Veterinary Anaesthesia

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Veterinary Anaesthesia

Eleventh Edition

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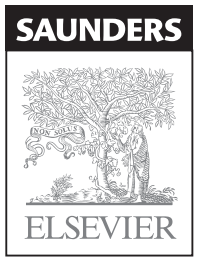

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Preface

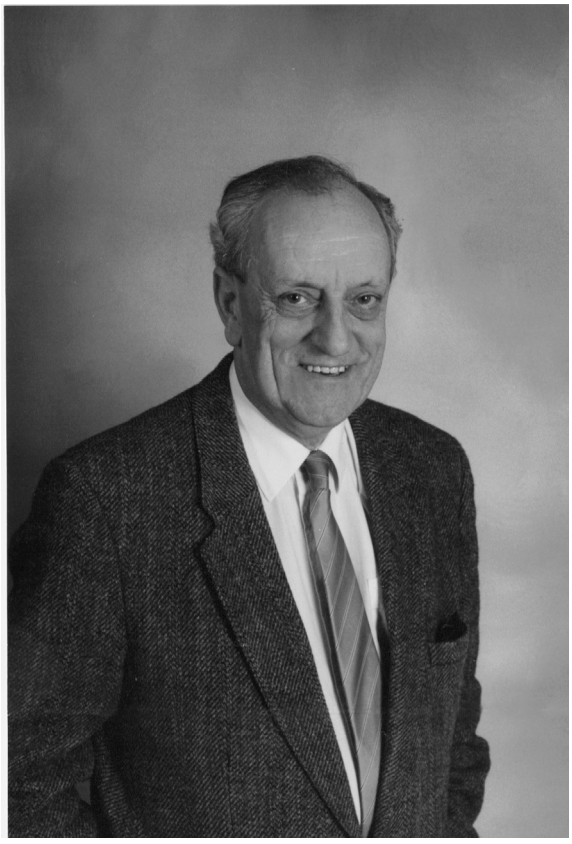
In this eleventh edition of *Veterinary Anaesthesia* we have attempted to continue Dr Leslie Hall's tradition of providing 'how to' advice on anaesthetizing animals. In addition, our goal has been to expand the evidence-based theme and provide published justification for most of our conclusions, particularly in relation to clinical advice, while also including information based on our own experiences. There are now hundreds of relevant published papers, and we have to acknowledge that in the space available we cannot cite all.

The aim of the book has always been to provide a text for veterinary students, a reference work for veterinarians in practice or working with laboratory animals, and a stimulating introduction to the subject for those wishing to specialize in veterinary anaesthesia. While following the format of previous editions, we have made several major changes in this edition. We have invited other authors to contribute chapters, and are grateful for their excellent reviews which provide added dimensions to the book. A chapter specifically devoted to analgesia recognizes the importance of pain relief and the major advances in the physiology and practice in this area. A new chapter is devoted to wild animal anaesthesia and another discusses anaesthetic management of small mammals, exotic pets and small wildlife. A chapter has been added to provide current information on cardiopulmonary cerebral resuscitation. We would also like to acknowledge valuable contributions to Chapter 1 by Craig Johnson (electroencephalography) and Daniel Pang (mechanisms of action of general anaesthetic agents) to ensure accuracy in these specialized and fast advancing areas.

We would wish to express our appreciation to David Gunn (AIIP) and to Charlotte Hall for many of the figures re-used from previous editions, and to those who have provided new figures for this edition and are acknowledged in the text. We also thank Kim Stevens and Flint Buchanan for their expert assistance with some of the figures. Our warmest thanks are due to the publishers for their patience, and in particular to Nicola Lally and Alison McMurdo for their constant encouragement. Finally, we must thank our families, who tolerated our constant 'absence', and carried out our day-to-day duties for us enabling us to concentrate on writing. Without them, the book would never have been completed.

K. W. Clarke
C. M. Trim

In memoriam



Leslie W. Hall (1927–2010)
MA, BSc, PhD, DVA, Dr (Hons Causa) Utrecht, DipECVAA, DipACVA (Hon), FRCA, FRCVS

Dr Leslie Hall's foresight and drive led to the development of veterinary anaesthesia as a speciality. His contributions to the veterinary profession as a scientist, clinician, teacher and author have been matched by very few.

Dr Hall qualified as a veterinary surgeon at the Royal Veterinary College, London in 1950, remaining there to obtain his PhD. At that time, anaesthesia was produced in most animals by administering large doses of the few drugs available, with no specific perianaesthetic care. He recognized that animals needed better care under anaesthesia and set out to address their most pressing needs.

Dr Hall developed suitable dosage regimens, promoted the use of endotracheal intubation, oxygen administration, and artificial ventilation. He also instituted the practice of monitoring the animals during and after anaesthesia and, importantly, began administering analgesics postoperatively, an approach that was not considered necessary for animals at that time.

Dr Hall then moved to Cambridge where he excelled as a scientist, a clinician and as a teacher and worked tirelessly to promote veterinary anaesthesia as a speciality. He developed liaisons with the human medical (physician) anaesthetists, and became an active member of their national and local associations. In 1977, he was honoured with the Faculty Medal of the Faculty of Anaesthesia of the Royal College of Surgeons and, in 2001, was awarded an Honorary Fellowship of the Royal College of Anaesthetists.

Of the many highlights in Dr Hall's career, we believe the following deserve specific mention. In 1964, with six of his colleagues, Dr Hall founded the Association of Veterinary Anaesthetists (AVA). This association now has members world-wide, and is the 'base society' for the European College of Veterinary Anaesthesia and Analgesia (ECVAA). On his retirement, Dr Hall was made an Honorary Fellow of AVA. Working with his colleague, Dr Barbara Weaver, Dr Hall helped develop the Diploma of Veterinary Anaesthesia (DVA) of the Royal College of Veterinary Surgeons, the first 'specialist' veterinary qualification in anaesthesia. For the first examination in 1968, they organized a syllabus, created a robust examination, and included a medical (physician) anaesthetist on the examination panel. The DVA provided the foundation for the current Diploma of the ECVAA and served as a model for the Diploma of the American College of Veterinary Anesthesia and Analgesia (ACVAA). Dr Hall was awarded an Honorary Diploma from the ACVAA in 1985.

