potent than sulfuric ether. Until 1946, investigators reported “clinically required” concentrations of whatever anesthetic they were testing.⁴⁶

In 1946, Robbins defined anesthetic ED₅₀ (or AD₅₀) as the concentration of anesthetic at which 50 per cent of mice failed to right themselves for 15 sec when placed in a rotating bottle with a known concentration of anesthetic. He defined the anesthetic concentration that caused apnea in 50 per cent of the mice in 10 min as the LD₅₀, and then considered the ratio LD₅₀/AD₅₀ to be an index of safety. Mice that survived this study to determine LD₅₀ were then removed and examined to “determine the time necessary to recover pain sensation (pressure on tail) and ability to walk.” Other concepts of anesthetic potency or measures of anesthetic “depth” using different organ responses included Guedel's clinical signs for ether, Saulconer's correlates of electroencephalographic activity with anesthetic blood levels,⁸ and Woodbridge's breakdown of anesthesia into analgesia, neuromuscular blockade, hypnosis, and reflex obdurator. The evolving ideas of dose, stimulus, and target organ response set the stage for the development of repeatable

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methods of measuring and comparing anesthetic potencies.

MAC

**Definition**

To compare two anesthetic agents, Merkel and Eger,\(^{11}\) in 1963, described an "index of comparison," coining the term MAC (minimum alveolar concentration). They initially defined MAC 1.0 as the "minimal anesthetic concentration in the alveolus required to keep a dog from responding by gross purposeful movement to a painful stimulus."\(^{11}\) Anesthetic dose then could be expressed as multiples of MAC, e.g., 1.5 MAC, 3.0 MAC. In 1964, Saidman and Eger\(^ {19}\) defined MAC for man as the "point at which 50 per cent of the patients moved" in response to a surgical incision. These early studies revealed two facts: first, that MAC was remarkably consistent, both in animals and in man; second, that beyond a certain point, an increase in stimulus intensity did not increase MAC (supramaximal stimulation).

Minimum alveolar concentration is defined in terms of percentage of one atmosphere, and therefore is an alveolar anesthetic partial pressure (i.e., MAC would be the same at sea level and at the top of Pike's Peak). Because partial pressures of anesthetics at equilibrium will be equal in all body tissues (e.g., alveolus, blood, brain), MAC should represent the anesthetic partial pressure (not the concentration) at the anesthetic site of action, the brain. For every inhalational anesthetic studied, MAC has proven remarkably constant for animals and man in response to any supramaximal stimulus, and is relatively easy to measure. In addition, MAC is predictably related to partial pressure at the anesthetic site of action. These facts have made MAC the major index of anesthetic potency in the anesthetic literature during the past 15 years.

**Technical Aspects of Obtaining MAC in Animals and Man**

The methods by which MAC is determined in animals and in man differ. The animal is anesthetized with the anesthetic in oxygen, and the trachea is intubated (usually without succinylcholine). An end-tidal anesthetic concentration predetermined by pilot study is obtained and held constant for at least 15 min in an attempt to reach equilibrium between alveolar gas (end-tidal), arterial blood, and brain. The animal is then stimulated with either a tail-clamp (full-length hemostat applied close to the base of the tail and clamped to full ratchet lock) or subcutaneous electrical current (50 volts at 50 cycles/sec for 10 msec). If no response to stimulation occurs, the end-tidal anesthetic concentration is lowered to 80 or 90 per cent of the initial concentration, and the stimulus is repeated after allowing 15 min for reequilibration. If a positive response to stimulation is obtained initially, the end-tidal anesthetic concentration is increased 10 to 20 per cent, and the process of 15 minutes' reequilibration followed by application of stimulus is repeated. The anesthetic concentration midway between that allowing and that preventing movement is MAC 1.0. The narrower the brackets (e.g., 10 per cent step changes in anesthetic concentration vs. 20 per cent changes), the more precise (and time-consuming) will be the determination.

When MAC is determined in man, the stimulus used is usually a skin incision. Since only one incision per patient is usually made, the "bracketing" technique used in animals does not apply. Electrical currents have also been used as stimuli\(^ {12}\) (30–45 volts AC with a 1.2-msec pulse at 50 cycles/sec for less than 60 sec via 20-gauge needles in the forearm). In all other respects, the determination of MAC in man is the same as that in animals. Anesthesia is induced with the anesthetic in oxygen. No premedication is given, and no other anesthetic agent is administered. A single preselected end-tidal anesthetic concentration is held constant for 15 min prior to skin incision. With the incision the patient is observed for movement or lack of movement. A group of patients must be so tested over a range of end-tidal anesthetic concentrations that permits and prevents movement. The patients may then be taken in groups of four or more, starting with the lowest actual end-tidal concentration (fig. 1). The percentage of patients moving within each group is plotted against the average end-tidal concentration for that group. A visual line of best-fit through these points yields the concentration at which 50 per cent of patients respond, i.e., MAC (fig. 2). A more rigorous analysis (Waud,\(^ {13}\) Litchfield and Wilcoxon\(^ {14}\)) yields the same value for MAC and adds one element: an estimate of the variance of MAC (a standard deviation).

Thus, the determination of MAC has three basic components: an applied noxious stimulus, a defined response, and the measurement of end-tidal anesthetic concentration. During early animal studies, Eger e al.\(^ {15}\) found that variability in MAC decreased as stimulus intensity increased, and that certain stimuli appeared to be supramaximal. Simultaneous application of two different supramaximal stimuli did not increase MAC to above that seen with a single supramaximal stimulus. It should be noted that skin incision was not quite a supramaximal stimulus in dogs. Because the tail-clamp was simply applied, and be-
FIG. 1. The responses to surgical incision of three groups of patients: Group A (halothane in oxygen); Group B (halothane in oxygen with morphine premedication); and Group C (halothane in 30 per cent oxygen and 70 per cent nitrous oxide). The alveolar (end-tidal) halothane concentration is plotted on the horizontal axis. Patient movement is recorded as an upward deflection at that patient’s alveolar (end-tidal) halothane concentration. When the patient did not move in response to the surgical incision, a downward deflection was recorded. From Saidman and Eger, with permission of the authors and publisher.

FIG. 2. The patients from figure 1 were taken in groups of four, starting at the lowest alveolar (end-tidal) halothane concentration. The percentage of patients responding (moving) within each group of four is plotted on the vertical axis against the mean alveolar (end-tidal) halothane concentration of that group of four patients, which is plotted on the horizontal axis. From Saidman and Eger, with permission of the authors and publisher.

cause no change in MAC resulted from application of a more intense stimulus, tail-clamping was chosen in animals for determination of MAC. Skin incision remains the standard stimulus in man.

