

## REFERENCES

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*To the Editor:*—In a recent editorial, the Doctors Waud suggested some limitations to the uses of MAC.<sup>1</sup> They noted that: 1) MAC represents a single point on a dose (anesthetic concentration)–response (depression) curve. 2) Multiples of such a point (*i.e.*, two times MAC or three times MAC) may not produce equivalent amounts of depression. 3) The dose–response curves for different anesthetics may not be parallel (this is a corollary of 2, above). And 4) studies of MAC or anesthetic dose–response curves *per se* are unlikely to shed much light on mechanism of action. I agree that points 1, 2, and 3 describe characteristics of MAC, but believe that such agreement does not detract from the usefulness of MAC. I disagree with point 4. It might be appropriate to outline my concept of the uses of MAC and defend their future application in the context of the limitations suggested by Doctors Waud.

Inhaled anesthetics produce a range of depression from analgesia to death. Although MAC is but one point within this continuum, it is of prime practical and theoretical significance. By our definition, anesthesia (*i.e.*, lack of movement in response to stimulation) is completely achieved at MAC, and concentrations exceeding MAC cannot cause more anesthesia. In this sense, then, MAC does not represent a middle point in a dose–response curve; it represents an end point, a point of complete anesthesia. This does not deny the importance of secondary effects of anesthetic agents, such as production of muscle relaxation or sympathetic stimulation or obtundation of reflexes. Some anesthetics produce minimal relaxation (fluroxene) or sympathetic stimulation (halothane) or may augment reflex responses to stimulation of the airway (cyclopropane), while others may do the opposite. Yet all are anesthetics; all permit surgery by inhibiting movement in response to a painful

or noxious stimulus; all have MAC's. Put another way, MAC is a universal characteristic of anesthesia.

Although depression and/or stimulation are hallmarks of individual anesthetics rather than criteria for defining anesthesia, nonetheless production of depression and/or stimulation is of great importance to the safety and use of a given anesthetic. We work within an anesthetic dose range extending from that just sufficient for surgical anesthesia (MAC) to that producing profound depression. MAC may be used to define the "elbow room," or margin of safety within this range. Thus, three to four times the halothane MAC may cause death in otherwise healthy young humans,<sup>2</sup> whereas three or four times the cyclopropane MAC presents no such hazard.<sup>3</sup> Within the clinical range of anesthetic partial pressures we also can use MAC to compare the depressant effects of different agents. For example, twice MAC for halothane depresses respiration, as evidenced by a 50 per cent increase in arterial P<sub>CO<sub>2</sub></sub>,<sup>4</sup> whereas twice MAC for ether causes no change in Pa<sub>CO<sub>2</sub></sub>.<sup>5</sup> Note that this means that the effect of 2 MAC of halothane is *not* the same as the effect of 2 MAC of ether. It also means that the dose–response relationships above MAC indeed are not parallel.

There are many reasons to quantitate points in the dose–response curve which lies below MAC and extends from zero anesthesia to MAC. For example, the alveolar concentration at which awakening occurs (MAC awake) allows prediction of the time it takes to achieve recovery from clinical anesthesia.<sup>6</sup> Another use of the MAC awake and other such sub-anesthetic dose points is that they give us information about whether sub-MAC curves are parallel. The constancy of the ratios of "MAC awake" to MAC for methoxyflurane, halothane, ether, and fluroxene suggests that these curves are roughly parallel. The additivity studies of Cullen *et al.*<sup>7</sup> and Miller *et al.*<sup>8</sup> provide still stronger support for the parallel nature of anesthetic effects in the sub-MAC range. If the effects of addition of one anesthetic to another were less or more than their sum, it would indicate non-parallelism. Such would obtain if ½ halothane MAC plus ½ ethylene MAC produced an anesthetic effect equal to MAC.

I would debate with Doctors Waud whether

MAC can be used to ". . . shed much light on mechanism of action (of anesthetics)." Our studies of the additive effects of anesthetics<sup>7,8</sup> suggest that if anesthetics exert their effects through hydrate formation<sup>9,10</sup> they cannot do so through production of a continuous "ice cover." Furthermore, the lack of correlation of MAC with hydrate dissociation pressure, particularly the deviation of the sulfur hexafluoride data, has thrown the hydrate theory of anesthesia into considerable doubt.<sup>11</sup> Last, the superb correlation of MAC and lipid solubility as defined by the oil/gas partition coefficient should serve to focus attention on a hydrophobic site of anesthetic action.<sup>11</sup>

EDMOND I. EGER, II, M.D.  
*Department of Anesthesia  
University of California  
Medical Center  
San Francisco, Calif. 94122*

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*To the Editor:*—The above letters raise some interesting points. Doctor Eger feels that MAC is associated with a special point on the dose-response curve—a point of "prime practical and theoretical significance." We would be cautious about emphasizing a theoretical uniqueness. We suspect that the alveolar concentration just sufficient to render a patient unconscious was not crucial when the laws of chemistry and physics were formed. Anesthesia is still just one expression of a general "depressant" action of anesthetics on the central nervous system. These agents produce other CNS effects at concentrations both below and above MAC. In fact, Doctor Eger himself, after trying to extract one point from a dose-response curve, proceeds in the next two paragraphs to discuss the regions above and below. He too finds it impractical to discuss MAC out of context.

What does "MAC is a universal characteristic of anesthesia" mean? Take it literally and you get "A minimal alveolar concentration just sufficient to produce anesthesia is a universal characteristic of anesthesia." Isn't it trivial to say that all anesthetics have a MAC?

Doctor Eger states that there are many reasons to look at concentrations below MAC, and we agree. In fact, we'd look above MAC as well. But is this any reason to relabel these points? Many end-points on the dose-response curve have already been defined. The introduction of the terms "MAC" and "MAC awake" amounts to little more than renaming these points with regard to the abscissa rather than to the ordinate. (Don't forget that MAC is a *concentration*. There is a tendency to treat it like a response; for example, see Eger's "MAC is but one point in this continuum (of depression)" and "it (MAC) represents an end-point.") The end-point for MAC is essentially entry into Stage III, Plane 1; the end-point for MAC awake is return to Stage I.

We agree that MAC may be used to define