Concepts and correlations relevant to general anaesthesia

B. W. Urban* and M. Bleckwenn

Klinik für Anästhesiologie und spezielle Intensivmedizin, Universitätsklinikum Bonn, Sigmund-Freud-Straße 25, D-53127 Bonn, Germany

*Corresponding author

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Why search for mechanisms of anaesthesia?

General anaesthesia has become so safe since its introduction just over 150 years ago that the risk associated with it has become almost immeasurably small: less than one death solely attributable to anaesthesia occurs per 200 000 procedures.16 This progress has been achieved in the absence of generally accepted hypotheses for the mechanisms of general anaesthesia. Does it matter whether mechanisms of anaesthesia are understood?

Providing more anaesthetic than is necessary is best avoided, as are the side-effects of anaesthetic procedures, but how little anaesthetic is sufficient? Patients are anxious that they might not wake up from anaesthesia but they are also very concerned that they may wake up during the surgical procedure. Awareness during general anaesthesia has become much more of a problem with the introduction of new (such as total intravenous) anaesthesia techniques. How can clinical outcome from different anaesthesia procedures (perioperative awareness, postoperative pain, emesis or recovery from surgery) be compared unless there are ways to quantitatively establish that these different procedures were identical in the level of anaesthesia they provided? There is a lack of devices that can monitor the level, or ‘depth’, of anaesthesia adequate for surgery. However, before an anaesthesia monitor can be constructed it must be clear what anaesthesia-related quantity the monitor should measure. This requires an understanding of the mechanisms of anaesthesia.

Concepts and correlations that are relevant to the study of mechanisms of anaesthesia will be discussed first. A number of concepts mentioned in this review were discussed by Overton more than a hundred years ago, some of which unfortunately seem to have been forgotten. In order not to re-invent the wheel, Overton’s book33 39 is still a book worth reading. However, we have made substantial progress in understanding and in experimental technology and have appreciated that the topic of general anaesthesia is much more complex than Overton could have been aware of. Subsequent reviews will present new scientific insights resulting from and in connection with the Sixth International Conference on Molecular and Basic Mechanisms of Anaesthesia (MAC2001), while the final review summarizes these findings on targets and mechanisms of anaesthetic actions and evaluates their implications for theories of anaesthesia. Concepts addressed at the conference and in these reviews have been brought together here in this first review. They may also help young researchers entering this field to be less naïve about the field than we were when we first entered it.

Concepts for defining general anaesthesia

Why try to define general anaesthesia? Because experience shows that different people use different definitions, as happened during MAC2001. How can we monitor something that has not been defined? How can we investigate mechanisms of general anaesthesia before we have spelled out what general anaesthesia is? Does it make sense trying to answer a question before it has been properly phrased? What is the phenomenon we are trying to investigate? How can we eliminate anaesthetic studies as irrelevant for general anaesthesia when there is no agreement as to what the essential features of general anaesthesia are? Thus there seems to be a real need to discuss concepts, as was done during MAC2001.

Historic and semantic definition of anaesthesia

The discovery of ether anaesthesia was the result of a search for means of eliminating a patient’s pain perception and
responses to painful stimuli. The expression ‘etherization’ was used initially to describe the pharmacological procedure of letting a patient inhale diethyl ether before surgery. Trying to give the procedure of etherization a name proved difficult as no single term appeared to describe the full effect. The terms anaesthesia (Greek: without feeling) and narcosis (Greek: stupor, paralysis) were introduced soon after the discovery of etherization. These terms highlight two different aspects: etherization renders a patient motionless (narcosis) and free of unpleasant and harmful sensation (anaesthesia). In order to describe these two aspects within one word Woodbridge a century later suggested the term ‘nothria’, which translated from the Greek means torpor (i.e. mental and motor inactivity with insensibility).

As Antognini points out, patients then had no a priori expectation that they should be unconscious but their hope was to be free of pain. Diethyl ether, chloroform and many other subsequent inhalation anaesthetics had the property that patients became unconscious before experiencing significant or complete analgesia. Unconsciousness was soon considered to be an important and desirable aspect of general anaesthesia as, from a practical aspect, unconscious patients were not anxious and did not remember pain.

