

Supporting technologies — MAC

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Supporting technologies

9.4 MAC

*Ether contributes other benefits besides preventing the pain.
It keeps patients still, who otherwise would not be.*

John Snow

From: Eger (1974),¹ p. 1

9.4.1 History

John Snow

John Snow (1813–1858) appears to have been the first person to appreciate the importance of controlling the inspired concentration of volatile anaesthetics, and within five years of William Morton’s ether demonstration² he had single-handedly established the scientific foundations underpinning the pharmacokinetics of volatile anaesthetics.

Snow was a London-based GP with hospital connections, and had been interested for a long time in the use of inhalation agents on respiration. He initially investigated the use of carbon dioxide, and had been experimenting with inhaled ether since 1843 believing it to be a useful medicine for improving circulation. In 1846 he published an article entitled “*Pathological effects of atmospheres*” (Maltby 2002; Vinten-Johansen *et al.* 2003).

Consequently, following Morton’s demonstration of ether anaesthesia (October 16, 1846) at the Massachusetts General Hospital (Boston, USA), and the subsequent demonstration in London in December 1846 by Mr J Robinson³, Snow found himself in the right place at the right time⁴. Furthermore, with his interest in chemistry and recent researches

¹This quotation, which heads Eger’s own chapter on MAC, is from: Snow (1847, p. 53).

²William Morton (1819–1868) gave his demonstration on October 16, 1846. For an excellent account of the history and background see MacQuitty (1969).

³Robinson J (1847). Correspondence. *Medical Times*, 15; 273–274.

⁴Indeed, Robinson (1847) indicates that he anaesthetised a patient “... in the presence of my friends—Mr. Stocks, Mr. Snow, and Mr. Fenny.”

into inhaled ether he also found himself to be just the right person to get involved in this new anaesthesia phenomenon. Since his GP work was not very profitable, Snow decided to take up anaesthesia.

Snow was extraordinarily industrious and productive. By mid 1847 he had (a) defined and published the temperature characteristics of ether vapour (January 1847), (b) designed a temperature-compensated ether inhaler, (c) defined a range of clinical stages of anaesthesia (his five ‘degrees of narcotism’), and (d) performed many animal experiments with a view to determining the effects of different inspired concentrations of both ether and chloroform. Snow appreciated the significance of knowing the saturated vapour pressure, and went on to show that the amount of volatile agent required to produce anaesthesia was inversely related to its solubility in the blood.

Snow published his findings in an eighteen-part series of articles in the journal *London Medical Gazette* during the period 1848 to 1851, entitled “On narcotism by the inhalation of vapours”. In the following extracts (all from Part–I of the series) Snow describes the effects on a mouse of a sequence of step increases in the inspired concentration of ether (from approximately 1.2 % to 4.7 %).⁵ Notice the detail of his observations, and how he pays particular attention to how well the mouse breathes (I have added a calculated concentration in $\text{MAC}_{\text{mouse}}^{\text{ether}}$ at each stage to make it easier to follow his experiments).

I consider, however, that I have found a plan of determining more exactly the [required] proportion of ether and of other volatile substances present in the blood in the different degrees of narcotism. It consists of ascertaining the most diluted mixture of vapour and of air that will suffice to produce any particular amount of narcotism; and is founded on the following considerations, and corroborated by its agreeing with the comparative physiological strength of the various substances.

... The plan which I adopted to ascertain the smallest quantity of vapour, in proportion to the air, that would produce a given effect, was to weigh a small quantity of the volatile liquid in a little bottle, and introduce it into a large glass jar covered with a plate of glass; and having taken care that the resulting vapour was equally diffused through the air, to introduce an animal so small, that the jar would represent a capacious apartment for it, and wait for that period when the effects of the vapour no longer increased. ...

Exp. 17. — Two grains of ether were put into a jar holding 200 cubic inches [1.16 %, 0.36 MAC], and the vapour diffused equally, when a tame mouse was introduced, and allowed to remain a quarter of an hour, but it was not appreciably affected.

Exp. 18. — Another mouse was placed in the same jar, with three grains of ether, being a grain and a half to each 100 cubic inches [1.75 %, 0.55 MAC]. In a minute and a half it was unable to stand, but continued to move its limbs occasionally. It remained eight minutes without becoming further affected. When taken out it was sensible to pinching, but fell over on its side in attempting to walk. In a minute and a half the effect of the ether appeared to have gone off entirely.

⁵ $\text{MAC}_{\text{mouse}}^{\text{ether}} = 3.2\%$ (Eger 1974, p. 5).