While teaching at Cambridge, Dr Hall provided postgraduate training in veterinary anaesthesia through research scholarships and through a clinical position of University Assistant Anaesthetist, a post equivalent to what is now termed a 'Residency'. He also used his influence to establish a career structure for those who entered the speciality. For example, he convinced surgeons that their clinical practice and the outcomes of their patients would be improved by including a trained anaesthetist. He also promoted the concept to veterinary school administrators that future veterinary surgeons needed a high standard of anaesthesia training before venturing into practice. As a result, university positions of Lecturer (and later, Professorships) in Veterinary and Comparative Anaesthesia started to appear.

In 1982, under Dr Hall's guidance, the first International (now World) Congress of Veterinary Anaesthesia was held at Cambridge. Due to the overwhelming success of that meeting, Congresses have been held, in several continents, every three years since that time. In the mid-1990s, Dr Hall served as one of the founding members of the ECVAA, the authority that grants certification for the speciality of veterinary anaesthesia and analgesia in Europe.

Leslie Hall was not just a clinician – but a brilliant scientist – indeed, he believed strongly in what is now called 'evidence-based medicine'. He authored more than 80 papers now cited in PubMed, and many more in other veterinary journals. Much of his work focused on the physiological responses to anaesthesia, particularly in horses and many of his publications are now considered 'classics'. Examples of the latter include an investigation of muscle relaxants in dogs (1953), recognition of malignant hyperthermia in pigs (1966), and the first demonstration of ventilation/perfusion mismatch in the anaesthetized horse (1968). Many anaesthetic agents were introduced into veterinary practice as a direct result of his experimental work and clinical trials. Classical examples include the introduction of halothane (1957), xylazine (1969), alphaxalone (as Saffan) (1972, 1975), and propofol (1985, 1987). Dr Hall's vision was far-reaching and involved research students from all over the world.

In addition to his scientific publications, Leslie was author/joint author of many review articles and several books. For more than 50 years he served as the primary author of this book. However, he also published a small book 'Fluid balance in canine surgery' in 1967, which includes information from some otherwise unpublished research studies, and 'Anaesthesia of the cat' in 1994 in collaboration with Dr Polly Taylor.

Leslie Hall was a knowledgeable and enthusiastic teacher of anaesthesia to veterinary and postgraduate clinical and research students. His enthusiasm for his subject was infectious, and postgraduate students were impressed by his unique ability to link clinical care with evidence-based research, and with his integrity within his research, always looking for the reason for an unexpected result. He was a superb clinician, a self-confessed workaholic, a hard taskmaster but a loyal mentor.

He imparted knowledge regardless of the venue, whether it was the surgery theatre or the local pub. Furthermore, he did all this with loving support of his family.

Although Leslie Hall had many opportunities to move elsewhere and upwards in rank, he preferred to remain Reader in Comparative Anaesthesia at Cambridge. Despite this reticence, he received many honours in the UK and elsewhere, including honorary degrees from Utrecht and the RCVS, the Francis Hogg Prize for advancing small animal practice, the Livesey Medal for alleviating pain and fear in animals, the Blaine award from the British Small Animal Veterinary Association, and Fellowship from the RCVS by election.

A fitting summation of his influence and impact comes from a note from one of his previous postgraduate students, now a Professor:

'Leslie was responsible for setting clinical standards that were rigorous and science-based and those of us lucky enough to be taught by him were the fortunate beneficiaries. Of course, Leslie's home-made beer was also legendary!'

K. W. Clarke
Cynthia Trim

Parts of this Eulogy, and the picture, were published as an 'Obituary to Dr L.W. Hall', in Veterinary Anaesthesia and Analgesia 2010 (37): 387–389, published by Wiley-Blackwell.

Chapter 1

An introduction to anaesthesia and general considerations

INTRODUCTION

Anaesthesia is one of the greatest 'discoveries' there has ever been – there are few scientific advances which have reduced pain and suffering in so many people and animals. It is difficult to remember that the first anaesthetic was administered only in the 1840s (there is argument as to who was first to administer it clinically), although analgesics (for example opiates) have been available for many centuries. The term *anaesthesia* was coined by Oliver Wendell Holmes in 1846 to describe using ether to produce insensibility in a single word and it comes from the Greek 'without feeling'. The term 'analgesia' is Greek for 'without pain'.

While anaesthesia has precisely the same meaning as when it was first coined, i.e. the state in which an animal is insensible to pain resulting from the trauma of surgery, it is now used much more widely. Starting with the premise that 'pain is the conscious perception of a noxious stimulus', two conditions may be envisaged: *general anaesthesia* where the animal is unconscious and apparently unaware of its surroundings, and *analgesia* or *local anaesthesia* where the animal, although seemingly aware of its surroundings, shows diminished or no perception of pain. Perioperative analgesia, a subject once much neglected by veterinarians, is now recognized as an essential component of the process, and the physiology of pain and mechanisms of how it can be controlled and treated are discussed in Chapter 5, Analgesia.

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VETERINARY ANAESTHESIA

The clinical discipline of veterinary anaesthesia is essentially a practical subject based on science. In addition to the scientific base for human anaesthesia, the veterinarian has to contend with species differences, particularly in anatomy and in metabolism that effects the actions and elimination of drugs.

In clinical veterinary anaesthesia, the major requirements of the anaesthetist are:

- Humane treatment of the animal
  - This includes prevention of awareness of pain, relief of anxiety and sympathetic animal handling
- Provision of adequate conditions for the procedure
  - This includes adequate immobility and relaxation
  - Ensuring neither the animal, nor the personnel are injured in any way.