However, the aspect of not injuring the patient during general anaesthesia is still not included, an aspect which, some 50 years after its discovery, Overton considered important when he called narcosis a state in which a patient was insensitive to surgical intervention without being harmed. Green, also considering the existing terminology too narrow, advocated a liberation from a 150-year-old semantic cul-de-sac and suggested the term metesthesia, something above and beyond an-aesthesia (without sensation). Saidman thought neither anaesthesia nor metesthesia was sufficient to describe the totality of what the specialty does (or should do) and suggested instead the term perioperative medicine and pain management (PMPM). This wrestling with terminology up to the modern day clearly indicates that the definitions from the past are still considered inadequate.

**Clinical definition of anaesthesia**

**Definition by professional bodies of anaesthesiology**

The modern definition of anaesthesiology provided by the American Board of Anesthesiology states that anaesthesiology is the practice of medicine providing insensibility to pain during surgical, obstetric, therapeutic and diagnostic procedures. It also emphasizes that anaesthesiology monitors and restores homeostasis during the perioperative period (i.e. it ensures that the patient suffers no harm during the operation).

Insensibility to pain as demanded by the American Board of Anaesthesiology does not necessarily imply unconsciousness or total unawareness and lack of sensation. Insensibility to pain may also be provided by local anaesthesia (Fig. 1), where the anaesthetic drug is usually injected into the tissue to numb only the specific location in the body requiring minor surgery, or by regional anaesthesia, where an injection is made near a cluster of nerves to numb the area of the body that requires surgery. In these procedures patients may remain awake, or they may be given a sedative. In general anaesthesia, according to the American Society of Anaesthesiologists, the patient is unconscious and has no awareness or other sensations while, in addition, the patient
is carefully monitored, controlled and treated by the anaesthesiologist.

In vain the curious reader searches the index and contents of one of the leading textbooks of anaesthesiology for a more detailed definition of general anaesthesia than given above, explaining what treating, controlling or not harming the patient implies. What are the essential clinical components of general anaesthesia?

**Definition of general anaesthesia by clinical effect**

The fact that right from the beginning two terms, anaesthesia and narcosis, were coined in an attempt to explain what happened during etherization clearly shows that what we now call general anaesthesia consists of more than one component. The terms narcosis and anaesthesia emphasize the aspects of immobility and of insensibility, including analgesia. Overton agreed that there were several components to narcosis and he implied that it involved unconsciousness and not harming the patient in addition to analgesia.

What did speakers at MAC2001 think about anaesthesia consisting of immobility, analgesia, unconsciousness and ‘not harming the patient’? Of these four components Eger, the originator of the minimum alveolar concentration (MAC) concept now considered as essential for general anaesthesia, only amnesia and immobility, while originally he had included analgesia as an essential property of anaesthesia. The surgeon cannot operate when the patient moves. A patient remembering pain during surgery will most likely not return for another surgical procedure and others will be dissuaded by such an experience. Will it be sufficient if the patient is amnesic and does not remember the surgical trauma? This view was hotly contested by others: Antognini and Heinke define general anaesthesia as the presence of unconsciousness, amnesia and immobility (in response to noxious stimulation); Antognini explicitly excludes analgesia and lack of haemodynamic responses as an absolute requirement. He reasons that pain is the conscious awareness of a noxious stimulus; therefore, if anaesthetized patients are unconscious, they cannot perceive pain. However, even if the patient does not have explicit memory of such an event, might implicit memory cause psychological trauma or chronic pain? In response to tissue damage there is not only a direct response of pain receptors but also a release of cellular factors such as prostaglandins and other cellular mediators. Lynch does add analgesia and cardiovascular stability to immobilization and amnesia.

Does the patient have to be unconscious? Lynch finds that loss of implicit or explicit recall might be considered to be equivalent to amnesia, albeit harder to measure than responsiveness as assessed by MAC-awake. The studies of Artusio demonstrated that heart surgery was possible on conscious patients as long as there was adequate suppression of pain during the surgical procedures. Hug considers a different combination and adds a new element when he states that, in most clinical situations, the objectives of general anaesthesia include the triad of unconsciousness, muscular relaxation and suppression of reflex responses to noxious surgical stimuli.