A positive response is considered to be “gross purposeful muscular movement,” usually of the head or extremities. Head movement does not include a twitch or grimace, but only a “jerking or twisting” motion. Extremity movements are most common; motion of the torso without head or extremity response is rare. Coughing, swallowing, and chewing are not considered positive responses.

The concept of MAC assumes that end-tidal, alveolar, arterial blood, and brain anesthetic partial pressures are equal after 15 min of equilibration. This assumption may be incorrect, but any error that results is usually small. End-tidal gas partial pressure in normal unanesthetized man is a reasonable approximation of “ideal” alveolar partial pressure. Anesthesia may enhance the ventilation–perfusion inequalities that exist even in normal patients, and some alveolar-to-arterial partial pressure gradient must result. This potential error is minimized when the inspired-to-alveolar (end-tidal) anesthetic partial pressure difference is small (i.e., with poorly soluble anesthetics; with normal ventilation and cardiac out-

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put, as opposed to hypoventilation or increased cardiac output; and/or after prior equilibration at a higher anesthetic partial pressure.

Several factors may combine to produce a difference between the end-tidal and arterial blood anesthetic partial pressures. End-tidal gas from nonperfused alveoli (alveolar deadspace) or poorly perfused alveoli (severe V/Q abnormalities) contains anesthetic partial pressures near to inspired and thereby increases the end-tidal anesthetic partial pressure. The greater the difference between inspired and "true" alveolar (normally ventilated and perfused alveoli) anesthetic partial pressures, the greater the error introduced by this admixture. If, in addition, the ventilated non-perfused portion of the lung empties more slowly, the error (difference between end-tidal and arterial blood partial pressures) will increase further. Finally, if the gas is very soluble in the airway tissues and is released during expiration, the contribution of this gas to the end-tidal sample will erroneously increase the estimate of the arterial partial pressure.

A third assumption is that 15 minutes' equilibration produces equality of arterial and brain partial pressures. This concept is based on known values for cerebral blood flow and the relatively modest brain-blood partition coefficients of most anesthetics. A lower tissue solubility or a greater tissue blood flow (as achieved by hypoventilation or anesthesia itself) will accelerate equilibration. Hyperventilation, particularly with relatively insoluble agents, may prolong equilibration slightly. In any case, the time to equilibration is probably shorter than that implied earlier, because the part of the brain important to the anesthetic process is probably grey matter, which has a blood flow one and a half to two times the mean cerebral blood flow.

What does and does not affect MAC

**Type of Stimulation.** MAC is unaffected by the type of stimulation, provided a maximal stimulus is applied.

**Duration of Anesthesia.** Gregory et al. found no difference in MACs for two herniorrhaphy incisions performed in human subjects at different times during the same anesthetic episode. Canine halothane MAC is constant for as long as 500 min of anesthesia. Recently, however, both acute and chronic tolerances to nitrous oxide-induced analgesia have been demonstrated. Mice can be made tolerant to nitrous oxide, with cross-tolerance to cyclopropane and isoflurane also occurring. These alterations in murine anesthetic requirement were small, however, i.e., 10-20 per-cent changes; and acute tolerance was complete after only 10 min of anesthesia. Chronic tolerance took several days to develop.

**Circadian Rhythms.** In the same animals MAC varies slightly (±10 per cent) when measured at different times. Circadian rhythms may play some role in this observed variation. MAC increases 10 to 14 per cent from the mean during the "dark" phase of the circadian cycle in the rat, which is the period of greatest metabolic activity in that species.

**Intra- and Interspecies Variations.** For most species of animals MAC varies 10 to 20 per cent. This variation is only slightly greater than that found for different determinations within the same animal (less than 10 per cent). Different species or classes of animals (e.g., amphibs vs. mammals) do not show large variations in MAC; MAC values for a given anesthetic remain within a twofold range (table 1). Given the structural diversities of animals, both on a macroscopic level and on a molecular level, it is hardly surprising that MAC varies slightly among species or classes. What is surprising is that it varies so little.

The interspecies variations in MAC may be partially explained by variations in the techniques used in its measurement. For example, variability in age, temperature, and circadian cycle undoubtedly contributed to these observed differences in MAC. The stimuli used also varied extensively, as did the end point of "anesthesia" itself (table 1). In addition, some investigators measured inspired rather than end-tidal anesthetic concentrations. Still, some variation in anesthetic requirement among different species of animals probably does exist, the cause of which may be a clue to the mechanism(s) of anesthesia itself.

Sex. Unpublished data from two laboratories indicate that MAC is not different between sexes in human beings or rats.

**Hypocarbia and Hypercarbia.** Reducing PaCO₂ from 42 to 14 torr (pH 7.7) does not alter halothane MAC in dogs. Halothane MAC in man is also unaffected by hypocapnia (PaCO₂ = 21 torr). Altering PaCO₂ between 15 and 95 torr (arterial and cerebrospinal fluid [CSF] pH 7.6 to 7.10) does not affect halothane MAC in dogs. Levels of PaCO₂ greater than 95 torr, associated with arterial blood and CSF pH values less than 7.10, are, however, increasingly narcotic. "Anesthesia" (i.e., MAC 1.0) can be achieved with a PaCO₂ of approximately 245 torr (CSF pH less than 6.90) (fig. 3). The degree of carbon dioxide narcosis correlates with cerebral CSF pH, but not with pH₄, PaCO₂, or the partial pressure of carbon dioxide in the CSF. Cullen and Eger demonstrated that extreme hypocapnia (PaCO₂ 10 torr) in dogs did not affect MAC when halothane was administered in oxygen, but caused a slight (10 per cent) reduction with halothane in air. They postulated
### Table 1. Anesthetic Potencies (MAC) of Various Anesthetics in Different Species (and Classes) of Animals*

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* All values are expressed as percentages of one atmosphere. The observed variance in MACs among species is in part due to variations in the techniques used in measuring MAC, as well as some variability in the ages, temperatures, and circadian cycles of the subjects tested. The stimulus used to obtain MAC in man was either a surgical incision or an electrical pulse. In the dog and horse, either a tail clamp or an electrical pulse was used. Monkeys, cats, rabbits, and rats were tested with a tail clamp. The stimulus in mice and rats was a rotating chamber, and the end point was loss of righting reflex. Toads were stimulated with a clamp to the lower extremity. Goldfish were electrically stimulated. End-tidal anesthetic concentrations were measured in man, monkey, dog, horse, cat, rabbit, and rat where indicated, † while for all other subjects inspired anesthetic concentration was used.


