Srinivasa N. Raja, M.D., Editor

Anesthesiology 2002; 96:238–9

A Brief History of the Origin of Minimum Alveolar Concentration (MAC)

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Minimum alveolar anesthetic concentration: A standard of anesthetic potency. By Eger EI II, Saidman LJ, Brandstater B. ANESTHESIOLOGY 1965; 26:756–63.

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.

THE first description of MAC (the minimum alveolar concentration of anesthetic that prevents movement in 50% of subjects in response to a noxious stimulus) appeared as part of an investigation of a new inhaled anesthetic, halopropane.[1] The original report resulted from a confluence of factors, beginning in 1958 with a lecture that John Severinghaus, M.D. (now Emeritus Professor of Anesthesia at the University of California, San Francisco [UCSF], CA), gave on uptake and distribution of inhaled anesthetics during my residency at the University of Iowa (Iowa City, IA) in 1958 (where John and I were both residents). I argued with John for an hour, trying to convince him that he incorrectly attributed diethyl ether's slow onset of action to its considerable solubility in blood. John, of course, was right. He almost always was right. I did catch him wrong once. John's lecture and an obscure book, *The Mode of Action of Anaesthetics*,[2] induced a fascination with uptake and distribution. So I came to San Francisco in 1960 to study with John, to learn all to be learned about inhaled anesthetic pharmacokinetics.Soon after I became John's fellow, John handed Giles Merkel, M.D. (Research Fellow, Department of Anesthesia, UCSF), and me a bottle containing a clear liquid labeled halopropane. Halopropane, produced by E.I. du Pont de Nemours & Co. (Wilmington, DE), was a newly discovered anesthetic. John asked if we wanted to define its properties, and like good fellows, of course we said yes. We asked John how that might be done. I have forgotten his answer (Giles died many years ago, so there is no asking him), but I think it reduced to "Go figure it out." That was not as flippant as it might seem. Giles and I were fellows at a wonderful time, a time of great ferment and enthusiasm at UCSF and beyond. One enthusiasm was for breath-by-breath analysis of respired gases, including anesthetics, an analysis that allowed an on-line estimate of the partial pressure of a gas in arterial blood.[3] The Beckman Corporation (Fullerton, CA) had devised an infrared analyzer (the LB1) that would analyze any anesthetic that had a halogen in it, including halopropane. The LB1 would not stand a chance against today's analyzers: it suffered with wetting of the sample chamber. It was alinear, not enormously sensitive, and affected by the concurrent presence of carbon dioxide, but it was head and shoulders above previous chemical approaches, and John could always make it work. From studies John and others had performed with carbon dioxide,[3] we knew that measuring the end-tidal concentration of a gas gave us a handle on the arterial partial pressure for that gas. Also, the work of Kety and Schmidt[4] indicated that the cerebral partial pressure of an inert gas should rapidly equilibrate with the partial pressure in arterial blood. So if we measured the end-tidal concentration of halopropane and held it stable for a sufficient period of time, the

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Received from the Department of Anesthesia, University of California, San Francisco, California. Submitted for publication August 20, 2000. Accepted for publication March 18, 2001. Support was provided solely from institutional and/or departmental sources. Dr. Eger is a paid consultant to Baxter Healthcare Corporation, Liberty Corner, New Jersey.

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end-tidal concentration would give us a measure of the anesthetic partial pressure at its site of action. With that, we had the first part of MAC.

The second part was not hard to come by. We had to have some index of anesthesia that would not be controversial. Fortunately, we did not know enough about electroencephalography to become bogged down in that morass, and we did not think that blood pressure and heart rate would provide us with a consistent response to stimulation, particularly because there was considerable to-do at the time about vagovagal reflexes. Movement, a categorical response, seemed just the thing (Lou Orkin [Distinguished University Professor Emeritus, Albert Einstein School of Medicine, New York, NY] later contended that he had known about MAC long before Giles' publication: "Every time I give anesthesia and the patient moves, the surgeon says 'Hey, MAC!'"]. So we married the end-tidal concentration with movement–no movement as an index of anesthesia, and MAC was born.

Everything except the name. John's group met every Monday morning to discuss the previous week's work and what might be done in the coming week—a show and tell. I loved it, and when I later had the chance, I imitated it. At one of these, Giles and I told of our technique for determining the minimal alveolar anesthetic concentration, and John connected this to the ratio of the speed of an airplane relative to the speed of sound (a MAAC ratio). John now says it never was clear why we chose MAC rather than MAAC. I don't remember either, except that we wanted to emphasize the word "alveolar." Besides, voicing "MAAC" might make us sound like bleating sheep rather than anesthesiologists.

The next step was to determine MAC in humans. Giles had left for private practice, but I was still there (slow learner). Enter Larry Saidman (then a mere research fellow in the Department of Anesthesia, UCSF; currently Professor of Anesthesiology, Stanford University, Palo Alto, CA). Larry and I applied the concept to patients, substituting incision for the tail clamp we had used in dogs,[5] ignoring the warning by Neri Guadagni (now deceased; then Associate Professor, Department of Anesthesia, UCSF) that MAC could not be determined in humans because of their variable responses to anesthesia. God favors the innocent.

It dawned on me (and several other fellows—I continued to be John's fellow) that we might be on to something useful. What was missing was a demonstration of MAC for a variety of anesthetics, and documentation of the factors that influence MAC. The result was the series of articles that were published in 1965.[6–8] Shortly after their publication, one of my heroes, Dr. Cullen (Stuart Cullen, then Chairman of the Department of Anesthesia at UCSF) called me into his office and asked what I was going to do next. He suggested to me that I had done all that might be useful with MAC and that it might be time to move on. Maybe he was right.

Today MAC serves as the standard of inhaled anesthetic potency. Despite its imperfections and limitations, it remains the standard because nothing thus far invented is better. It allows quantitative comparisons of cardiorespiratory, neuromuscular, and central nervous system properties of inhaled anesthetics. It facilitates studies of the mechanisms by which inhaled anesthetics act. And clinicians use it to describe how deeply they anesthetize their patients and to appreciate the factors that influence anesthetic requirement (*e.g.*, temperature) in a given patient. Its importance is certified by the absence of citation in its use in reports: it has attained the status of other units, such as the centimeter and degrees Celsius.

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