All patients require an adequate standard of monitoring (Chapter 2), and of general care throughout the anaesthetic process. However, other than this, there is a myriad of acceptable methods from which the anaesthetist can choose to satisfy the above aims. Certain drugs and/or systems may be put forward as 'best practice' but, in veterinary anaesthesia, there is rarely the 'evidence base' to prove that they are so. Choice of methods used may be limited by a number of factors. Legal requirements, which will depend on the country concerned, need to be observed. Examples include laws involving the control of dangerous drugs, or the choice of drugs in animals destined for human consumption. In the European Union, currently, the 'cascade' is a major barrier to anaesthetists' choice. This law implies that if there is a drug licensed for a species, it is criminal to use another unlicensed agent for the same purpose, unless the veterinary surgeon can prove that their alternative choice was justified for welfare of the specific individual animal concerned. Facilities may be limited, and while expense should not be the governing factor, it does need to be considered; animals throughout the world require anaesthesia and if the owners cannot afford the cost, the animal will be denied treatment. The objective of this book is to give the reader the information enabling them to make an informed choice of the best method of anaesthesia and care for their patient in their circumstances.

GENERAL ANAESTHESIA

General anaesthesia is and has been given many different definitions (reviewed by Urban & Bleckwenn, 2002), but a simple practical one that has been used in the previous editions of this book is 'the reversible controlled drug induced intoxication of the central nervous system (CNS) in which the patient neither perceives nor recalls noxious or painful stimuli'. Professors Rees and Grey (1950) introduced the concept that the requirements from general anaesthesia were analgesia, muscle relaxation and 'narcosis', these being known as the 'Liverpool Triad'. This idea has been expanded to add suppression of reflexes (motor and autonomic) and unconsciousness or at least amnesia and, most importantly, that these requirements should be achieved without causing harm to the patient. For over 100 years anaesthesia was achieved mainly with a single drug, most commonly ether. Now, as well as a number of anaesthetic drugs which are administered by inhalation as is ether (see Chapter 7), single-agent drugs that are given by injection (see Chapter 6) are also employed. However, in clinical practice, it is now usual to use many different agents, which act at multiple receptors, in the CNS and peripherally, in order to achieve the goals required to provide good anaesthesia.

Currently, when considering single-agent anaesthetics, many authorities now believe that the state of general anaesthesia requires only two features: immobility in response to noxious stimulation and amnesia (the latter often taken as unconsciousness) (Eger et al., 1997; Urban & Bleckwenn, 2002). The argument is that the immobility is required for surgery; if the patient is unconscious they cannot perceive pain (although the autonomic system may still react to noxious stimuli), and if they don't remember the pain, it is similar to lack of perception. This theory ignores evidence and theories relating to pain and hypersensitization as described in Chapter 5. However, it considers that analgesia is desirable but is not an essential feature of the state of 'general anaesthesia'. Thus the 'definition' of a single-agent anaesthetic drug, such as the injectable agent, propofol or the volatile anaesthetic agents is that they have these two actions of preventing movement and causing amnesia (Franks, 2006). Some compounds which from structure and lipophility might be expected to be anaesthetics can cause amnesia without immobility; these are sometimes termed 'non-anaesthetics' (Johansson & Zou, 2001), their major interest being related to studies of mechanism of anaesthetic action.

Mechanisms of action of general anaesthetic agents

The central nervous system control of the functions altered by anaesthesia and related drugs is incredibly complex. Sherrington in 1906 pointed out the importance of the synapse in the CNS in providing connections between multiple neuronal systems (Fig. 1.1). At synapses, transmission involves release of transmitter that will 'trigger' the action of the next neuron. Receptors sensitive to the transmitter may be postsynaptic, or presynaptic feeding back on the original nerve terminal and modulating further action. Transmitters act through two main types of receptor: ionotropic and metabotropic. With inotropic or

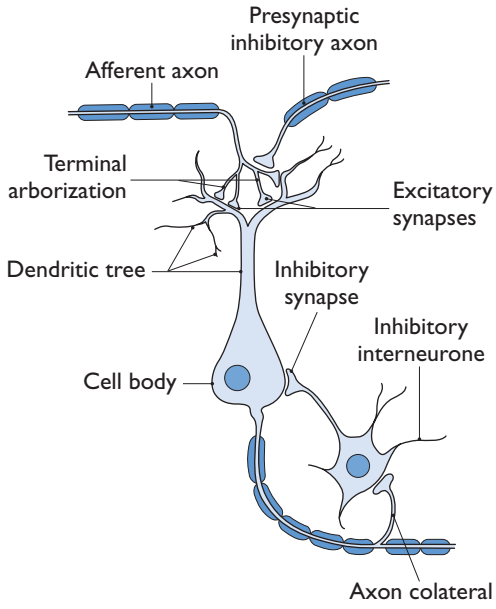

Figure 1.1 Schematic diagram of the organization of a synaptic relay within the CNS.

'ligand-gated' receptors, the transmitter binds directly with the ion-channel proteins, allowing the channel to open and the ions to pass. Binding of a transmitter to metabotropic receptors involves G-proteins as secondary messengers. Recent roles for voltage-gated channels, where changes in cellular membrane potential triggers a response, such as two-pore potassium channels have also been identified.

In the CNS, three major transmitters are considered most directly relevant to general anaesthesia. Gamma-amino-butyric acid (GABA) is inhibitory and decreases the excitability of neurons. Glycine is inhibitory in most circumstances and is the most important inhibitory transmitter at the spinal cord. The main excitatory transmitter in the CNS is glutamate. Anaesthetic drugs that are thought to act at the N-methyl d-aspartate (NMDA) receptor, one of at least three types of ligand-gated glutamate receptor, inhibit the effect of glutamate, thus again inhibiting the CNS. However, there are many other relevant transmitters, for example acetylcholine, dopamine, norepinephrine, endogenous opioids and others (Sonner et al., 2003) and their resultant actions may influence (modulate) the actions, directly or indirectly, of the GABA, glycine and glutamate pathways.