Exp. 19. — A white mouse in the same jar, with four grains of ether [2.33 %, 0.72 MAC], was unable to stand at the end of a minute, and at the end of another minute ceased to move, but continued to breath naturally, and was taken out at the end of five minutes. It moved on being pinched, began to attempt to walk at the end of a minute, and in two minutes more seemed quite recovered.

Exp. 20. — Five grains of ether, being two and a half grains to each 100 cubic inches [2.92 %, 0.91 MAC], were diffused throughout the same jar, and a mouse put in. It became rather more quickly insensible than the one in the last experiment. It was allowed to remain eight minutes. It moved its foot a very little when pinched, and recovered in the course of four minutes.

Exp. 21. — A white mouse was placed in the same jar with six grains of ether [3.5 %, 1.1 MAC]. In a minute and a half it was lying insensible. At the end of three minutes the breathing became laborious, and accompanied by a kind of stertor. It continued in this state till taken out, at the end of seven minutes, when it was found to be totally insensible to pinching. The breathing improved at the end of a minute; it began to move at the end of three minutes; and five minutes after its removal it had recovered.

Exp. 22. — The same mouse was put into this jar on the following day, with seven grains of ether, being 3.5 grs to the 100 cubic inches [4.08 %, 1.28 MAC]. Stertorous breathing came on sooner than before; it seemed at the point of death when four minutes had elapsed; and being then taken out, was longer in recovering than after the last experiment.

Exp. 23. — Two or three days afterwards the same mouse was placed in the jar, with eight grains of ether, being 4 grains to the 100 cubic inches [4.66 %, 1.46 MAC]. It became insensible in half a minute. In two minutes and a half the breathing became difficult, and at a little more than three minutes it appeared that the breathing was about to cease, and the mouse was taken out. In a minute or two the breathing improved, and in the course of five minutes from its removal it had recovered.

... We find from the eighteenth experiment, that a grain and a half of ether for each 100 cubic inches of air, is sufficient to induce the second degree of narcotism in the mouse; and a grain and a half of ether make 1.9 cubic inches of vapour, of sp. gr. 2.586. Now the ether I employed boiled at 96°[F].⁶ At this temperature, consequently, its vapour would exclude the air entirely; and the ether vapour in contact with the liquid giving it off, could only be raised to 100° by such a pressure as would cause the boiling point of the ether to rise to that temperature. That pressure would be equal to 32.4 inches of mercury [1.082 Atm.], or 2.4 inches above the usual barometrical pressure; and the vapour would be condensed somewhat, so that the space of 100 cubic inches [at 1.082 Atm.] would contain 108 cubic inches at the usual pressure [1 Atm.]. This is the quantity, then, with which we have to compare 1.9 cubic inches, in order to ascertain the degree of saturation of the space in the air-cells of the lungs, and also of

⁶96°F = 35.5°C. ($\frac{F-32}{9} = \frac{C}{5}$). Pure diethyl-ether boils at 34.51°C (CRC Handbook of chemistry and physics; 1972).

the blood; and by calculation, as when treating of chloroform,

1.9 is to 108 as 0.0175 is to 1

So that we find 0.0175 [1.75 %], or 1/57th, to be the amount of saturation of the blood by ether necessary to produce the second degree of narcotism;

Snow (1848a)

Notice the interesting way in which Snow calculates the vapour concentration resulting from 1.5 grains⁷ of liquid diethyl-ether⁸ in 100 cubic inches⁹ of air at 100°F¹⁰ as 1.75%. My own calculation runs as follows. Since the molecular weight of diethyl-ether is 74.12, the volume of pure ether vapour at STP occupied by 96.75 mg liquid ether (1.5 grains) is given by¹¹

$$22.4 \times \frac{96.75}{74.12} = 29.24 \text{ cc}$$

If we now correct this volume for a temperature of 100°F¹² (37.7°C) we obtain $29.24 \times 310.7/273 = 33.3$ cc. Adding this volume of pure vapour to 100 cubic inches of air¹³ (also at 37.7°C) gives a concentration of

$$\frac{33.3}{33.3 + (100 \times 2.54^3 \times 310.7/273)} = 0.01754 \equiv 1.75 \%$$

However, we have made some simplifying assumptions (e.g., constant pressure and complete mixing), and since Snow only used a glass jar with a simple lid, it is likely that some of the mixture escaped from the jar before mixing was complete.¹⁴

It is clear from these extracts from Snow's publications, that Snow was seeking the inspired concentration associated with each of his five 'degrees of narcotism', and that he was guided by two key principles, namely (a) to determine 'the most diluted mixture' which gave these effects (i.e., the minimum concentration), and (b) waiting until 'the effect no longer increased' (i.e., at equilibrium).