The reduction in MAC in the halothane-plus-air group was due to cerebral hypoxia secondary to cerebral vasoconstriction and a reduced blood oxygen content.

*Metabolic Acidosis.* Eger et al.15 decreased halothane MAC in dogs from 0.90 to 0.73 per cent by infusing 60 to 80 mEq ammonium chloride intravenously. End-tidal $P_{CO_2}$ was held constant, while $pH_{a}$ fell from 7.38 to 7.50. This modest change in MAC may be attributable to the increase in ammonia rather than to a decrease in $pH$. Intragastric infusion of hydrochloric acid sufficient to lower $pH_{a}$ to 6.9 ($P_{CO_2}$ 35 torr, CSF $pH$ 7.1–7.3) causes only a slight (less than 15 per cent) reduction in canine halothane MAC.45

**Metabolic Alkalosis.** Eisele et al.45 administered 30 mEq/kg sodium bicarbonate intravenously to dogs anesthetized with carbon dioxide, halothane, and oxygen (fig. 3). The induced respiratory acidosis was at least partially neutralized, and values of $pH_{a}$ ranged from 7.1 to 7.4; CSF $pH$ remained about 6.87. These investigators determined that the anesthetic effects of halothane and carbon dioxide were unaffected by ad-
ministration of bicarbonate, and concluded that metabolic alkalosis (base excess plus 7 mEq/l) did not alter MAC.

**Hypoxia and Hyperoxia.** The lowest limit of $P_{\text{a}}$, in normal man that is compatible with consciousness lies between 25 and 35 torr.\(^{47,48}\) The mechanism by which such severe hypoxia produces narcosis is unknown. Hypoxia does not alter halothane MAC in dogs until $P_{\text{a}}$ falls below 38 torr.\(^{15,49-51}\) Halothane MAC in dogs is unaffected by $P_{\text{aO}}$s of 38–500 torr.\(^{15,49-51}\) Below 38 torr, hypoxia induces progressive narcosis. Values for MAC were decreased to 40 per cent of control when $P_{\text{aO}}$ was approximately 28 torr, whereas at $P_{\text{aO}}$ 38 torr, MAC was still 80 per cent of control.\(^{48}\) Metabolic acidosis indicating anaerobic metabolism always accompanied this hypoxia-induced decrease in MAC. MAC decreased more rapidly during normocapnic hypoxia ($\rho_{\text{H}} = 7.29$) than during hypocapnic hypoxia ($\rho_{\text{H}} = 7.39$), probably because the Bohr effect produced a higher oxygen content at the same $P_{\text{aO}}$ during hypcapnia. It was not possible to differentiate the effects of arterial acidosis from those of decreased oxygen content.\(^{49}\) Regression lines drawn for $\rho_{\text{H}}$ vs. MAC could be extrapolated to zero MAC when $\rho_{\text{H}}$ equaled 6.87 with hypcapnia and when it equaled 6.89 with normocapnia.\(^{49}\) This finding differs from the data reported by Eisele et al.\(^{48}\) for severe metabolic acidosis without hypoxemia. This apparent discrepancy may be explained by the different physiologic implications of endogenously induced, as opposed to exogenously induced, metabolic acidosis. The former implies tissue hypoxia with anaerobic metabolism and intracellular acidosis, while the latter may have a minimal effect on intracellular pH. It is not surprising, therefore, that hypoxia-induced metabolic acidosis reduces anesthetic requirement, whereas exogenous administration of hydrogen ions does not. In a subsequent study, Cullen et al.\(^{50}\) did not find a consistent correlation between hypoxia-induced halothane MAC reduction in dogs and cerebral extracellular fluid $\rho_{\text{H}}$, $P_{\text{aCO}}$, or $\rho_{\text{H}}$ obtained with cortical surface electrodes. This was true despite the fact that surface extracellular fluid measurements more closely reflect cerebral acid–base status than do cisternal CSF measurements.

Cullen and Eger\(^{51}\) further tested the relationship of decreased oxygen content to decreased MAC by lowering oxygen content without changing $P_{\text{aO}}$. Using graded isovolemic anemia, they found that halothane MAC for dogs was unchanged until arterial blood oxygen content decreased to less than 4.3 ml oxygen/100 ml blood (hematocrit 10 per cent) (fig. 4). In this model, unlike the hypoxic models, no evidence of metabolic acidosis indicated impaired tissue oxygenation or perfusion.

The major difference between the hypoxia and anemia experiments lies in the $P_{\text{aO}}$ values. Cullen and Eger suggested that the oxygen gradient between blood and the tissues is of fundamental importance. During hypoxia, the small oxygen gradient reduced
oxygen transfer to the tissues, and cellular hypoxia with resulting systemic lactic acidosis occurred. In contrast, anemia reduced oxygen content without altering the oxygen gradient and therefore, oxygen delivery.

Increased anesthetic requirements for halothane and methoxyflurane, but not ether or cyclopropane, have been found in toads breathing 100 per cent oxygen. These animals were hyperventilated ($pH_\text{a}$ 7.6) and were hypothermic, and the effects of these variables are not known. The $ED_{90}$ of oxygen alone is estimated to be 5.3 atm in mice.\textsuperscript{59}

**Hypotension.** It has generally been believed that hypotension reduces anesthetic requirement.\textsuperscript{15,34,55} Tanifuji and Eger\textsuperscript{56} studied the effects of arterial hypotension induced by trimethaphan on three groups of dogs (fig. 5). In the first group, mean arterial blood pressure (MAP) was reduced to 40–50 torr, and halothane MAC decreased by 20 per cent after the first hour. No further reductions in MAC occurred during the ensuing three hours of similar hypotension. Neither arterial blood nor CSF lactate and pyruvate concentrations were affected, and $pH_\text{a}$ declined only minimally. In a second group of dogs, MAP was successively reduced to 40–50 torr, 30–40 torr, and 20–30 torr. There were concomitant decreases in MAC, which was 50–70 per cent of control at the lowest pressures. In the third group, MAP was decreased rapidly to 20–30 torr, and MAC was reduced to 25–35 per cent of control, a significantly greater reduction in MAC than occurred with a slower three-stage pressure reduction. Hysteresis of anesthetic requirement was evident following recovery in the last two groups of dogs, implying that a structural or biochemical alteration in central nervous system (CNS) function had occurred. This premise is supported by the fact that three of the four dogs in Group III (rapid pressure reduction) suffered strokes and/or died after the return of MAP to control levels. All dogs in Groups I and II survived. A reduction in halothane MAC in dogs rendered hypotensive with pentolinium, trimethaphan, and nitroprusside when MAP was reduced to 60 per cent of control has been demonstrated.\textsuperscript{§}