In the 1900s, for the inhalation agents (no injectable had been discovered), Meyer and Overton independently noted the correlation between anaesthetic potency and solubility in oil, which led to the 'lipid theory' that general anaesthetics acted through a non-specific mechanism by changing the lipid bilayer of nerve cells. There are exceptions which disprove the hypothesis but, nevertheless, for most the correlation is amazing, and this theory, with modifications, held sway until Franks and Lieb (1984) showed that inhalational general anaesthetics inhibited protein activity in the absence of lipids. This finding led to the explosion of studies on (a) where in the CNS anaesthetics act, (b) differences between motor and amnesic actions and, finally, (c) the molecular targets for action. (Franks (2006) quotes a review that cites 30 possible such targets.) All these three points are inextricably interlinked. A full discussion is beyond the remit of this book, but the following very simplified summary is based on reviews by Urban & Bleckwenn (2002), Sonner et al. (2003), Rudolph & Antikowiak (2004), Franks (2006) and Perouansky et al. (2012).

All anaesthetic agents do not act in the same way or in the same place. Classified by their mode and place of actions, there appear to be four main types of anaesthetic agent: (1) injectable agents such as propofol, etomidate and alfaxalone; (2) volatile anaesthetic agents such as halothane, isoflurane and sevoflurane; (3) the injectable dissociative agents such as ketamine; and (4) the gaseous agents, nitrous oxide and xenon.

It is now considered that the inhibition of motor actions occurs at the spinal cord, at least for the volatile anaesthetic agents, while amnesia and unconsciousness are the remit of the higher centres in the brain (Eger et al., 1997) – these two aspects of anaesthesia being separate. Most anaesthetics can cause amnesia at subhypnotic doses, although the relative dose for amnesia in relationship to that required for unconsciousness varies between drugs. The area of brain critical for amnesia appears to be the hippocampus and basal nucleus of the amygdala. Other centres are involved in the production of sedation and unconsciousness. For example, functional neuroimaging demonstrated that when propofol was administered at sedative doses and a noxious stimulus applied, evoked responses were attenuated only in the somatosensory cortex, but once doses reached hypnotic levels, thalamic and cortical responses ceased. Ketamine, a dissociative anaesthetic, however, did not depress sensory inflow through the thalamus. Perouansky et al. (2012) summarize by pointing out that anaesthesia is a very complex state, and that current evidence shows that general anaesthetics produce separate 'agent specific' substates, probably at different areas of the CNS.

Three very differing molecular targets have been suggested as the major sites of anaesthetic actions: $GABA_A$ receptors, NMDA receptors and glycine receptors. Anaesthetic drugs that act at the $GABA_A$ receptors are the classical IV anaesthetics; these potentiate the action of GABA, hence increase overall CNS inhibition. The volatile anaesthetic agents have similar actions at $GABA_A$ receptors in addition to actions at other targets, and their mode of action is more complex. Dissociative anaesthetics such as

ketamine and the gaseous anaesthetic agents are thought to be antagonistic at the NMDA receptor, thus blocking the action of the excitatory glutamate, but again, this does not explain all their actions.

A great deal is known about the $GABA_A$ receptor (there are also $GABA_B$ and $GABA_C$). It is a polymeric receptor with five subunits; there have been at least 30 types of subunit cloned so the potential for heterogenicity is enormous. Different arrangements of subunits are sensitive to different anaesthetic agents. For example, genetically engineered 'knock-out mice' in which one particular subunit was missing were insensitive to the anaesthetic effects of the steroid anaesthetic, alfaxalone, but not to propofol suggesting that these two apparently similar IV anaesthetics were working through different configurations of $GABA_A$ receptor. The mode of action of the volatile anaesthetic agents, in particular in the brain, is less proven (and more complex) than for the IV agents; the volatile anaesthetic agents do have some actions at the $GABA_A$ receptor but at a much lower potency. Subunits of $GABA_A$ essential for efficacy differ between the volatile and IV agents. It is thought that glycine receptors are involved in the actions of the volatile agents, in particular those in the spinal cord which inhibit movement. The reason for giving these examples (there are very many more) of differing modes of actions between apparently similar types of anaesthetics is to point out that to say 'an anaesthetic acts at the $GABA_A$ receptor' is certainly not the whole story.

Knowledge of the mode of action of the anaesthetics that work at the NMDA receptor is less well developed. The anaesthetics (ketamine and the gaseous agents) are thought to cause their effects on memory and consciousness at least partly through these receptors. Sonner et al. (2003) consider that NMDA receptors in the spinal cord might be a target for all inhalation anaesthetic agents (not just those those termed 'gaseous') in the production of immobility. However, once again, action at the NMDA receptor does not explain all the actions seen.

The methods of investigation used to study anaesthetic actions are multiple, and readers are referred to the reviews cited above. All reviews point out the number of other potential molecular, ion or voltage-gated possible sites which might be the target for anaesthetic action. Other routes of investigation have examined the modulating influence of alternative CNS pathways. Following the findings of Franks and Lieb (1984), it was anticipated that a (relatively) simple pharmacological pathway for anaesthetic action might be found to explain anaesthetic actions, as has been for many other systems (e.g. opioids, see Chapter 5, α_2-adrenoceptor agonists, see Chapter 4). This has not happened, although our knowledge is greatly expanded. However, we have yet really to know how general anaesthetics work, and indeed Sonner et al. (2003) raise a question that, at least for volatile agents, some variant of the Overton–Meyer lipid theory may yet play a partial role.

DEPTH OF ANAESTHESIA

Many authorities consider that 'depth of anaesthesia' is impossible to define, but anaesthesiologists need some guidelines to ensure that the patient comes to no harm. Only two years after the first demonstration of general anaesthesia, John Snow (1847) stated, quite emphatically, that the point requiring most skill in the administration of anaesthetics is to determine when it has been carried far enough. Snow described five stages of anaesthesia produced by diethyl ether, the last stage in his experiments with animals being characterized by feeble and irregular respiratory movements heralding death – clearly a stage too far. A major problem faced by all anaesthetists since that time is to avoid both 'too light' anaesthesia with the risk of sudden violent movement, and the dangerous 'too deep' stage. Snow suggested guidelines whereby anaesthetists could reduce the risk of either too light or too deep ether anaesthesia. Guedel, in 1918, devised a scheme involving observation of changes in respiratory rate, limb movement and eye signs which formed the basis of his celebrated 'Signs and Stages of Ether Anaesthesia' which has been included until very recently in all text books of anaesthesia, and is the basis for that described in Chapter 2.