Thus there is consensus that general anaesthesia consists of several components, but which ones are essential? There may be agreement on a general definition of general anaesthesia, ‘general anaesthesia then might be viewed as a pharmacological intervention used to prevent psychological and somatic adverse effects of surgical trauma and also to create convenient conditions for surgery’, but there does not seem to be agreement on specifics. There is no single pharmacological-induced physiological state that we will call general anaesthesia. The spectrum of pharmacological actions used in the intervention can include the components shown in Figure 2. The spectrum of these actions can vary in accordance with the goal of anaesthesia; they contain not only actions to be achieved but also those to be avoided (side-effects). However, as Antognini points out, what are non-essential but desirable goals and what are the essential goals of general anaesthesia may well depend on the perspective of the ‘definer’. Thus, preceding any evaluation as to whether targets or mechanisms are relevant for general anaesthesia must be a statement on which components essentially belong to it.

**Definition of general anaesthesia by clinical procedure**

There appears to exist no consensus defining general anaesthesia by its (essential) clinical effects. Perhaps general anaesthesia (i.e. the result of a general anaesthetic procedure) has to be defined by the procedure itself, as was done in the beginning when the term etherization was used.
Whilst failing to provide a definition of general anaesthesia, the same leading textbooks of anaesthesia describe many general anaesthetic techniques that are adapted to a great number of surgical scenarios (Fig. 1). Anaesthetic procedures have greatly increased with time. Single-agent anaesthesia is rarely administered any more, if at all. One of

Fig 3 CPK models of (A) inhalation anaesthetics and (B) intravenous anaesthetics.
the main reasons for this development is that every general anaesthetic that has been examined produces undesirable clinical side-effects. This is one of the main reasons why so many experimental anaesthetics never make it into clinical practice. Overton, anticipating that modern anaesthesia procedures would involve the use of more than one drug, stated, ‘in fact, it is reasonable to partially eliminate undesirable side-effects of one narcotic by the opposite side-effects of another one. However, if this is impossible, then it is desirable to at least reduce the harmful side-effects or render them harmless as follows: first of all, small doses of one narcotic are employed which reduce both its narcotic effect and side-effects. Then, a second narcotic having different side-effects is added to produce complete narcosis. Under these conditions, the various side-effects of the two narcotics are acceptable in their weaker form. It seems very likely to me that the narcosis of anaesthesia of the future will depend on a practical combination of several narcotics.’

Most anaesthetic procedures today therefore involve the combination of different drugs, using anaesthetics in concentrations that are considerably smaller than those needed if one drug were to be used by itself. Modern general anaesthetic techniques typically involve the co-application of a hypnotic drug, an analgesic drug and a muscle relaxant. Many different combinations arise, depending on which drugs are given together, their relative concentrations with respect to each other, and whether they are given as a bolus or continuously. Apart from producing amnesia and immobility, removing pain or the perception of pain and normally rendering the patient unconscious, the general anaesthetic procedures vary greatly in how they provide homeostasis during the perioperative period, being concerned with maintaining cardiovascular stability and blunting the effects of surgical stress such as the release of stress hormones.

Defining general anaesthesia by general anaesthetic procedures is unambiguous but the consequence could be that there may be several different forms of general anaesthesia, rather than just one. Comparisons of how different anaesthetic procedures (Fig. 1) achieve the same clinical endpoints such as, for example, amnesia or immobility, will settle this question.