Snow's pharmacological approach of linking particular inspired concentrations of vapour to particular states or depths of anaesthesia, and then using this information to try and deliver a safer form of anaesthesia by controlling the inspired vapour concentration was, therefore, strikingly similar to our modern use of MAC.¹⁵ His experiments were

⁷1 grain = 64.5 mg.

⁸ $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$; molecular weight = 74.12; BP = 34.51°C

⁹1 cubic inch = $2.54^3 = 16.38$ cc.

¹⁰100°F = 37.7°C.

¹¹1 gm mol of vapour occupies 22.4 L at STP.

¹²Note that this is roughly mouse body temperature.

¹³We keep the pressure constant and assume complete mixing.

¹⁴Please email me if you improve on this analysis.

¹⁵The first paper on MAC was by Merkel and Eger (1963). The definition of MAC is as follows:-- the minimum alveolar concentration, at equilibrium, and at 1 atmosphere pressure, which prevents movement in 50% of patients to a standard surgical incision. For an excellent early overview of MAC see Chapter 1 in the timeless classic book by Eger (1974).

carefully performed, observed, and well documented—in fact so much so that they even allow us to make a reasonably accurate estimate of MAC for the mouse. For example, Snow's experiments 20 and 21 suggest that the inspired concentration of ether associated with 50 % movement was between 2.9 % and 3.5 %, giving an estimate close to the modern value of MAC_{mouse}^{ether} for the mouse¹⁶ of 3.2 %.

100 years or so later in the early 1960s Eger and Severinghaus embodied Snow's concepts in the form of MAC (Merkel and Eger 1963; Saidman and Eger 1964; Eger, Saidman, and Brandstater 1965a).

Edmond Eger

In 1960 Edmond Eger joined the San Francisco Department of Anaesthesia, and became a 'Research Fellow' to John Severinghaus (Eger 2002, Maltby 2002). Eger and Dr Giles Merkel (Research Fellow) were given the task of defining the properties of a new volatile anaesthetic agent called halopropane. Eger describes the early steps as follows.

From studies John [Severinghaus] 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 Schmidt 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. ... Movement. A categorical response, seemed just the thing ... 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 ... 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 emphasise 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. ... The result was the series of articles that were published in 1965 (Eger, Saidman and Brandstater 1965a, 1965b; Eger *et al.* 1965).

Eger (2002)

¹⁶Eger (1974), p. 5.

John Severinghaus

Severinghaus (Severinghaus 2009, Maltby 2002) recalled this episode in a recent journal interview as follows (Kofke 2003).

Dr. Eger was interested in the relative potency of anesthetics. He wanted a way to compare them numerically in terms of their alveolar concentrations at the time of establishment of a minimal level of anesthesia to permit surgery. It was clear to all that for each patient or animal, there was a critical alveolar (and thus arterial and ultimately brain) pressure of an agent that just prevented a motor response to pain. He believed this would be a relatively invariant number between patients. This would be the minimal alveolar anesthetic concentration. I recalled that in aviation, a similar index, Mach, was the ratio of an aircraft's speed to the speed of sound.¹⁷ A hypersonic flight was defined, for example, as Mach 2, twice the speed of sound. I suggested the same symbol be used for the ratio of concentration of the anesthetic in the alveoli (as determined in the airway at end expiration) to that critical no-movement level, which would be defined as 1 MAC, originally MAAC. It still should be MAAC since we can't agree on whether the single 'A' refers to alveolar or anesthetic or both.

Kofke (2003)

William Mapleson

In 1979, a far-sighted William Mapleson anticipated the increasingly central role of MAC with respect to how anaesthetists delivered a given depth of anaesthesia, as follows (see also Maltby 2002).

... To this end, the anaesthetist will be invited to set his flows of oxygen and nitrous oxide in the normal way and then to set the brain tension of anaesthetic he requires, not in kPa or mmHg, but in total MAC units.

Mapleson (1979).

More recently the clinical utility of MAC has been extended by establishing its variation with age (Mapleson, 1996), temperature (Eger 2001) and hair colour (Liem *et al.* 2004).

9.4.2 Age-corrected MAC

Although several factors are known to be associated with altered anaesthetic requirements,¹⁸ age is the most important owing to the increasingly large age-range met with in clinical practice.

While age has long been known to influence anaesthetic requirement (Gregory, Eger and Munson 1969), the exact variation of MAC with age was formalised only recently by Mapleson (1996), following a meta-analysis of the available data (see Table 9.1). In

¹⁷Severinghaus worked on radar technology during World War II (Kofke 2003).