The introduction of neuromuscular blocking drugs, which remove all the somatic responses on which Guedel's scheme is based, completely changed the picture and the emphasis swung from the danger of too deep anaesthesia to that of too light anaesthesia with the risk of conscious awareness and perception of pain. Cullen et al. (1972), in an attempt to produce new guidelines indicating depth of anaesthesia, were forced to conclude that it was difficult to categorize the clinical signs of anaesthesia for any one inhalation anaesthetic let alone for inhalation agents in general. The signs also differed markedly when the dissociative anaesthetic agents such as ketamine were used. Today a very much broader range of different drugs are employed during anaesthesia. These include agents to give analgesia, amnesia, unconsciousness and relaxation of skeletal muscles as well as suppression of somatic, cardiovascular, respiratory and hormonal responses to surgical stimulation. All may influence the classical signs of 'depth' of anaesthesia.

Electroencephalography (EEG)

It is only possible to describe the EEG changes related to anaesthesia in the most general terms. The responsive alpha rhythm associated with awareness changes on induction of anaesthesia in terms of frequency and amplitude. The most common pattern seen with light general anaesthesia has low amplitude and is dominated by high frequency activity; it is often referred to as desynchronized. Increasing concentrations of anaesthetics tend to produce

increasing amplitude and decreasing frequency, a phenomenon known as synchronization. In addition, some anaesthetics produce periods of burst suppression where the EEG is isoelectric, repetitive high amplitude spikes and complexes or even the epileptoid activity characteristic of the anaesthetic ethers.

The majority of attempts to monitor the depth of anaesthesia objectively have focused on the EEG, but the raw data are of limited practical value to the clinical anaesthetist. To simplify the extraction of useful information from complex waveforms, a number of methods of compressing, processing and displaying EEG signals have been developed and these techniques have, in many cases, been applied to a limited number of channels of EEG rather than the 16 channels normally studied.

Power spectrum analysis

In this technique, the EEG signal, after being digitalized, is subjected to Fast Fourier Transformation (FFT) in which it is separated into a series of sine waves. The sum of these sine waves represents the original integrated signal. Breaking up the original waveform in this way makes it possible to compare one non-standard wave form with another and, in particular, to extract the distribution of components of different frequency within the EEG signal. The power in each frequency band is derived from the sum of the squares of the amplitude of the sine waves into which the FFT has separated the original signal. Power spectrum analysis has been used in a number of experimental situations related to veterinary anaesthesia (e.g. Otto & Short, 1991; Murrell et al., 2003; Johnson et al., 2005, 2009).

Cerebral function monitors

A number of monitors, including the Bispectral Index (BIS), the Cerebral Function Monitor (CFM) and the Patient State Index (PSI) feed the EEG signals from a limited number of leads into a 'black box' which, on the basis of an algorithm derived from analysis of EEGs from a large number of human patients, produces a number which is related to depth of anaesthesia. All these monitors have a number of limitations in clinical use. They may be influenced by other electrical 'noise' such as the electromyogram (EMG). The algorithms are based mainly on anaesthetic drugs that have their hypnotic effect through actions at the $GABA_A$ receptors. The monitors are ineffective for the anaesthetic agents that act at the NMDA receptors such as nitrous oxide, xenon or ketamine. Of great concern is the fact that when neuromuscular blocking drugs were given to conscious human volunteers, BIS reduced to values suggestive of very deep anaesthesia (Messner et al., 2003). The use of these monitors may reduce the incidence of awareness under anaesthesia but has not eliminated it. The most common of these monitors is the BIS; its use and limitations in veterinary anaesthesia are described in Chapter 2.

Evoked responses

Evoked responses are changes in the EEG produced by external stimuli, surgical or otherwise. Anaesthetic depth is a balance between cerebral depression and surgical (or other) stimulation. Thus, cerebral function during anaesthesia is most easily assessed by putting in a stimulus – auditory or somatic or visual – and observing the EEG response. That response can then be compared for amplitude and latency with the response to the same stimulus in the presence of differing brain concentrations of any anaesthetic. Evoked responses can be used as monitors of anaesthetic depth when agents acting at the NMDA receptor are being employed.

The 'classic' signs of anaesthesia

Use of the term 'depth of anaesthesia' is now so ingrained in common usage that it must be accepted since it probably cannot be eradicated. It is important, however, to realize that it commonly refers to depression of brain function beyond that necessary for the production of 'general anaesthesia'.

The so-called 'classic signs' of anaesthesia, such as described in Chapter 2 for convenience of newcomers to the subject, were provided by the presence or absence of response of the anaesthetized subject to stimuli provided by the anaesthetist or surgeon. Particular signs of anaesthesia were, therefore, equated with particular anatomical levels or 'planes' of depression of the central nervous system. These signs were often likened to a series of landmarks used to assess the progress made on a journey. Such empirical, traditional methods of assessing the progress of anaesthesia and the anatomical implications that went with these methods incorporated a fallacy, because they took no account of the fact that the changing function of any biological system can only be made in terms of magnitude and time. A depth of unconsciousness is really a particular moment in a continuous temporal stream of biological or neurological phenomena to be interpreted by the magnitude and quality of these phenomena obtaining to that moment.

In general, the volatile anaesthetic agents halothane, enflurane, isoflurane, sevoflurane and desflurane produce a dose-dependent decrease in arterial blood pressure and many veterinary anaesthetists use this depression to assess the depth of anaesthesia. The effect is not so marked during anaesthetic techniques involving the administration of opioid analgesics and nitrous oxide. If the depth of unconsciousness is adequate, surgical stimulation does not cause any change in arterial blood pressure. There are, however, many other factors which influence the arterial blood pressure during surgery such as the circulating blood volume, cardiac output and the influence of drug therapy given before anaesthesia. If ketamine or high doses of opioids are given, arterial blood pressure may

change very little if the depth of unconsciousness is increased by the administration of higher concentrations of inhalation anaesthetics.