**Hypertension.** Lamson et al.\textsuperscript{57} and Milosevic\textsuperscript{58} reported potentiation of chloral- and barbiturate-induced CNS depression following parenteral administration of large doses of epinephrine. Conversely, Westfall\textsuperscript{59} had found earlier that epinephrine antagonized pentobarbital anesthesia. The effects of various vasoressors on halothane MAC in dogs have since been evaluated.\textsuperscript{10,60} Halothane MAC increased significantly only during infusion of ephedrine (50 per

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cent increase in MAC), although the increase with mephentermine (21 per cent) approached statistical significance. Phenylephrine, metaraminol, methoxamine, norepinephrine, and epinephrine did not alter MAC. Mean arterial blood pressure was increased 50–100 per cent in all cases. These results support the hypothesis that anesthetic requirement is related to release of CNS catecholamines (see "Neurotransmitter Release"), since ephedrine and mephentermine are known to cause central release of norepinephrine (ephedrine more than mephentermine); whereas metaraminol, phenylephrine, methoxamine, norepinephrine, and epinephrine exert only peripheral effects in the doses that were administered. These results also indicate that arterial hypertension per se does not affect MAC.

Neurotransmitter Release. Drugs that affect central neurotransmitter release may alter anesthetic requirement (MAC) (table 2). Miller et al. demonstrated dose-related reductions of halothane MAC in dogs after acute and chronic administration of alphamethyl dopa and reserpine, drugs that reduce both central and peripheral catecholamines and serotonin. Administration of guanethidine, which reduces norepinephrine peripherally but not centrally, did not affect MAC (fig. 6). Conversely, pretreatment with monoamine oxidase inhibitors (iproniazid) slightly but significantly increased cyclopropane requirement in rats. Iproniazid interferes with normal degradation of catecholamines and serotonin, thereby elevating intracellular levels of these neurotransmitters. When Mueller et al. selectively blocked catecholamine- and serotonin-containing nerve terminals in rat brain, a slight reduction in halothane requirement occurred.

Acute intravenous administration of dextroamphetamine (DA) in dogs during halothane anesthesia increases MAC as much as 96 per cent. In contrast, chronic treatment with DA decreases halothane MAC by 22 per cent. Acute administration of DA increases norepinephrine release in CNS nerve terminals, whereas chronic administration depletes CNS norepinephrine, indicating that increases in the release of CNS catecholamines will increase anesthetic requirement. These investigators could not demonstrate similar effects of DA on fluoxetine MAC, probably because fluoxetine is itself a sympathomimetic drug that increases release of norepinephrine both centrally and peripherally. They subsequently reported that the increase in halothane MAC in dogs secondary to acute intravenous DA administration could be partially blocked by pretreatment with large doses of reserpine or alpha-methyl-p-tyrosine (an inhibitor of norepinephrine synthesis). Pretreatment with parachlorophenylalanine, a serotonin depleter,
did not affect halothane MAC. This finding does not agree with results obtained earlier by Mueller et al. in a study of rats.

A dose-dependent increase in halothane MAC has been demonstrated in dogs with 2 or 4 mg/kg of intravenously administered cocaine. Cocaine inhibits catecholamine reuptake in CNS nerve terminals, thereby increasing extracellular catecholamine concentrations. Moderate intravenous doses of levodopa reduce halothane MAC in dogs. Large doses (50 mg/kg) transiently increase halothane requirement, but cause a reduction of halothane MAC three hours after injection. Dogs chronically pretreated with levodopa do not have consistently altered anesthetic requirements. Levodopa is a precursor of catecholamine synthesis in the CNS, but results in greater increases in concentration of dopamine than norepinephrine. Because dopamine is an inhibitory neurotransmitter—as opposed to norepinephrine, which is excitatory—it was suggested that smaller doses of levodopa reduced MAC by increasing central dopamine concentrations, and that larger doses of levodopa may have displaced norepinephrine and caused CNS excitement.

Both cyclopropane and halothane selectively increase catecholamines and serotonin in discrete areas of rat brain, suggesting that these anesthetics depress neurotransmitter release at highly specific sites in the CNS. Recently, it has been shown that stereotactic electrolytic lesions produced in these specific brain sites in rats decrease MAC for both halothane and cyclopropane by as much as 35 per cent.

**Age.** In 1937, Guedel observed that anesthetic requirement decreased with age. Fifteen years later, Deming demonstrated that infants needed higher blood concentrations of cyclopropane than did adults to achieve similar CNS depression, as measured by EEG. Gregory et al. determined MAC for halothane in eight age groups of patients and confirmed Deming's earlier conclusion: that MAC was greatest (1.1 per cent) in the newborn (0–6 months) and least (0.64 per cent) in the elderly (72–91 years) (fig. 7). They found that this generalised decrease in anesthetic requirement with age paralleled several physiologic variables that also decreased with age, namely cerebral blood flow, cerebral oxygen consumption, and neuronal density. Nicodemus et al. measured MAC in three groups of pediatric patients. They used the log dose–probit transformation described by Litchfield and Wilcoxon to analyze data, and concluded that halothane potency was age-related, i.e., MAC for infants less than 24 months of age was 1.18 per cent, whereas in children 25–48 months of age, it was 1.07 per cent, and in adults, 0.94 per cent. Halothane-induced hypotension occurred more frequently at MAC in infants than in adults, implying a smaller cardiovascular margin of safety. Stevens et al. determined isoflurane MAC with and without nitrous oxide in three patient populations grouped by age (fig. 7). Their results agree with those of Gregory et al. and Nicodemus et al., i.e., isoflurane requirement decreased with age. Addition of 70 per cent nitrous oxide decreased isoflurane requirement by 57–65 per cent, regardless of age.