¹⁸The key factors are narcotics (see section on remifentanyl in the appendix), age, temperature, pregnancy, and hair colour (Liem *et al.* 2004, showed that patients with red hair had a 19% increased MAC requirement).

particular, Mapleson showed that semi-log plots of MAC against age (age ≥ 1 year) for all inhalational agents are linear and parallel, and hence it is probable that all the inhalational agents achieve their effects by a similar mechanism. On this basis, therefore, Mapleson derived the following relationship between age and MAC from the pooled data,

$$\text{MAC}_{age} = \text{MAC}_{40} \times 10^{-0.00269(\text{age}-40)}$$

which expresses MAC for a given age as a function of that at 40 years (MAC_{40}).

Table 9.1:

MAC data based on age ≥ 1 year. The 95 % confidence limits (CL) for ages 1 and 80 years are up to 1 % greater than at MAC_{40} (from Mapleson 1996). * For the CO_2 value see Eisele and Eger (1967).

Agent	1 year	40 years	80 years	95 % CL (\pm % MAC_{40})
Halothane	0.95	0.75	0.58	6
Isoflurane	1.49	1.17	0.91	6
Enflurane	2.08	1.63	1.27	17
Sevoflurane	2.29	1.80	1.40	6
Desflurane	8.3	6.6	5.1	10
Carbon dioxide*	—	≈ 30	—	—
Xenon	92	72	57	16
Nitrous oxide	133	104	81	8

The computed real-time MAC as displayed by the Datex AS/3 and S/5 anaesthesia monitors relates to normothermic patients aged approximately 35 years-old. However, since many of the thoracic patients are quite elderly it is more appropriate clinically to use an age-corrected MAC. A real-time software version which incorporates nitrous oxide is shown in Figure 9.5 (page 149). Print versions¹⁹ in the form of graphs which allow for nitrous oxide use have been designed (Nickalls and Mapleson 2003), a separate chart being used for each volatile agent as shown in Figures 9.1–9.3. The use of nitrous oxide is accommodated in the charts by offsetting the right-hand N_2O scales vertically by the amount given by

$$F_{\text{E}'\text{N}_2\text{O}} \times \frac{\text{MAC}_{age, \text{volatile}}}{\text{MAC}_{age, \text{N}_2\text{O}}}$$

The print versions are available for download²⁰ and also in Allman and Wilson (2006). A nomogram by Lerou (2004) also gives age-corrected MAC.

¹⁹These allow anyone to confidently use the common volatile agents with patients of any age without any guesswork or the need for superhuman memory. The motivation for developing a convenient graphic version arose from my wanting a paper-equivalent for use when working at another hospital, since I then had no access to my own real-time computer version based in the thoracic theatre at the City Hospital.

²⁰<http://www.nickalls.org/dick/xenon/rwdnXenon.html#workstation-mac>

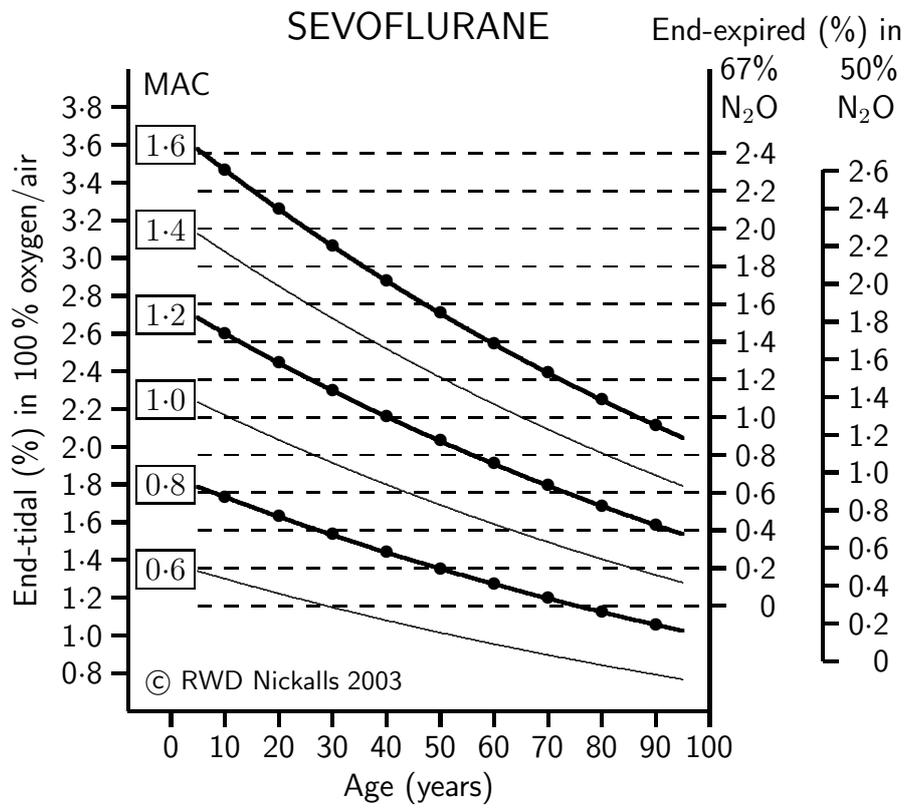


Figure 9.2:

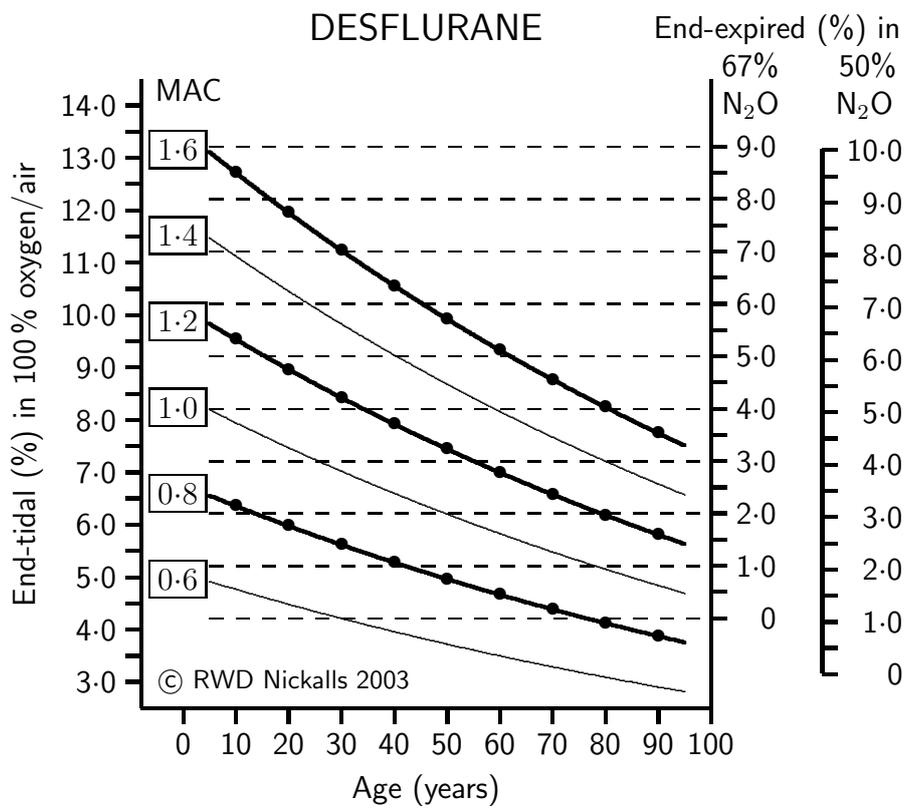


Figure 9.3:

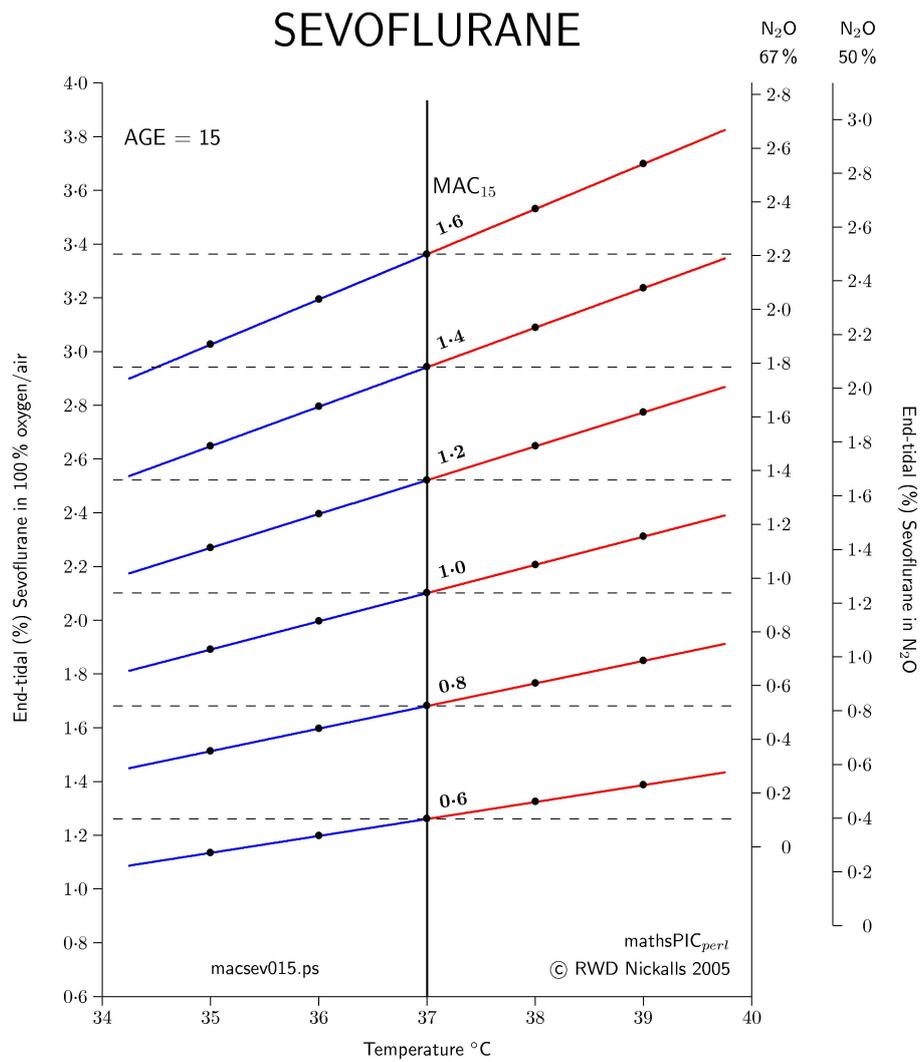


Figure 9.4:

An example of one of the new age and temperature-corrected MAC charts (see Section 9.4.3 for details). A Perl program prompts the user for agent name and patient age and then prints the chart out in the operating theatre.

Software

The iso-MAC information is also available for some hand-held devices, for example, as the software *MACpalm* and *ACTc*.

MACpalm: The MACpalm program is available from <http://www.medicaldownload.com/medicalsoftware/macpalm.html>. The installation is described in the MACpalm manual.

ACTc: The Anesthesia Clinical Tutor and Calculator (ACTc) program is available from <http://www.gasshead.com/>. A manual is available at <http://www.gasshead.com/content/TutorACTc.pdf>

9.4.3 Temperature corrected MAC

It is well established that MAC decreases as body temperature decreases. In fact even John Snow was aware of the influence of temperature, as the following extract shows.²¹

As the narcotism of frogs, by vapour too much diluted to affect animals of warm blood, depends merely on their temperature, it follows that by warming them, they ought to be put into the same condition, in this respect, as the higher classes of animals; and although I have not raised their temperature to the same degree, I have found that as it is increased, they cease to be affected by dilute vapour that would narcotise them at a lower temperature.

Snow (1848a)

However, it is less well known that (a) MAC decreases *linearly* with core temperature fall (approximately 2–5 % reduction in MAC per degree centigrade from 37°C), and (b) the rate of MAC decrease with temperature fall is considerably more for vapours than for gases; for example the change in MAC/°C for halothane and cyclopropane in dogs is 5.3 % and 2 % respectively (Eger, Saidman, and Brandstater 1965b; Eger 1974). In humans the linear rate of fall of MAC with temperature in the clinical range is approximately 5 % per degree centigrade for isoflurane, sevoflurane and desflurane, while that for nitrous oxide shows essentially no change (Eger 2001).

These findings can be used to combine both age and temperature correction for MAC in a single chart—most easily done by creating a separate chart for each year of age—as shown in Figure 9.4. The additional functionality of such a chart is particularly useful, since the end-tidal agent requirement is most likely to be underestimated in young patients with a pyrexia. In practice, it is a simple matter to create and print this combined age and temperature-corrected iso-MAC chart for a specific patient on demand in the operating theatre.²²

For example, suppose we wish to deliver 1.2 MAC to a 15 year-old patient with a temperature of 39°C. The Datex AS/3 and S/5 monitors show a value of 1.2 MAC

²¹This temperature work relates to chloroform—see his Experiment 16 (Snow 1848a).

²²I have written a Perl program for this which is freely available. This program and separate charts for the ages 0–120 yrs are available on the thoracic CD-ROM in PDF format.

for an end-tidal sevoflurane concentration (in air) of approximately 2.2 %, whereas the age/temperature correction chart (see Figure 9.4) indicates that to achieve the same MAC value in this patient (age 15 yrs; temp 39°C) actually requires an end-tidal value of 2.8 % (i.e., a 27 % increase compared with the Datex displayed value).

9.4.4 Dosage and MAC correction

Awareness

The problem of awareness and the need for research in this area is often highlighted (Bergman *et al.* 2002, Guidry 2005, Leslie and Davidson 2010) and, as one might expect, data gathered by automatic anaesthesia management systems (AIMS) has been particularly useful in this regard. For example, using archived AIMS data, Driscoll *et al.* (2007) were not only able to establish volatile agent underdosing as the cause of awareness in three cases, but were also able to show that the clinicians' manual component of the relevant parts of the anaesthesia records were unreliable and failed to reflect events accurately.

