Similarly, Vasiloff and his co-workers achieved an effect in some patients before the full 10 mg had been given. While giving two 10-mg doses three minutes apart will not give the same plasma level as one 20-mg dose, the former will certainly give a higher plasma level than that following a single 10-mg dose of drug, similar to the level at which Macris et al. saw an effect during injection.

Second, Dr. Macris' point that most of his patients were awake, while ours were anesthetized, is correct. Those of Vasiloff et al. were, however, anesthetized. We agree that there may be a difference between effects in conscious and anesthetized patients.

GEORGE A. GREGORY, M.D.
Assistant Professor in Residence
Anesthesia/Pediatrics

WALTER L. WAY, M.D.
Associate Professor of Anesthesia/Pharmacology
University of California
San Francisco Medical Center
San Francisco, California 94122

MAC and Dose–Response Curves

To the Editor:—The editorial by Waud and Waud in the July 1970 issue of Anesthesiology was most necessary. Potency ratios, if obtainable, would be of great practical value to anesthesiologists in helping them choose the more desirable anesthetic agents. Side-effects and toxicity must be related to potency before a meaningful selection process can occur.

I, too, believe that Eger's concept of MAC has been an imaginative and useful contribution. However, minimum alveolar concentration is a poor term for the measurement. There is no indication that the concentration at which the patient does not move is the minimum alveolar concentration for that patient, because only one concentration is administered to each patient. Actually, Eger and colleagues and others have been determining (albeit roughly) the median effective alveolar concentration.

The median effective dose (ED$_{50}$), when determined appropriately, permits comparison of the potencies of drugs in different groups of subjects, converting the dose response to a straight line by a log dose–probit transformation. In addition, the method provides a test for goodness of fit, checks for parallelism of two dose responses and estimates the confidence limits of ED$_{50}$ before calculating potency ratios.

This concept has utility in establishing a point to compare side effects and toxicity. For example, the dose at which 50 per cent of patients are effectively anesthetized might cause 30 per cent side effects with one drug and 5 per cent with another drug. This kind of information would be of considerable practical importance in helping anesthesiologists toward a more rational selection of anesthetics. My colleagues and I have used this concept to show that the median effective alveolar concentrations of halothane differ for adults and children.

Undoubtedly, a dose–response curve featuring variable depths of anesthesia plotted against alveolar concentrations would be extremely useful. Major barriers now prevent realization of this ideal in human and animal experimentation. The changes in alveolar concentration would have to be established for at least 15–20 minutes before initiation of a stimulus in order to ensure that alveolar–brain equilibrium had occurred. No quantitative method of measuring depth of anesthesia that allows a variable plot exists.

Under the circumstances, the only acceptable method of comparing anesthetic potency with side-effects and toxicity is by use of the ED$_{50}$ concept. This concept has had acceptance by pharmacologists for several decades and can provide useful information for anesthesiologists.

LEONARD BACHMAN, M.D.
Division of Anesthesiology
The Children's Hospital
of Philadelphia
18th and Bainbridge Streets
Philadelphia, Penna. 19146
REFERENCES

To the Editor.—In a recent editorial, the Doctors Waud suggested some limitations to the uses of MAC.¹ 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 (flurane) 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,² whereas three or four times the cyclopropane MAC presents no such hazard.³ 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 Pco₂,⁴ whereas twice MAC for ether causes no change in Paco₂.⁵ 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.⁶ Another use of the MAC awake and other such subanesthetic 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 fluoxetine suggests that these curves are roughly parallel. The additivity studies of Cullen et al.⁷ and Miller et al.⁸ 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-parallelleness. 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