Changes in heart rate alone are a poor guide to changes in the depth of unconsciousness. The heart rate may increase under isoflurane and desflurane anaesthesia due to the agents' effects. Arrhythmias are common during light levels of unconsciousness induced by halothane, when they are usually due to increased sympathetic activity. In general, however, tachycardia in the absence of any other cause may be taken to represent inadequate anaesthesia for the procedure being undertaken.

Anaesthetic agents affect respiration in a dose-dependent manner and this was responsible for the original classification of the 'depth of anaesthesia'. In deeply anaesthetized animals, tidal and minute volumes are decreased but, depending on the species of animal and on the anaesthetic agents used, respiratory rate may increase before breathing eventually ceases once the animal is close to death. As inadequate anaesthesia also is often indicated by an increase in the rate and/or depth of breathing the unwary may be tempted to administer more anaesthetic agent to the deeply anaesthetized animal in the mistaken impression that awareness is imminent. Laryngospasm, coughing or breath-holding can indicate excessive airway stimulation or inadequate depth of unconsciousness.

All anaesthetic agents, other than the dissociative drugs such as ketamine, cause a dose-related reduction in muscle tone and overdosage produces complete respiratory muscle paralysis. In the absence of complete neuromuscular block produced by neuromuscular blocking drugs, the degree of muscle relaxation may, therefore, usually be used as a measure of the depth of anaesthetic-induced unconsciousness. However, even in the presence of muscular paralysis due to clinically effective doses of neuromuscular blockers, it is not uncommon to observe movements of facial muscles, swallowing or chewing movements in response to surgical stimulation if the depth of unconsciousness becomes inadequate.

When animals are breathing spontaneously, there are several signs which are generally recognized as indicating that the depth of unconsciousness is adequate for the performance of painful procedures, i.e. the animal is unaware of the environment and of the infliction of pain – it is anaesthetized.

Unfortunately, there are many differences between the various species of animal in the signs which are usually used to estimate the depth of unconsciousness. One fairly reliable sign is that of eyeball movement, especially in horses and cattle, although even this may be modified in the presence of certain other drugs, such as the α_2-adrenoceptor agents (see Chapter 11). Unless neuromuscular blocking drugs are in use, very slow nystagmus in both horses and cattle and downward inclination of the eyeballs in pigs and dogs usually indicates a satisfactory level of unconsciousness and, at this level, breathing should be smooth although its rate and depth may alter depending on the prevailing severity of the surgical stimulation. Rapid nystagmus is usually a sign that anaesthesia is light but it is a common feature of ketamine anaesthesia and it also seen sometimes seen in horses just before death. Absence of the lash or palpebral reflex (closure of the eyelids in response to light stroking of the eyelashes) is another reasonably reliable guide to satisfactory anaesthesia. In dogs and cats, it is safe to assume that if the mouth can be opened without provoking yawning or curling of the tongue, central depression is adequate. In all animals, salivation and excessive lacrimation usually indicate a returning awareness.

Disappearance of head shaking or whisker twitching in response to gentle scratching of the inside of the ear pinna is a good sign of unawareness in pigs, cats, rabbits and guinea pigs. Pupil size is a most unreliable guide to anaesthetic depth as various ancillary agents (e.g. opioids, atropine) may influence it. The pupils do, however, dilate when an overdose of an anaesthetic has been given or when awareness is imminent.

The experienced anaesthetist relies most of the time on an animal's response to stimuli produced by the surgeon or procedure to indicate adequate depth of unconsciousness. The most effective depth is taken to be that which obliterates the animal's response to pain and/or discomfort without depressing respiratory and circulatory function.

Computer control in anaesthesia

With the current sophistication of computers, there have been many attempts to obtain a method of anaesthesia totally controlled by the computer; various parameters being monitored, results fed back into the system, and the system then altering the dose of anaesthetic administered accordingly – i.e. a closed-loop system.

The use of computers (including microprocessors) has improved many aspects of anaesthesia. Monitoring can be more sophisticated, and give more accurate results. Ventilators can be programmed to provide very specific requirements of, for example, tidal volume, or respiratory pressures. Constant infusion pumps provide a very accurate flow rate which is useful for fluid administration, but also can be utilized to provide targeted plasma levels of intravenous anaesthetic agents (this is known as Target Controlled Infusion or TCI). The most validated versions of this are the Propofusor® and the Remifusor®, which will deliver infusions to achieve set plasma levels of propofol and remifentanil respectively. Their programming is based on a very accurate knowledge of the pharmacokinetics in humans of these drugs so their algorithms are not necessarily correct for other animals, although the Propofusor has been modified successfully for use in dogs (Beths et al., 2001; Musk et al., 2006). There is computer-software available to use with other agents (RugloopII); it can be

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).

General considerations in the selection of the anaesthetic method

The first consideration will be the nature of the operation to be performed, its magnitude, site and duration. In general, the use of local infiltration analgesia may suffice for simple operations such as the incision of superficial abscesses, the excision of small neoplasms, biopsies and the castration of immature animals. Nevertheless, what seems to be a simple interference may have special anaesthetic requirements. Subdermal fibrosis may make local infiltration impossible to effect. Again, the site of the operation in relation to the complexity of the structures in its vicinity may render operation under local analgesia dangerous because of possible movement by the conscious animal, e.g. operations in the vicinity of the eyes.

When adopting general anaesthesia, the likely duration of the procedure to be performed will influence the selection of the anaesthetic. Minor, very short operations may be performed after IV administration of a small dose of an agent such as propofol or thiopental sodium. For longer operations, anaesthesia may be induced with an ultrashort acting agent and maintained with an inhalation agent with or without endotracheal intubation. However, the ability to perform endotracheal intubation, to administer oxygen and to apply some form of ventilation must always be available and to hand for use should an emergency arise. Similarly, the fact that anaesthesia is brief does not remove the need for minimal monitoring. For most operations under general anaesthesia, preanaesthetic medication ('premedication') will need to be considered, particularly when they are of long duration and the animal must remain quiet and pain-free for several hours after the operation. Undesirable effects of certain agents (e.g. ketamine) may need to be countered by the administration of 'correcting' agents (e.g. α_2-adrenoceptor agonists, atropine). Although sedative premedication may significantly reduce the amount of general anaesthetic required, it may also increase the duration of recovery from anaesthesia.