More recently, the role of underdosing as a cause of awareness during anaesthesia has been highlighted in two large studies (Ghoneim *et al.* 2009, Xu *et al.* 2009), both of which found that awareness was associated with reduced drug dosage, being younger, and with non-volatile anaesthetic techniques. Similarly, Kent (2010) found that the two main causes of awareness in the Closed Claims database were light anaesthesia and anaesthetic delivery problems.

Unfortunately EEG *depth of consciousness* monitoring techniques (e.g., BIS) are still problematic and unreliable (Mychaskiw *et al.* 2001, Rampersad and Mulroy 2005). Furthermore, in spite of several well publicised large neuromonitoring trials and surveys (Ekman *et al.* 2004, Myles *et al.* 2004; Sebel *et al.* 1997; Sebel *et al.* 2004; Avidan *et al.* 2008) there are still no data to suggest, in those cases where volatile agents are used, that neuromonitoring offers any advantage with regard to preventing awareness, over the *rigorous* implementation of 'corrected' MAC monitoring. Indeed, it is significant that the study of 20,000 patients by Sebel *et al.* (2004) actually showed that the BIS-monitored cohort had a *higher* incidence of awareness (0.18%) than the control cohort²³ (0.1%) (McCulloch 2005). In the BIS/MAC study by Avidan *et al.* (2008) the authors concluded that "...Our findings do not support routine BIS monitoring as part of standard practice." Indeed, the associated editorial by Orser (2008) expressed concern regarding BIS-like devices, as follows.

... the delegation of critical elements of patient care to a "black box" approach, in which decisive factors are under proprietary control, must be avoided."

Since the MAC paradigm has been so successful (White, 2003), and because there are no known *convincingly* documented cases of awareness which are not associated with possible underdosing, it was recently suggested (Nickalls and Mahajan 2010)

²³See letter by McCulloch (2005).

... that the time has come to reformulate the concept and adopt a new and pragmatic working premis, namely, that *all cases of awareness are due to underdosing unless there is convincing verifiable information to the contrary*. ... We ... must confront the problem of underdosing by putting in place systems which we can have confidence in to deliver an adequate dose, implementing the latest alarms (Umesh 2009), algorithms (Mashour, Esaki Vandervest *et al.* 2009), and corrections for age (Mapleson 1996, Nickalls and Mapleson 2003, Eger 2001), temperature (Eger 2001), and so forth as they come available.

In practice, however, there are studies showing a very low incidence of awareness even without using brain function monitoring (Pollard *et al.* 2007), and when volatile agents are used the end-tidal MAC approach is still the most reliable method for avoiding awareness, and is recommended by the Royal College of Anaesthetists (see RCOA 2006). Indeed, anaesthetists can easily be made even more aware of the current MAC status simply by using use a real-time colour-coded dial-display of corrected MAC (see Figure 9.5).

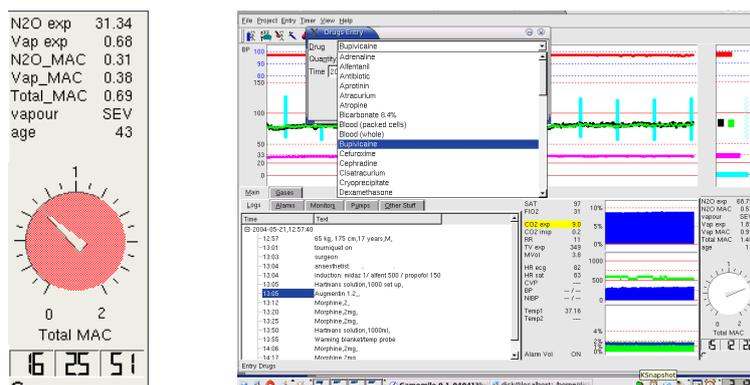


Figure 9.5:

Left: Example of the real-time age-corrected MAC-widget displayed by the author's open-source anaesthesia workstation software^a interfaced to the Datex S/5 monitor. If the corrected MAC is too low (as shown in this case—total MAC \approx 0.7) then, in addition to sounding an audible alarm, the dial of the MAC-widget turns red.

Right: Screenshot showing the MAC widget displaying a white dial (corrected MAC in the normal range). The MAC-widget software can easily be run on a laptop interfaced to an anaesthesia monitor.

^a© Nickalls RWD, Dales S and Nice AK (1996–2011).