**Temperature.** A decrease in body temperature decreases anesthetic requirement. In 1954, Callaghan

<table>
<thead>
<tr>
<th>Table 2. Effects of Various Centrally Acting Drugs on MAC</th>
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<tr>
<td><strong>CNS Effect</strong></td>
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<tr>
<td>----------------------------------------------------------</td>
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<tr>
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<tr>
<td>Acute levodopa</td>
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<td>Ephedrine</td>
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* CNS = central nervous system.
Fig. 7. MACs for halothane (Gregory et al.78) and isoflurane (Stevens et al.79) decrease with increasing age. With permission of the authors and publisher.

et al.84 observed that “animals and humans enter a narcotic state when the rectal temperature falls below 30 °C.” Cherkin and Catchpool85 found that “anesthetizing” partial pressures in goldfish were positively correlated with body temperature for diethyl ether, chloroform, halothane, and methoxyflurane. The MACs of halothane and cyclopropane in dogs vary directly and linearly with body temperature, but the slopes of the responses for these two anesthetics differ.86 For a 10 °C decrease in body temperature, halothane MAC decreases 50 per cent; whereas cyclopropane MAC decreases only 25 per cent. These data closely correlate with those of Cherkin and Catchpool86 for the halothane requirement of goldfish. The effects of hypothermia (32 °C and 28 °C) on MAC in dogs for cyclopropane, diethyl ether, fluroxene, halothane, and methoxyflurane have been studied.87 For all five anesthetics, MACs declined rectilinearly. For cyclopropane, the least oil-soluble anesthetic, MAC declined the least; while MACs for halothane and methoxyflurane, the most lipid-soluble anesthetics, declined the most. Diethyl ether and fluroxene were intermediate in lipid solubilities and in responses of MAC to alterations in temperature. Extrapolating these data for halothane or methoxyflurane suggested that temperatures between 18 and 21 °C might themselves be anesthetic. These potentially anesthetizing temperatures were not reached, however, because cardiac irritability and death from ventricular fibrillation occurred. Munson88 demonstrated similar though greater decreases in cyclopropane and halothane MACs in hypothermic (25–32 °C) rats. The effects of hypothermia (32 °C and 27 °C) on halothane MAC and isoflurane MAC in tracheotomized rats have been studied (fig. 8).89 Rectilinear decreases in MAC occurred with both agents. For both agents MACs were decreased to about 40–50 per cent of control at 27 °C. The effect of hyperthermia on canine halothane requirement has also been measured.90 The MAC increases linearly at 8 per cent per degree C (from 37.3 to 40.7 °C). At temperatures greater than 42 °C, MAC decreases. Death occurs at a mean temperature of 45.9 °C. Temperature affects anesthetic requirement by altering cerebral oxygen consumption (CMRox), not by altering whole-body oxygen consumption (Vo2) (see “Thyroid Function”).

Thyroid Function. Guedel77,21 believed that anesthetic requirement correlated with metabolic activity. As mentioned, anesthetic requirement is related to CMRox, as demonstrated by the effects on MAC of age and temperature. Anesthetic requirement is not pro-

Fig. 8. Effects of temperature on halothane (△) and isoflurane (○) MACs in tracheotomized rats breathing spontaneously. Mean values ± SE are shown. From Vize, White, and Eger,88 with permission of the authors and publisher.
portional to whole-body \( \dot{V}_{O_2} \). One hundred per cent alteration of whole-body \( \dot{V}_{O_2} \) (from gross hypothyroidism to gross hyperthyroidism) in dogs increases halothane MAC only 20 per cent.\(^{92,93}\) Cerebral oxygen consumption is not affected by thyroid function, which may explain why metabolic changes induced by changes in thyroid function have less effect on MAC than age or temperature.\(^{93,94}\)

**Electrolytes.** In 1906, Meltzer and Auer\(^{85}\) reported that intravenous administration of magnesium salt in animals produced sedation, followed by paralysis and respiratory arrest. In 1916, Peck and Meltzer\(^{96}\) proposed that magnesium had a definite, albeit limited, role as an adjunct to general anesthesia. However, Aldrete *et al.*\(^{97}\) reported that the “anesthetic” effect of magnesium was really cerebral hypoxia due to progressive cardiac and respiratory depression, and that the observed electroencephalographic changes resulted from decreased cerebral perfusion. Magnesium-induced peripheral neuromuscular blockade occurs at lower serum magnesium concentration than does the central sedative effect, and human beings remain conscious when skeletal muscular function is depressed.\(^{98,99}\) Aldrete\(^{100}\) concluded that although direct application of magnesium depresses neural tissue function, the small amounts of magnesium crossing the blood–brain barrier are insufficient to produce narcosis.

Lithium enhances morphine analgesia in mice.\(^{101,102}\) Tanifuji and Eger (unpublished data) found that administration of lithium decreases MAC.

The anesthetic potencies of halothane and cyclopropane in cats vary directly with CSF calcium ion concentrations,\(^{95}\) and in fact, very high CSF calcium ion concentrations alone may produce a state resembling general anesthesia.\(^{103}\)

Bromine produced by biodegradation of halothane may result in postoperative sedation.\(^{104,105}\) Bromine’s ability to sedate appears to vary, and although sedation has been observed at a level of 6 mEq/l, toxicity may occur at concentrations greater than 10 mEq/l.\(^{104}\) Bromide has a serum half-life of 12–25 days.\(^{104,105}\) Serum bromide elevations (2.4–4.2 mEq/l) have been found for nine days following halothane anesthesia in seven normal subjects given prolonged, high-dose anesthesia.\(^{104}\) These concentrations represent sedative levels. The findings of Tinker *et al.*\(^{105}\) in patients given halothane are in agreement.

The effects of hyperkalemia, hypernatremia, and hyper- and hypoosmolality on halothane MAC in dogs have been studied.\(^{106}\) Hyperkalemia did not alter CSF potassium concentration or affect MAC. Hypernatremia proportionally increased CSF sodium concentration and osmolality, and increased halothane MAC by 43 per cent. Serum hyperosmolality increased CSF osmolality without consistently altering CSF sodium concentration or MAC. Serum and CSF hypoosmolality diluted CSF sodium and reduced halothane MAC by 24 per cent. These data suggest that changes in serum electrolytes or osmolality alter anesthetic requirement when they are accompanied by changes in brain sodium (fig. 9).