The species of animal involved is a pre-eminent consideration in the selection of the anaesthetic method (see later chapters). The anaesthetist will be influenced not only by size and temperament but also by any anatomical or physiological features peculiar to a particular species or breed. Experience indicates that the larger the animal, the greater are the difficulties and dangers associated with the induction and maintenance of general anaesthesia. Methods which are safe and satisfactory for the dog and cat may be quite unsuitable for horses and cattle. In vigorous and heavy creatures the mere upset of locomotor coordination may entail risks, as also may prolonged recumbency.

Individual animals

The variable reaction of the different species of animals, and of individuals, to the various agents administered by anaesthetists will also influence the choice of anaesthetic technique. In addition, factors causing increased susceptibility to the toxic actions of anaesthetic agents must be borne in mind. These include:

1. Prolonged fasting. This, by depleting the glycogen reserves of the liver, greatly reduces its detoxicating power and when using parenterally administered agents in computed doses, allowance must be made for increased susceptibility to them.
2. Diseased conditions. Toxaemia causes degenerative changes in parenchymatous organs, particularly the liver and the heart, and great care must be taken in giving computed doses of agents to toxaemic subjects. Quite often it is found that a toxaemic animal requires very much less than the 'normal' dose. Toxaemia may also be associated with a slowing of the circulation and unless this is recognized it may lead to gross overdosing of IV anaesthetics.

EVALUATION OF THE PATIENT BEFORE ANAESTHESIA

It is probable that most veterinary operations are performed on normal, healthy animals. The subjects are generally young and represent good 'anaesthetic risks'. Nevertheless, enquiry should be made to ensure that they are normal and healthy – bright, vigorous and of hearty appetite. Should there be any doubt, operations are best delayed until there is assurance on this point. Many a reputation has been damaged by performing simple operations on young animals which are in the early stages of some acute infectious disease or which possess some congenital abnormality.

When an operation is to be performed for the relief of disease, considerable care must be exercised in assessing the factors which may influence the choice or course of the anaesthetic. Once these are recognized, the appropriate type of anaesthesia can be chosen and preoperative measures adopted to diminish or, where possible, prevent complications. The commonest conditions affecting the course of anaesthesia are those involving the cardiovascular and respiratory systems, but the state of the liver and kidneys cannot be ignored.

The owner or attendant should always be asked whether the animal has a cough. A soft, moist cough is associated with airway secretions that may give rise to respiratory obstruction and lung collapse when the cough reflex is suppressed by general anaesthesia. Severe cardiovascular disease may be almost unnoticed by the owner and enquiry should be made to determine whether the animal appears to suffer from respiratory distress after exertion, or indeed appears unwilling to take exercise,

since these signs may precede other signs of cardiac and respiratory failure by many months or even years. Dyspnoea is generally the first sign of left ventricular failure and a history of excessive thirst may indicate the existence of advanced renal disease, diabetes mellitus or diabetes insipidus.

The actual examination may be restricted to one which is informative yet will not consume too much time nor unduly disturb the animal. While a more complete examination may sometimes be necessary, attention should always be paid to the pulse, the position of the apex beat of the heart, the presence of cardiac thrills, the heart sounds and the jugular venous pressure. Examination of the urine for the presence of albumin and reducing substances may also be useful.

Tachycardia is to be expected in all febrile and in many wasting diseases and, under these circumstances, is indicative of some myocardial weakness. It can, however, also be due to nervousness and where this is so it is often associated with rather cold ears and/or feet. Bradycardia may be physiological or it may indicate complete atrioventricular block. In horses, atrioventricular block that disappears with exercise is probably of no clinical significance. In all animals, the electrocardiogram may be the only way of determining whether bradycardia is physiological or is due to conduction block in the heart.

The jugular venous pressure is also important. When the animal is standing and the head is held so that the neck is at an angle of about 45° to the horizontal, distension of the jugular veins should, in normal animals, be just visible at the base of the neck. When the distension rises above this level, even in the absence of other signs, it indicates an obstruction to the cranial vena cava or a rise in right atrial or ventricular pressures. The commonest cause of a rise in pressure in these chambers is probably right ventricular hypertrophy associated with chronic lung disease, although congenital conditions such as atrial septal defects may also be indicated by this sign and it should be remembered that cattle suffering from constrictive pericarditis, or bacterial endocarditis, may have a marked increase in venous pressure.

The presence of a thrill over the heart is always a sign of cardiovascular disease and suggests an increased risk of complications arising during anaesthesia. More detailed cardiological examination is warranted when a cardiac thrill is detected during the preoperative examination.

Auscultation of the heart should never be omitted, particularly when the animal's owner is present because owners expect this to be carried out. Accurate location of the apex beat is an important observation in assessing the state of the cardiovascular and respiratory systems. It is displaced in many abnormal conditions of the lungs (e.g. pleural effusion, pneumothorax, lung collapse) and in the presence of enlargement of the left ventricle. In the absence of any pulmonary disorder, a displaced apex beat indicates cardiac hypertrophy or dilatation.

Pulmonary disorders provide particular hazards for an animal undergoing operation and any examination, no matter how brief, must be designed to disclose their presence or absence. On auscultation, attention should be directed towards the length of the expiratory sounds and the discovery of any rhonchi or crepitations. If rhonchi or crepitations are heard, excessive sputum is present, and the animal is either suffering from, or has recently suffered, a pulmonary infection. Prolongation of the expiratory sounds, especially when accompanied by high-pitched rhonchi, indicate narrowing of the airways or bronchospasm. Respiratory sounds may be absent in animals with pneumothorax, extensive lung consolidation, or severe emphysema; they are usually faint in moribund animals.