**Definition of general anaesthetic**

Strictly speaking, the term general anaesthetic should only be applied to those substances that can be used in a general anaesthetic procedure without the aid of any other drug. Sometimes the terms complete or total anaesthetics have been used to indicate that these drugs by themselves can achieve all the essential goals of general anaesthesia and therefore can be used as a sole drug for surgical anaesthesia. We shall retain the term general anaesthetic to carry this meaning; all other drugs with anaesthetic properties will be called simply anaesthetics. Diethyl ether and chloroform passed this test for more than a century before they were replaced by modern compounds (Fig. 3A). In this sense, halothane and clinically discontinued agents such as cyclopropane, fluroxene and methoxyflurane are also general anaesthetics. Diethyl ether and cyclopropane were discontinued because of their inflammability, chloroform and fluroxene because of hepatotoxicity, and methoxyflurane because of nephrotoxicity.

Modern inhalation anaesthetics such as the halogenated ethers are also considered to be general anaesthetics, although it is already questionable whether isoflurane, for example, because of its absent analgesic or even hyperalgesic properties, could be used by itself as universally as diethyl ether was. The barbiturates are even more problematic, as has been demonstrated by the disastrous results during Pearl Harbor. Therefore they cannot be considered to be true general anaesthetics. The other intravenous anaesthetic agents are also not being used as sole anaesthetic agents and therefore do not qualify as general anaesthetics either. Even the intravenous anaesthetic ketamine cannot be considered to be a general anaesthetic because it is commonly co-administered with benzodiazepines to counteract the possible undesirable psychological reactions that occur during awakening from ketamine anaesthesia.

Modern general anaesthetic techniques typically involve the co-application of a hypnotic drug, an analgesic drug and a muscle relaxant. Hypnotic drugs in clinical use today are inhalation anaesthetics such as desflurane, isoflurane and sevofoflurane as well as sometimes xenon (still experimental), while the use of enfurane and halothane is declining (Fig. 3A). Propofol, etomidate, midazolam and ketamine are commonly used intravenous hypnotic agents (Fig. 3B). Barbiturates are mainly used for the induction but not the maintenance of anaesthesia. Analgesics include nitrous oxide and the opiates. Muscle relaxants comprise both the depolarizing (succinylcholine) as well as non-depolarizing (curare and synthetic compounds) agents.

In this context it is important to realize that Meyer as well as Overton made an important distinction between non-specific narcotics and other narcotics. Overton called non-specific narcotics those compounds that are not of the nature of a base, an acid or a salt (page 32). The Meyer–Overton correlations and the Meyer–Overton hypothesis apply only to non-specific narcotics, a fact that is often overlooked. Thus it seems that Meyer and Overton would have considered the modern inhalation anaesthetics (Figs 3A and 4A), but not the intravenous anaesthetics (Figs 3B and 4B), as belonging to the class of non-specific narcotics, as the pKa values (Fig. 4B) indicate that intravenous anaesthetics can be protonated or deprotonated. It is even questionable whether strong hydrogen bond formers such as the modern halogenated ethers (Fig. 4A) that are in clinical use today would have been counted by Meyer or Overton as belonging to the class of non-specific narcotics.

**Diethyl ether anaesthesia – a gold standard?**

Why has there been a persistent attempt to search for a theory of general anaesthesia? All attempts at defining general anaesthesia in this review so far have lost sight of
one aspect that has been perhaps the most fascinating of all: a single chemical substance can achieve all of the actions of general anaesthesia (even the ones where there is dispute) that have been considered clinically essential. Diethyl ether and chloroform, for example, were used as sole agents in a general anaesthetic procedure for almost a century (Fig. 5).

By themselves they produce unconsciousness, analgesia, amnesia, immobility and lack of stress and haemodynamic responses (in response to noxious stimulation). These agents switch off many bodily functions but in a systematic way such that life is sustained and those functions most relevant to life are turned off last. Is this pure coincidence or is there
a mechanism behind it, which we might term the mechanism of general anaesthesia? If so, how can we define general anaesthesia in a way that can be quantified?

Although diethyl ether has some undesirable side-effects, no other general anaesthetic agent has ever been as widely used as a sole anaesthetic agent without any adjuvant. Diethyl ether dominated general anaesthesia for the first 100 yr of its existence. In fact, the term anaesthesia was coined to describe what happens during the process of ‘etherization’. Thus, in the absence of any other generally agreed upon quantitative means of measuring general anaesthesia, a very pragmatic definition of general anaesthesia might be useful: ‘The state of general anaesthesia consists of a spectrum of distinguishable physiological states, comparable to those brought about by diethyl ether, which are suitable for human surgery.’ This definition does not rely on any mechanisms; instead, it uses as a reference or gold standard the very substance that introduced the concept of general anaesthesia into medicine. In our opinion there cannot be any theory of general anaesthesia that does not explain how diethyl ether anaesthesia works in all its details.