**Alcohol.** Standard textbooks\(^{107–109}\) and clinical reports\(^{110}\) since 1937 have suggested that alcoholic subjects need larger doses of inhalational anesthetics than do non-alcoholic subjects. Abreu and Emerson\(^{111}\) demonstrated in 1939 that mice chronically pretreated with alcohol were “significantly more resistant to induction of ether anesthesia . . . than saline treated controls.” Twenty-five years later, Lee *et al.*\(^{112}\) came to a similar conclusion using rats. After ten days of continuous ethanol ingestion, isoflurane ED\(_{50}\) in mice was increased from 1.35 to 1.54 per cent; after 20 days of ethanol ingestion, to 1.69 per cent.\(^{112}\) This increase in isoflurane ED\(_{50}\) persisted for 55 days after discontinuation of ethanol (ED\(_{50} = 1.65\) per cent), with the

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ED\textsubscript{90} returning to control (ED\textsubscript{90} = 1.32 per cent) after 80 days of abstinence. Halothane MAC increased (from 0.86 to 1.07 per cent) in cats given alcohol for one month.** A further increase to 1.25 per cent occurred when ethanol was given for four months; thereafter, MAC remained the same. Han\textsuperscript{114} found that the human halothane MAC was "significantly above normal for alcoholics." In a retrospective analysis, Tammisto and Takki\textsuperscript{118} reported that despite higher doses of anesthetics given for induction and supplementation of anesthesia, alcoholic subjects were frequently judged to be inadequately anesthetized. The halothane MACs of seven alcoholic patients and seven age-matched controls have recently been compared.†† For the control group, MAC was 0.75 per cent; for the alcoholic group, 1.0 per cent. This increase was proportional to that found for isoflurane in mice.\textsuperscript{113} Cross-tolerance between ethanol and general anesthetics has been demonstrated in rats.\textsuperscript{116} Ethanol increases the fluidity of cell membranes in mice, and ethanol-dependent (i.e., tolerant) mice are resistant to this membrane-fluidizing effect.\textsuperscript{117} If the mechanism of anesthesia is related to membrane fluidization, then this relationship may explain the increased anesthetic requirement found for alcoholic patients, as well as the "anesthetizing" effect of alcohol itself.

Acute administration of ethanol reduces isoflurane requirement in mice\textsuperscript{112}; however, the effects are not always additive, implying a possible antagonistic effect. Other investigators, however, consistently find a simple additive relationship between ethanol and halothane requirements.\textsuperscript{118} These differences have not been explained. Intravenous administration of 1 g/kg ethanol to nonalcoholic cats decreases halothane MAC from 0.90 to 0.70 per cent.** Alcoholic cats responded to the same acute dose of ethanol with a similar percentage reduction in halothane MAC (from 1.15 to 0.91 per cent).**


Narcotics. Narcotics reduce anesthetic requirements.\textsuperscript{6} Seegers et al.\textsuperscript{119} reported in 1934 that dogs premedicated with morphine and scopalamine needed less cyclopropane to achieve a given plane of anesthesia. Subsequent investigations in animals have confirmed this conclusion.‡‡\textsuperscript{126,121} Hoffman et al.\textsuperscript{121} demonstrated dose-related reductions in cyclopropane requirements for morphine and meperidine in rats. This anesthetic-sparing effect of morphine and meperidine increased in a log dose fashion to the maximal dose of each drug tested (8 mg/kg and 60 mg/kg, respectively). Pentazocine, unlike morphine and meperidine, had a "ceiling effect"; that is, above a given dose (about 20 mg/kg), little additional reduction in anesthetic requirement occurred (fig. 10). In 1957, Taylor\textsuperscript{122} administered 10 mg morphine intravenously to patients 10 min before induction of ether anesthesia. The arterial blood ether concentration necessary to produce a predetermined level of electroencephalographic suppression decreased approximately 15 per cent. Numerous clinical studies since 1957 have demonstrated similar results.\textsuperscript{5,123,124} Han et al.‡‡ studied dogs addicted to morphine and found that halothane MAC increased linearly during the course of addiction, and that the effect of a given dose of morphine on halothane MAC decreased as the dog became tolerant to morphine.

Sedatives and Tranquilizers. Nonnarcotic premedicants also decrease anesthetic requirement.\textsuperscript{120} Barbital, 150 mg/kg, iv, given to dogs 30 min before anesthesia, decreases cyclopropane requirement 49–67 per cent, while 250 mg/kg, iv, decreases anesthetic requirement 66–77 per cent.\textsuperscript{120} A 42–59 per cent decrease in cyclopropane requirement occurs in dogs when amobarbital (30 mg/kg, iv) is used as the premedicant; with 45 mg/kg, iv, the reduction is 66–70 per cent.\textsuperscript{120} Chlorpromazine, 50 mg, given intramuscularly an hour before anesthesia, decreases by 12 per cent the ether concentration needed to produce a specific level of electroencephalographic suppression in patients.\textsuperscript{122} Pentobarbital, 200 mg, given intravenously 10 min before anesthesia, causes a 27 per cent reduction.\textsuperscript{122} Halothane MAC in man is only 0.43 to 0.48 per cent 15 to 30 min after intravenous administration of 0.2 to 0.5 mg/kg diazepam.\textsuperscript{124,125} Since halothane MAC in unpremedicated patients is approximately 0.75 per cent,\textsuperscript{124,125} this reduction in anesthetic requirement is significant. The higher dose of diazepam significantly depressed respiration without causing an additional decrease in MAC.\textsuperscript{125} Hydroxyzine, 2 mg/kg, reduces halothane MAC in human subjects by 24 per cent.\textsuperscript{134}

Miscellaneous Drugs. Delta-9-tetrahydrocannabinol reduces cyclopropane MAC in rats; 1.0 and 2.0 mg/kg injected intraperitoneally two hours before cyclopropane anesthesia decrease MAC by 15 and 25 per cent, respectively.\textsuperscript{127} Neither acute (2 or 10 mg/kg

intravenously) nor chronic (10 mg/kg/day orally for ten days) administration of propranolol affects halothane MAC in dogs. Isoproterenol also does not affect halothane MAC in dogs. Ketamine reduces anesthetic requirement in rats in a dose-dependent fashion. Rat halothane MAC is decreased by as much as 50% per cent one to two hours, and 14% per cent five to six hours, after intramuscular injection of ketamine, 50 mg/kg. Small doses of promethazine (0.1–0.15 mg/kg) do not affect halothane MAC in dogs. The same doses of promethazine, given to block the histamine-releasing effect of trimethaphan and followed by infusion of 25 mg/kg trimethaphan over two hours, do not alter halothane MAC in the dog. Mean arterial blood pressure, however, must be maintained at normal levels, and norepinephrine must be infused simultaneously. Pancuronium reduces halothane MAC in man by 25 per cent.

