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

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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 hyperventilation or hypocarbia or by mild hypoxia (PaO₂ 30 to 60 mm. of mercury). Hemorrhagic hypotension or marked metabolic acidosis reduced MAC by 10 to 20 per cent. Severe hypoxia (PaO₂ 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. 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, 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 Schmidt4 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
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. Larry and I applied the concept to patients, Professor of Anesthesiology, Stanford University, Palo Alto, CA). Enter Larry Saidman (then a mere research learner). Giles 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.

### References