Uneven movement between the two sides of the chest is a reliable sign of pulmonary disease and one which is easily and quickly observed. The animal should be positioned squarely while the examiner stands directly in front of it and then directly behind it. In small animals, uneven movement of the two sides of the chest is often better appreciated by palpation rather than by inspection.

The mouth should be examined for the presence of loose teeth which might become dislodged during general anaesthesia and enter the tracheobronchial tree. Other mucous membranes should be inspected for evidence of anaemia, denoted by paleness.

Biochemical tests prior to anaesthesia

The question as to whether preanaesthetic urine and blood analysis should be performed routinely before every elective anaesthetic is, and has always been, controversial. While targeted tests are essential to confirm or exclude disease conditions suspected as a result of clinical history and examination, the cost/benefit of their use in animals which appear perfectly healthy can be argued on the basis that the results rarely would alter the anaesthetic protocol to be employed. Urine testing is simple, inexpensive and is particularly important in dogs for, in these animals, renal disease and previously undiagnosed diabetes mellitus are common. Urine samples may be less readily obtainable from other species of animal. The Association of Veterinary Anaesthetists (AVA) debated (Spring Meeting, 1998) the question as to the need for routine preanaesthetic checks on haematological and biochemical profiles, and voted that they were unnecessary if the clinical examination was adequate. In a more recent AVA debate led by medical anaesthetists, they pointed out that a major disadvantage of non-targeted screening was 'over-diagnosis' when an apparent abnormality of no significance was found. An advantage of prescreening, however, is that abnormalities occurring early in the course of a disease without current clinical symptoms may be identified. These values then become the baseline for comparison if abnormalities occur following anaesthesia and surgery. There may well be a place for routine screening older

animals. Although in a very occasional case (e.g. the detection of a partial hepato-portal shunt in a young dog) biochemical tests may detect an unsuspected disease state, in the vast majority of young apparently fit healthy animals, they constitute an unnecessary expense and, indeed, the extra cost involved may prevent an owner from agreeing to continuation of treatment necessary for the well-being of the patient.

Provided a brief examination such as that described is carried out thoroughly, and that the examiner has sufficient skill and experience to recognize the significance or lack of significance of the findings, most of the conditions that have a bearing on the well-being of an animal in the perioperative period will be brought to light so that appropriate measures can be taken to protect it from harm.

SIGNIFICANCE OF CONDITIONS FOUND BY PREANAESTHETIC EXAMINATION

Cardiovascular and respiratory disease

The cardiovascular and respiratory systems are those which govern the rate at which oxygen can be made available to the tissues of the body. Oxygen supply is equal to the product of the cardiac output and the oxygen content of the arterial blood. Since the arterial oxygen content approximates to the product of the oxygen saturation and the quantity of oxygen which can be carried by the haemoglobin (about 1.34 mL/g of haemoglobin when fully saturated), the oxygen made available to the body can be expressed by a simple equation:

$$\text{Available oxygen (mL/min)} = \text{cardiac output (mL/min)} \times \text{arterial saturation (\%)} \times \text{haemoglobin (g/mL)} \times 1.34$$

This equation makes no allowance for the small quantity of oxygen which is carried in physical solution in the plasma, but it serves to illustrate the way in which three variables combine to produce an effect which is often greater than is commonly supposed. If any one of the three determining variables on the right-hand side of the equation is changed, the rate at which oxygen is made available to the tissues of the body is altered proportionately. Thus, if the cardiac output is halved, the available oxygen is also halved. If two determinants are lowered simultaneously while the third remains constant, the effect on the available oxygen is the product of the individual changes. For example, if the cardiac output and the haemoglobin concentration are both halved while the arterial oxygen saturation remains at about the normal 95%, only one-quarter of the normal amount of oxygen is made available to the body tissues. If all three variables are reduced the effect is, of course, even more dramatic.

Drug metabolism and disease states

Drugs are usually metabolized through several pathways so that they are changed from fat-soluble, active, unexcretable drugs into water-soluble, inactive drugs that can be excreted by the kidneys and in the bile. Since the mammalian body metabolizes many thousands of compounds every day and has far fewer enzymes, each enzyme metabolizes many substrates. Only very rarely, if ever, will one enzyme metabolize only one substrate. Many things change enzyme function. Mechanisms for enzyme induction are poorly understood, unlike inhibition, which has been much more extensively studied. Enzyme induction is a slow process involving an increased amount of enzyme in the cell over about 24 to 48 hours, whereas inhibition is quick and sometimes occurs after only one dose of an inhibitor. Since enzymes are proteins their concentrations inside cells may be changed by a variety of factors (Fig. 1.2).

There is now an increasing amount of information about how enzymes change in response to one stressful stimulus but it is important to recognize that usually several stimuli exist at the same time in each critically ill animal. Most chemical reactions are sensitive to temperature, speeding up as the temperature increases and slowing

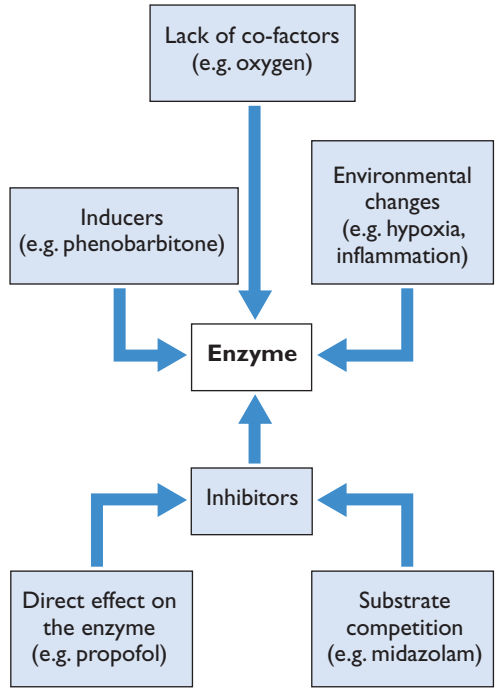

Figure 1.2 Factors which may change enzyme function.