**Naloxone.** Initial studies in mice and rats suggested that naloxone antagonized analgesia induced by nitrous oxide and anesthesia with cyclopropane, enflurane, halothane, or barbiturates. However, more rigorous subsequent studies have not demonstrated a significant effect of naloxone on anesthesia with halothane, nitrous oxide, or thiopental in rats, mice, or human beings, respectively. These results are important because anesthetics might be attributable in part to the release of endogenous morphine-like substances (EMLS). Although the analgesic component of general anesthesia may result from release of EMLS, the failure to demonstrate a significant increase in halothane MAC by naloxone suggests that this component is not vital to the production of general anesthesia. In opposition to this view, it has recently been shown that continuous perfusion of the fourth cerebral ventricle of the dog with naloxone antagonizes the hypnotic effects of halothane, as reflected by both an increase in responsiveness to stimulation and a reversal of electroencephalographic suppression. In addition, naloxone reverses nitrous oxide-induced analgesia in man. The conflicting nature of the above data leaves the importance of EMLS in the maintenance of the analgetic and hypnotic components of general anesthesia unsettled.

**Cholinesterase Inhibitors.** Physostigmine and neostigmine decrease halothane MAC in dogs in a dose-dependent fashion. Physostigmine, unlike neostigmine, transiently (within the first 30 min of intravenous injection) increases anesthetic requirement. The clinical significance of these findings is unclear because the doses used were at least ten times greater than those used clinically.

**Local Anesthetics.** Local anesthetics have been used systematically to supplement general anesthesia for more than 25 years. Lidocaine reduces cyclopropane MAC in rats linearly until blood lidocaine concentrations each 1.0 μg/ml. Higher concentrations decrease anesthetic requirement slightly more, the
maximum reduction being 42 per cent. In man, a plasma lidocaine concentration of 3.2 µg/ml plus 70 per cent nitrous oxide equals 1.0 MAC. In dogs, plasma lidocaine concentrations less than 1.0 µg/ml cause little or no decrease in halothane MAC. Above this level, halothane MAC decreases, reaching a 45 per cent reduction at a lidocaine concentration of 11.6 µg/ml. In dogs, arterial plasma concentrations of lidocaine of 1.0–3.5 µg/ml produce a dose-related decrease in enflurane MAC of as much as 37 per cent (fig. 11). The quantitative differences between lidocaine-induced MAC reductions in the dog during halothane anesthesia and during enflurane anesthesia are surprising. Three additional dogs anesthetized with either halothane or isoflurane were studied in an attempt to resolve this apparent discrepancy. With both anesthetics, MAC was reduced between 16 and 36 per cent over the same range of plasma lidocaine concentrations that were used in the enflurane studies (1–4 µg/ml), suggesting that the differences may be more apparent than real. Alterations in anesthetic requirement induced by lidocaine may result from blockade of nociceptive impulses by suppression of spinal cord neurons.

Pregnancy. Selye was the first to report that steroids such as progesterone possessed anesthetic activity. Sleep has been induced in women by giving large daily doses of progesterone intravenously. Pregnancy in sheep is associated with reductions in MAC of 32 per cent for methoxyflurane, 25 per cent for halothane, and 40 per cent for isoflurane, possibly due to alterations in hormonal production. In ewes, plasma progesterone increased ten- to twentyfold during late pregnancy. In rats, pregnancy also decreases halothane MAC, but the reductions do not correlate with changes in progesterone levels. It thus appears that changes in progesterone are not entirely responsible for reductions in MAC associated with pregnancy.

Effects of Other Inhalational Anesthetics. The effects of combinations of inhalational anesthetics are cumulative, and in general appear to be simply additive (fig. 12). Some combinations, however, are synergistic or even antagonistic. In man, nitrous oxide lowers the blood concentration of diethyl ether needed to produce a given level of electroencephalographic suppression. Similarly, nitrous oxide decreases MAC (table 3). Presuming additivity, the data in table 3 suggest that MAC for nitrous oxide equals 105 to 110 per cent of one atmosphere. Under hyperbaric conditions, nitrous oxide MAC in man has been determined to be 105 per cent of one atmosphere, supporting the data obtained by extrapolation. The effects of the combinations of halothane plus xenon and halothane plus ethylene appear to be additive. However, not all inhalational anesthetics have additive effects. Low concentrations of cyclopropane with either nitrous oxide or ethylene appear to produce antagonistic effects whereas cyclopropane and isoflurane are synergistic. The combinations of sulfur hexafluoride (SF6) plus nitrous oxide and argon (Ar) plus nitrous oxide are additive in mice; however, Ar plus SF6 is less than additive (i.e., it is antagonistic). Clark et al. concluded that such anomalies are insufficient to cast serious doubts about the theories of anesthetic action related to hydrophobicity.

Uses of MAC

The concept of MAC as a biologic unit of anesthetized CNS depression has proven useful to both the clinician and the investigator. As pointed out by Waud and Waud, these uses of MAC need to be qualified. The MAC defines one point on a hypothetical dose-

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response curve that plots anesthetic dose (end-tidal concentration) against one index of "depth" of anesthesia (CNS depression). Since no other points on this curve are experimentally defined, one cannot be certain that such curves for different anesthetics are indeed parallel. Whether these curves are parallel is an important consideration, because the inference might be made that the same multiples (or fractions) of MAC of different anesthetics represent equal levels of CNS depression. That is to say, that 2.0 MAC of anesthetic A and 2.0 MAC of anesthetic B produce equal levels of anesthesia. This is not necessarily true, nor was it ever claimed to be.103 However, the need to express anesthetic dose in concentrations above and below MAC is real, and multiples or fractions of MAC do provide the necessary yardstick.

This use of MAC can be defended on two grounds. First, no more precise measure of equipotent anesthetic doses has been devised. Second, several lines of experimental evidence suggest that the curves for anesthetic dose vs. CNS response are indeed parallel. For example, the ratios of anesthetic concentrations producing both more103,104 and less105,106 CNS depression than that which occurs at MAC have been shown to be relatively constant for several anesthetics. In addition, the additivity studies mentioned previously provide even stronger support for parallelism in at least the sub-MAC range.109,110

The use of MAC-hours has also been criticized, on the grounds that it is not an accurate reflection of the total dose of anesthetic delivered. Although MAC-hours is a crude index of total anesthetic dose, there is no other relatively simple method of making this estimation. In addition, for all the potent inhalational agents, the solubility coefficients are such that uptake and release by fat and muscle will buffer peak and trough blood anesthetic levels to a large extent. Therefore, little difference in enzyme saturations will occur with, for example, two hours of 1.0 MAC halothane vs. one hour of 2.0 MAC halothane. This implies that the extent of metabolism will not be greatly different in the two circumstances just cited.