**Concepts for measuring general anaesthesia**

**Monitoring of general anaesthesia**

**Stages of anaesthesia**

Right from the beginning it became clear that there was no single anaesthetic state. Instead, it was observed that anaesthetic states change with the concentration of inhalation anaesthetic and that they can be quite different qualitatively. Within a year after the successful demonstration of ether anaesthesia in the ether dome at the Boston Massachusetts General Hospital in 1847, John Snow divided the effects of ether into five stages or degrees, progressing from consciousness to deep coma, muscle flaccidity and respiratory paralysis: ‘In the first degree of etherization I shall include the various changes of feeling that a person may experience, while he still retains a correct consciousness of where he is, and what is occurring around him, and a capacity to direct his voluntary movements. In what I call the second degree, mental functions may be exercised, and voluntary actions performed, but in a disordered manner. In the third degree, there is no evidence of any mental function being exercised, and consequently no voluntary motions occur; but muscular contractions, in addition to those concerned in respiration, may sometimes take place as the effect of the ether, or of external impressions. In the fourth degree, no movements are seen except those of respiration, and they are incapable of being influenced by external impressions. In the fifth degree (not witnessed in the human being), the respiratory movements are more or less paralysed, and become difficult, feeble, or irregular.’ Guedel extended these observations and during World War I developed a scheme that took account of patient responses in order to determine the degree of anaesthesia present.

Similar observations were made for chloroform. Overton described the following stages of narcosis to occur with increase in the concentration of chloroform in blood plasma: ‘1. Decrease in, and loss of, sensitivity to pain, while partly retaining intelligence, tactile sensation and reflexes. 2. Loss of sensation of taste and loss of reflexes, and finally the loss of the reflex of the conjunctiva. 3. Complete relaxation of the musculature, followed, if the concentration of the chloroform in the blood plasma increases further, by cessation of breathing movements and heart beat.’ However, Overton also noticed that no two
anaesthetics behaved completely alike and that there were differences in the sequence and degree in which various effects occurred or did not occur.

This observation also holds for modern inhalation anaesthetics. Therefore the Guedel\textsuperscript{21} scheme, developed for diethyl ether during World War I, has to be modified for each inhalation anaesthetic. However, inhalation anaesthetics are a much more homogeneous group than are intravenous anaesthetics, which show much greater variability. Even more extreme are narcotics: opioids may be used for certain surgical procedures as sole anaesthetics in some patients but not in all patients.\textsuperscript{25}

Depth of anaesthesia

The term ‘depth of anaesthesia’ is still widely (ab)used. The concept of depth of anaesthesia implies that the adequacy of clinical anaesthesia can be measured and described by mono-parametric quantities. When Snow\textsuperscript{48} spoke of a patient that had ‘been more deeply etherized . . . ’ he clearly used the term ‘deep’ in reference to the concentration of ether. Also, when Overton and Guedel used the term ‘deep’ they meant the concentration of the anaesthetic. While the term ‘etherized’ eventually was replaced by ‘anaesthetized’ and depth of etherization became the depth of anaesthesia, the concept of a mono-parametric quantification remained. In the case of anaesthetic procedures dominated by a single inhalation agent this concept still made sense. For example, if the inhalation anaesthesia were ‘deep’ enough that a patient did not show any movements at all, the anaesthetist could also be sure that later the patient would not recall any events during surgery.

