used for research projects (Ribeiro et al., 2009) but, as it classifies as a 'medical device', there may be legal limitations (country specific) to its clinical use in humans. It is also possible to have target controlled inhalation anaesthesia; the volatile anaesthetic is injected into the circuit so as to maintain a targeted end-tidal anaesthetic concentration. The anaesthetic machine named 'Zeus' from Draeger has this facility as well as programmable infusion syringes and the advertisement talks of *target controlled anaesthesia*. However, neither of these systems involves a feedback loop within the computer; the feedback loop is the anaesthetist who asks it for a different target, 'up or down' according to the patient requirements.

In order to have a feedback loop, there have to be patient data measured and returned to the computer. To date, the most common parameter used for this purpose is the 'anaesthetic depth monitor', BIS (see Electroencephalography). As has been discussed, this is a monitor based on the 'hypnosis' resulting from the anaesthetic agents that act primarily on the $GABA_A$ receptor, and therefore is most accurate with propofol anaesthesia. Not surprisingly, computer-controlled anaesthesia has been most effective with systems involving propofol infusions (Hemmerling et al., 2010). Recently, Liu et al. (2011) used computer-controlled infusion of propofol together with remifentanil, and found it more effective in maintaining a steady BIS target than was manual control. However, as discussed previously, in any one individual, steady BIS does not always represent the ideal 'depth' of anaesthesia so the anaesthetist is still needed to assess the patient's overall response, in particular cardiopulmonary changes and autonomic responses to stimulation. Absalom et al. (2011) have reviewed the current status of computer-controlled anaesthesia and consider that the limitations are such that it is a goal not yet achieved.

Minimum Alveolar Concentration (MAC) and Minimum Infusion Rate (MIR)

Minimum alveolar concentration

In 1963, Merkel & Eger proposed the concept of MAC, and Eger et al. (1965) expanded the idea further, suggesting that it would be useful as a measurement of volatile anaesthetic potency. MAC is defined as the alveolar concentration of an anaesthetic that prevents muscular movement in response to a painful stimulus in 50% of the test subjects. It is therefore what is known in pharmacology as the ED_{50} (effective dose). If adequate time is allowed for the anaesthetic in the brain to equilibrate with the anaesthetic agent in the blood, the alveolar partial pressure of the anaesthetic (which can be measured) is a reasonably accurate expression of the anaesthetic state. The stimulus, standardized as far as possible to be 'supramaximal', usually consists of tail clamping or an electrical stimulus in animals and is usually measured in triplicate, concentration of anaesthetic being lowered until there is a response, then raised again until the response is lost. In humans, the most common stimulus is a single surgical incision; if the patient responds the next patient gets a higher dose and so on, until the ED_{50} is found. A single stimulus of this type is certainly not supramaximal, and the difference in measurement techniques may explain why MAC in humans usually is less than in experimental animals. End-tidal anaesthetic gas concentration is taken as an approximation of alveolar gas. With a forced expiration (as is requested when similar technology is used for the alcohol 'breathalyser'), this is reasonable, but under anaesthesia a forced breath cannot be obtained. For really accurate experimental results, sampling should be via a catheter passed down the trachea but, in the clinical situation, sampling at the ET tube suffices.

A number of factors affect MAC. It is not affected by the duration of anaesthesia, hyperkalaemia, hypokalaemia, hypercarbia or metabolic acid–base changes, but is reduced by hyponatraemia. MAC is reduced by 8% for every °C reduction in body temperature, and similarly, raised by hyperthermia. Young animals have high MAC values, but MAC decreases with age (Mapleson, 1996; Eger, 2001). MAC is measured as vol%, and so is dependent on atmospheric pressure, thus explaining the increased doses of volatile agents required to maintain anaesthesia at high altitudes (Quasha et al., 1980). MAC is reduced by many other anaesthetic related agents which add to neuronal depression. The MACs of two volatile and/or inhalation agents are themselves additive (Eger et al., 2003), hence the use of nitrous oxide as part of the carrier gas for volatile agents.

It is now considered that MAC is a measurement that relates to the spinal cord, and not to the brain (Eger et al., 1997). Its end-point is movement and, as discussed above (mode of action), it is movement that is considered to be prevented by the actions at the spinal cord. Interestingly, in relation to analgesia, volatile anaesthetic agents do prevent 'wind-up' of nociceptive neurons in the cord, and it is suggested that this may play a part in preventing movement.