What is the minimum MAC multiple which avoids awareness? 1 MAC has long been regarded as a significant boundary since isoflurane at 1 MAC was shown to prevent implicit memory during surgery (Dwyer *et al.* 1992). More recently this problem was addressed

by Hardman and Aitkenhead (2005), who stated that a stable end-tidal value greater than 1 MAC makes awareness extremely unlikely, as follows.

Risk of awareness correlates with depth of anaesthesia. ... Fortunately, clinical investigations have shown a reasonably reliable association between recall and MAC; patients exhaling more than 0.8 MAC are unlikely to recall intraoperative events, and spontaneous recall is virtually eliminated if > 1 MAC is exhaled, except after a sudden increase in inspired concentration.

Hardman and Aitkenhead (2005)

That the end-tidal agent concentration should be maintained $\geq 1 \text{ MAC}_{age}$ in order to reliably avoid awareness is consistent with a recent fMRI finding by Kerssens *et al.* (2005), namely that while auditory activation in a group of 6 subjects (mean age 23 years) was detected when breathing 1% end-tidal sevoflurane in oxygen/air (0.5 MAC_{age}), such activation was absent when breathing 2% end-tidal sevoflurane (i.e., when breathing 1 MAC, since $\text{MAC}_{23}^{\text{sevo}} = 2\%$).

It is significant, therefore, that in the BIS/MAC study by Avidan *et al.* (2008) the end-tidal agent concentration was less than 0.7 MAC in three of the four cases of definite awareness, and in seven of the nine cases of possible awareness. Thus the lower acceptable limit of 0.5 MAC suggested by Eger and Sonner (2005), Myles (2007) would seem to be far too low to reliably prevent awareness. Consequently the values suggested by Hardman and Aitkenhead (2005)—see above—particularly when age and temperature corrected, would seem to be the best current advice.

Note that the MAC value displayed by monitors having no age and temperature correction is most likely to underestimate the true MAC requirement in young patients with a high temperature (Section 9.4.3) and (possibly) with red hair (Liem *et al.* 2004). Indeed, it may be significant, therefore, that the two patients with documented awareness during BIS monitoring with sevoflurane reported by Ekman *et al.* (2004) were quite young (aged 16 and 22 years). Unfortunately the details of the aware patients who received volatile agents in the non-BIS group were not given.

Research

In all work relating to depth of anaesthesia or awareness, it is essential to collect accurate real-time end-tidal anaesthetic gas (ETAG) concentrations and core temperatures using automated anaesthesia record keeping (AARK) equipment, drugs and doses used, as well as patient age, height, gender and hair-colour. The presented awareness-related data must be sufficient to enable readers to calculate the corrected MAC for *each patient*; consequently the observed ETAG concentrations for each patient should always be presented. Where MAC corrections have been applied, the literature source of the corrections used must be indicated. Furthermore, mean age-corrected values need to be correctly determined; for example, the age correction for MAC is non-linear and hence the mean MAC value for a group must be derived from the corrected MAC of each individual subject/patient.

In view of the importance of determining minimum MAC values for reliably preventing awareness, journal editors should ensure that awareness-related MAC data presented in journal articles are sufficient to allow readers to determine the corrected MAC values for each patient (Nickalls and Mahajan 2010).

Data sharing

Ideally all cases of inadvertent awareness should be documented, and archived, together with all the anaesthesia data associated with such cases (including all machine-automated end-tidal data) and placed in the public domain. Such a database could then form the basis of research, and may therefore, help "... recognise those few cases which may suggest either that the accepted dosage threshold should be raised or, perhaps, a significant pharmacogenetic difference" (Nickalls and Mahajan 2010).

However, although original data documented in journals is still often difficult to access from the authors or organisation (Wicherts *et al.* 2006, Anon 2006, Kaiser 2008), fortunately the climate of opinion is now strongly in favour of data-sharing, with funding organisations increasingly stipulating that authors place their data in open-access repositories within a set period after publication in peer-reviewed journals (Short 2007, Wadman 2009). Nevertheless, we should continue to press for even more safeguards; for example, the adoption by anaesthesia journals of an authorship policy specifying the preservation and sharing of original data (Anon 2009a). Authors and researchers need to embrace the new culture of '*integrity, access and stewardship*' (Anon 2009b)—not only making the data available, but safe-guarding it as well.

9.4.5 References

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²⁴The full title is: *On the inhalation of the vapour of ether in surgical operations: containing a description of the various stages of etherization, and a statement of the result of nearly eighty operations in which ether has been employed in St. George's and University College Hospitals*. At least four facsimile editions have been published—for details see the introductory essay by RH Ellis in the Royal Society of Medicine facsimile edition (1991) of Snow (1848b)

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²⁵6NS indicates New Series No 6.