Modern assessment of adequate general anaesthesia

Modern general anaesthesia techniques typically use a combination of an analgesic, a hypnotic and a muscle relaxant. Each of the individual agents can be independently dosed and a single parameter no longer suffices to establish whether a patient is adequately anaesthetized. A patient who has received adequate muscle relaxant cannot move even if he or she is wide awake and would like to draw somebody’s attention to this calamity. Yet while a few devices have been developed that can assess the hypnotic component in a number of general anaesthetic procedures, the construction of monitors that predict responses to noxious stimuli has met with much less success, and the personal clinical judgement of the anaesthesiologist is still required.\textsuperscript{4,49}

Depending on the general anaesthetic procedure and on the patient, the concentration of each drug has to be titrated independently and, thus several functional variables (such as muscle relaxation, suppression of stress responses, hypnosis) have to be monitored independently and simultaneously in order to ensure that therapeutic goals of the general anaesthetic procedure are being achieved. At present there are no objective standards for quantifying the entire set of clinical goals for any particular modern general anaesthetic procedure such as, for example, immobility, suppression of stress responses to noxious stimuli, and hypnosis. Thus, for general anaesthetic procedures involving more than one drug there are no hard data against which any theory of general anaesthesia could be tested.

Quantification of anaesthetic function

Models of general anaesthesia and its components

Soon after the discovery of diethyl ether as a general anaesthetic for human surgery, many more chemical compounds were tested as to whether they could equal or even better the performance of diethyl ether as a general anaesthetic. Before being tried on patients, these compounds were examined in a variety of \textit{in vivo} and \textit{in vitro} preparations. Irrespective of animal, plant or preparation, the terms narcosis and anaesthesia were also used to describe the effects of these compounds on animals as well as on tissues and cells. For Overton, narcosis simply meant a reversible cessation of physiological function (page 5)\textsuperscript{39} in cells, organisms and animals. Summarizing his investigations involving more anaesthetic compounds than most contemporary anaesthesia researchers have ever studied, Overton came to the conclusion that ‘ether and chloroform produce narcosis in humans, mammals, tadpoles, and entomostraca (tiny crabs) at about the same concentration in the blood plasma. The same is probably more or less correct for other pure-acting (i.e. free of side-effects) non-specific narcotics.’ (page 181)\textsuperscript{35} While acknowledging that larger concentrations of anaesthetics are required to anaesthetize various groups of worms, plant cells, protozoa, or ciliary cells (page 32),\textsuperscript{35} Overton observed, ‘Thus, all non-specific compounds that narcotize the brain also have a narcotizing effect on plant cells, ciliary cells, muscle fibres, and other parts of organisms, if the concentration of the compounds is sufficient.’ (page 70)\textsuperscript{35} Overton assumed ‘that essentially the same mechanism produces narcosis in the neurons and other cell tissues (either plant or animal) that is caused by non-specific narcotics.’ This assumption of common mechanisms of anaesthesia has been one of the reasons why, from the beginning of anaesthesia research, a variety of \textit{in vivo} responses and \textit{in vitro} model systems have been employed to reflect general anaesthesia completely, to describe partial aspects of it or to measure it indirectly.

Even before Meyer and Overton and ever since, various animals and their motor activities such as swimming, righting or withdrawal have been used to study anaesthesia, with the assumption that conclusions could be drawn about their anaesthetic state from observing their motor reflex behaviours. In a similar vein, Eger’s concept of MAC\textsuperscript{15} uses a motor reflex as a measure of general anaesthesia by quantifying a patient’s movement response to surgical incision. Initially, it was thought that these movement responses were controlled by large motor neurones in the
Definitions and correlations

The relationship between the concentration of a drug and the magnitude of the observed effect may be complex, even when responses are measured in simplified systems in vitro. This may be an indication that the response being measured is a composite of several effects, and that it could possibly be resolved into simpler curves for each of its components. Simple concentration–response curves may vary in shape but they are generally characterized by four independent variables: potency, slope, maximal efficacy and individual variation. The potency of an anaesthetic is indicated by the position of the concentration–response curve along the concentration axis, while its maximal effect is quantified by the maximal efficacy. Potency is often quantified by determining the concentration at which a half-maximal effect is observed (EC$_{50}$ or IC$_{50}$). The slope or steepness of the curve, as well as its shape, give clues as to the mechanisms of action, while the biological variability is reflected in the individual variation. The argument that concentrations used in experimental studies should match those required to reach the clinical endpoint under investigation leads some investigators to avoid studying concentrations higher than ‘clinical’ from fear of their system being
perceived as ‘insensitive’ and therefore unimportant. Irrespective of the fallacy of such an attitude, following the proven pharmacological practice of establishing complete concentration–response curves normally produces data of higher quality and usefulness.