Despite its limitations, however, the concept of MAC has now been used for more than five decades to enable the relative potencies of anaesthetics to be compared (Antognini & Carstens, 2005). This reproducible method may be contrasted with the difficulty in using physiological parameters as an indication of anaesthetic depth, or the EEG, which varies according to the agent used. Although the MAC value represents the anaesthetizing dose for only 50% of subjects, the anaesthetist can be reasonably certain that increasing the alveolar concentration to between 1.1 or 1.2 times MAC will ensure satisfactory anaesthesia in the vast majority of individuals because the dose–response curve is relatively steep. In veterinary practice, it is also important to note that, according to Eger, the variability of MAC is remarkably low between mammalian species and, as long as conditions remain the same, is quite constant in any one animal. Finally, it is important to remember that MAC is determined in healthy animals under laboratory conditions in the absence of other drugs and circumstances encountered during clinical anaesthesia which may alter the requirement for anaesthesia.

Minimum infusion rate

The accurate control of depth of unconsciousness is more difficult to achieve with intravenous anaesthetic agents. To obtain unconsciousness, they must be administered at a rate which produces a concentration of drug in the bloodstream sufficient to result in the required depth of depression of the central nervous system. The concept of minimum infusion rate (MIR) was introduced by Sears in 1970 to define the median ED_{50} of an intravenous anaesthetic agent which would prevent movement in response to surgical incision (or in experimental animals, a supramaximal stimulus). Unlike MAC, in which alveolar concentrations can be considered to equate to arterial, blood cannot be analysed rapidly for injectable anaesthetic concentrations. MIR is therefore measured similarly to MAC using movement as an end-point. However, MIR may change with time if the drug is cumulative; a lower infusion rate being required as the tissues become saturated. The term 'context sensitive MIR' is used to describe these changes with duration of infusion. As changes with context depend on pharmacokinetic parameters, MIR may differ markedly between species depending on rate of drug metabolism and elimination. In veterinary anaesthesia, to date, the greatest knowledge of MIRs in anaesthesia has been with propofol infusions (Beths et al., 2001; Bettschart-Wolfensberger et al., 2001; Oku et al., 2005; Boscan et al., 2010; Rezende et al., 2010), but the same concept (using different end-points) has been employed for choosing suitable infusion rates of sedative drugs (see Chapter 4).

ANAESTHETIC RISK

General anaesthesia and local analgesia do not occur naturally and their induction with drugs that even today are never completely devoid of toxicity must constitute a threat to the life of the patient. This can be a major or trivial threat depending on the circumstances, but no owner must ever be assured that anaesthesia does not constitute a risk. When an animal owner raises the question of risk involved in any anaesthetic procedure the veterinarian needs, before replying, to consider:

1. The state of health of the animal. Animals presented for anaesthesia may be fit and healthy or suffering from disease; they may be presented for elective ('cold') surgery or as emergency cases needing immediate attention for obstetrical crises, intractable haemorrhage or thoracic injuries. In the USA, the American Society of Anesthesiologists (ASA) has adopted a classification of physical status into categories, 'E' being added after the number when the case is presented as an emergency (Table 1.1). This is a useful classification but, most importantly, it refers only to the physical status of the patient and is not necessarily a classification of risk because additional factors such as its species, breed and temperament contribute to the risk involved for any particular animal. Moreover, the assessment of a patient's 'correct' ASA classification varies between different anaesthetists (Haynes & Lawler, 1995; Wolters et al., 1996; McMillan & Brearley, 2013).
2. The influence of the surgeon. Inexperienced surgeons may take much longer to perform an operation and by rough technique produce intense and extensive trauma to tissues, thereby causing a greater metabolic disturbance (and increased postoperative pain). Increased danger can also arise when the surgeon is working in the mouth or pharynx in such a way as to make the maintenance of a clear airway difficult, or is working on structures such as the eye or larynx and provoking autonomic reflexes.
3. The influence of available facilities. Crises arising during anaesthesia are usually more easily overcome in a well-equipped veterinary hospital than under the primitive conditions which may be encountered on farms.
4. The influence of the anaesthetist. The competence, experience and judgement of the anaesthetist have a profound bearing on the degree of risk to which the patient is exposed. Familiarity with anaesthetic techniques leads to greater efficiency and the art of anaesthetic administration is only developed by experience.

Table 1.1 American Society of Anesthesiologists' physical status classification system

Category 1	Normal healthy patient
Category 2	A patient with mild systemic disease
Category 3	A patient with severe systemic disease
Category 4	A patient with severe systemic disease that is a constant threat to life
Category 5	A moribund patient who is not expected to survive without the operation

American Society of Anesthesiologists (2010).