Clinical anesthesia is delivered using concentrations of anesthetics extending from that which is just sufficient to produce amnesia (below MAC) to that which produces profound CNS depression (above MAC). The MAC may be used to gauge the margin of safety with respect to vital organ depression within this dose (concentration) range. The fact that the dose–response curves of different anesthetic agents with respect to vital organ depression are certainly not parallel demonstrates one of the major uses of MAC. Thus, a therapeutic index may be characterized for any anesthetic agent with respect to any untoward or desired side effect (e.g., respiratory or cardiac depression; neuromuscular blockade; cerebral, renal, hepatic, or coronary blood flow). The denominator in any such ratio is MAC. For example, three times halothane MAC may produce cardiac arrest in healthy young adults, whereas three times fluoroxene MAC results in cardiac outputs greater than control values.158 Each anesthetic possesses unique qualities with respect to these anesthetic side effects, yet at MAC, all produce equivalent CNS depression. Such information has proven vital for the safe and rational delivery of modern clinical anesthesia.

In the laboratory, MAC has been useful in defining

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**Table 3. Effects of Nitrous Oxide on Anesthetic Requirements in Man**

<table>
<thead>
<tr>
<th>Per cent</th>
<th>Anesthetic</th>
<th>Reduction in MAC</th>
<th>Reference</th>
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<tr>
<td>nitrous oxide</td>
<td>Enflurane</td>
<td>30</td>
<td>Torri et al.157</td>
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<td>Suhdam and Eger112</td>
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the therapeutic indices mentioned earlier. In addition, MAC has been used to quantitate the anesthetic effects of various drugs, such as local anesthetics, anti-depressants, narcotics, tranquilizers, and even muscle relaxants; and to gauge the effects on anesthetic requirement of various clinical situations, such as hypothermia, hypotension, hyponatremia, hypoxemia, and hypovolemia. In short, MAC has been used by investigators to provide information concerning the anesthetic requirements and tolerances of patients under a wide variety of clinical situations.

Finally, MAC has been used to test various theories of narcosis. Theories of anesthetic action are frequently tested by alterations induced in a model system—for example, in a lipid bilayer. Any viable theory must create in the model system an order of potency of anesthetic agents that is proportional to the anesthetic potencies as defined by MAC.

Summary

From the discovery of the first anesthetic, the need to measure potency was apparent. Early reports emphasized inspired anesthetic concentrations or concentrations in arterial or venous blood. Perhaps the major contribution of MAC was the emphasis on end-tidal ("alveolar") anesthetic partial pressure, which at equilibrium represents the partial pressure at the anesthetic site of action, the brain. The use of MAC gained wide acceptance, and it has become the major index of anesthetic potency in the anesthetic literature. There are several reasons for this. First, abolition of movement in response to a surgical incision is the basic concern of clinical anesthesia, and as such, is of obvious interest to all clinicians. Second, MAC applies equally to all inhaled anesthetics, unlike clinical signs of anesthesia such as pupillary dilatation or respiratory depression, which vary from drug to drug. Third, MAC is easily determined and remarkably reproducible in the laboratory, making it attractive to those involved in research.

Since the description of MAC, its determining variables have been studied in detail. A long list of physiologic and pharmacologic interventions in various species of animals that will or will not alter anesthetic requirements has thus been established. The MAC has emerged as a remarkably consistent index of anesthetic potency, which for any given anesthetic will vary within a twofold range in widely different classes of animals.

The uses of MAC are many and varied. For example, MAC has been used to test theories of anesthesia and the therapeutic indexes of various agents with respect to vital organ depression. Controversy has arisen over these uses of MAC. In man, MAC is essentially the midpoint of a cumulative frequency distribution. The quantal nature of MAC, strictly speaking, does not allow pharmacologic comparisons between agents at MAC multiples or fractions, but many studies have suggested the clinical and experimental validity of doing so. Despite these problems, MAC remains the only widely accepted measure by which comparisons between anesthetics can be made or the relative margins of safety established.

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References

1. Bigelow HJ: Surgical operations performed during insensibility, produced by the inhalation of sulphuric ether. Lancet 1:5–8, 1847
4. Boothby WM: The definition of the anesthetic tension of ether vapour in man, with some theoretical deductions therefrom, as to the mode of action of the common volatile anesthetics. J Pharmacol Exp Ther 5:379–392, 1913–14
51. Cullen DJ, Eger EI II: The effects of hypoxia and isovolemic anemia on the halothane requirement (MAC) of dogs. III. The effects of acute isovolemic anemia. Anesthesiology 32:46–50, 1970
gic neuronal effects on minimum alveolar concentrations (MAC) of halothane and cyclopropane in rats. *Anesthesiology* 42:143–152, 1975


73. Hornykiewicz O: Dopamine (3-hydroxytyramine) and brain function. *Pharmacol Rev* 18:925–964, 1966


89. Vitez TS, White PF, Eger EI II: Effects of hypothermia on halothane MAC and isoflurane MAC in the rat. *Anesthesiology* 41:80–81, 1974

90. Steffey EP, Eger EI II: Hyperthermia and halothane MAC in the dog. *Anesthesiology* 41:392–396, 1974

91. Guedel AE: Metabolism and reflex irritability in anesthesia. *JAMA* 83:1736–1738, 1929


95. Meltzer SJ, Auer J: Physiological and pharmacological studies of magnesium salts.—II. The toxicity of intravenous injections; in particular the effects upon the centres of the medulla oblongata. Am J Physiol 15:387–405, 1906


111. Abreu BE, Emerson GA: Susceptibility to ether anesthesia of mice habituated to alcohol, morphin or cocaine. Anesth Analg (Cleve) 18:294–300, 1939


140. Arndt JO, Freye E: Perfusion of naloxone through the fourth cerebral ventricle reverses the circulatory and hypnotic effects of halothane in dogs. Anesthesiology 51:68–63, 1979


150. Seyle H: Studies concerning the anesthetic action of steroid hormones. J Pharmacol Exp Ther 75:127–141, 1941

166. Stoehing RK, Longnecker DE, Eger EI II: Minimum alveolar concentrations in man on awakening from methoxyflurane, halothane, ether and fluoxetine anesthesia: MAC awake. Anesthesiology 33:3–9, 1970