**Quantification of anaesthetic concentration**

The effect of an anaesthetic depends on its concentration at the site of action. In vivo it is a function of the amount of anaesthetic administered as well as of the extent and rate of its absorption, distribution, binding or localization in tissues, biotransformation and excretion. Thus, concentrations in blood, tissues, membranes and the site of action will be different from each other, even when the distribution of the drug has reached equilibrium in the body.

However, at equilibrium the partial pressures of a gas will be the same in all body compartments, including the site of action. This is why when defining the MAC concept Eger followed the proven pharmacological practice of establishing complete concentration–response curves normally produces data of higher quality and usefulness.

**Modulation of concentration–response curves**

General statements such as: ‘at clinically relevant concentrations the GABA<sub>A</sub> receptor is affected by general anaesthetics while the sodium channel is not’ are common in the discussion of anaesthetic mechanisms. Implicit in such statements are (unreflected) assumptions that there is only one GABA<sub>A</sub> receptor channel or only one sodium channel, that there is only one anaesthetic action on an individual channel, and that effective concentrations are constant. None of these assumptions is true, and there are many factors modulating an anaesthetic response and changing EC<sub>50</sub> and IC<sub>50</sub> values, such as protein subtype and subunit composition, membrane and cellular environment (Figs 6 and 7), protein interactions, second messenger pathways and network connections.

**Correlations of anaesthetic effects**

Establishing correlations between two sets of experimental data is a means of summarizing data as well as organizing and structuring them. Correlations may also be used to suggest ideas as to the underlying mechanisms generating the experimental data. In this case, anaesthetic functional endpoints are correlated with mechanism-related functional endpoints. For example, a good correlation of IC<sub>50</sub> values for anaesthetic block of a protein with physicochemical properties of the anaesthetic (Fig. 8A) may suggest that this physicochemical property is an important aspect of the mechanism underlying the protein block. On the other hand, a good correlation of IC<sub>50</sub> values for anaesthetic block of a protein with concentrations needed to achieve a clinical endpoint (Fig. 8B) may suggest an important role for this protein in the clinical endpoint. While correlations may support a hypothesis, they cannot prove it; however, they can disprove and thus exclude certain hypotheses from further consideration. By studying a range of anaesthetics together and establishing correlations it becomes possible to separate anaesthetic effects they have in common from those that are specific to a particular drug.
There is a bewildering variety of small organic molecules and even inert gases that have anaesthetic potency. They include the noble gases neon, argon, krypton and xenon, cyclic and straight-chain alkanes, halogenated alkanes such as chloroform and halothane, the homologous series of alcohols, ketones, esters, aldehydes, ethers, and halogenated ethers such as isoflurane, desflurane and sevoflurane. While these anaesthetically active compounds may vary greatly in size, in other physical and physicochemical properties, as well as in their pharmacological behaviour, there is one thing most of them have in common. Already at the turn of the nineteenth century, Meyer and Overton independently found that the anaesthetic potency of these drugs correlated with their preference to dissolve in lipophilic rather than in polar or gaseous phases. This linear correlation, called the Meyer–Overton correlation, is obtained when anaesthetic potency is plotted against partition coefficient, such as octanol/water, oil/gas or membrane/buffer partition coefficients. The Meyer–Overton correlation (Fig. 8A) holds in human and in whole-animal anaesthesia (Fig. 8A). It also holds (Fig. 7 in reference 50) for in vivo and in vitro actions of anaesthetics at different levels of integration within the central nervous system. These include molecular, subcellular, cellular and microcircuit levels, as well as network, behavioural responses and clinical anaesthetic endpoints such as immobility. This correlation holds over more than five concentration decades.

**Fig 6** Effect of cholesterol on pentobarbital-induced sodium channel suppression – comparison of sodium channel properties in the absence and presence of cholesterol. The higher the cholesterol concentration, the less effective is pentobarbital, a thiopental analogue, in suppressing currents through sodium channels. (A) Current traces in control (phosphatidylethanolamine and phosphatidylcholine, 4:1 ratio) lipids and with 4% of 50% (weight/weight, corresponding to 7.3 and 65.3 mol% respectively) cholesterol added. Synaptosomal fractions of human brain cortex were prepared, incorporated into planar bilayers in the presence of 250 nM batrachotoxin, and voltage clamped (−40 mV, filtered at 200 Hz). (B) Current traces in the presence of 680 μM pentobarbital. From Rehberg et al. with permission.

**Fig 7** Comparison of sodium currents (A) and pentobarbital effect (B) in SH-Sy5Y cells (filled circles), N1E-115 cells (filled diamonds), HEK293 cells (grey triangles), and for rat brain (open diamonds) and rat muscle (open triangles) sodium channels expressed in Chinese hamster ovary (CHO) cells. The concentration–response curves for pentobarbital clearly depend on sodium channel subtype, subunit composition and/or cell environment. (A) Voltage dependence of sodium current activation (solid lines) and inactivation (dashed lines). Mean (SEM of the fit) potentials of half-maximum activation and inactivation, respectively are −14.9 (3.5) and −65.2 (3.2) for N1E-115; −22.7 (3.4) and −74.7 (10.7) for SH-Sy5Y; −21.4 (4.9) and −62.5 (9.1) for HEK293; −20.9 (8.7) and −53.2 (6.5) for CHO rat brain, and −24.3 (9.6) and −63.0 (7.9) mV for CHO rat muscle. (B) Pentobarbital suppression of maximum inward currents. Lines are fits of a Hill function to the data. Data points are means of 3–5 experiments for SH-SY5Y and HEK293 cells, and of 5–6 experiments for N1E-115 cells. From Rehberg et al. with permission.
The Meyer–Overton correlation has often been declared dead because there are a number of anaesthetics that do not follow it. If only those substances that Meyer and Overton considered are included (i.e. non-specific narcotics, see above) the exceptions become much fewer. The exceptions do not invalidate the rule that is followed by hundreds of compounds. Instead, the rule helps to identify those compounds that, by breaking the correlation, suggest themselves as compounds to be studied in detail and promise to shed further insight into certain aspects of anaesthetic mechanisms. Only a proponent of a unitary hypothesis of general anaesthesia could claim that any particular correlation would have to be obeyed by every single general anaesthetic.

There are many other ways of correlating anaesthetic effects, some examples of which are shown in Figure 8. Anaesthetic effects are correlated with physical properties so as to test mechanisms of action (Fig. 8B) or with clinical concentrations (Fig. 8C, D) in order to suggest that the mechanism is relevant for a number of anaesthetics and that it is consistent with playing a role in anaesthesia, as is the case in these examples for a role of GABA_A receptors or for hydrogen bonding in anaesthesia mechanisms.

The rank order of potency within a group of anaesthetics differs and depends on the clinical endpoint. For example, the anaesthetic concentration at which analgesia or the threshold of a verbal response is observed is not a constant fraction of MAC for different general anaesthetics. The use of different anaesthetic endpoints (such as righting reflex, tail clamp or heat application) to determine anaesthetic potency results in data that cannot be reconciled by applying a simple scaling factor between different anaesthetics, an observation that Overton had already made (page 178). Thus, if an \textit{in vitro} effect were to play a role for a clinical
endpoint of anaesthesia, then the rank orders of both would be expected to correlate.

An extension of this approach would be the comparison of a group of structurally systematically altered compounds, some of which are active and produce a clinical anaesthetic endpoint, some of which are inactive (or less active) and do not (or only do so less effectively), on an in vitro target thought to play a role in that endpoint. This approach has been taken for compounds showing cut-off effects in potency, for the so-called non-immobilizers, for propofol analogues to establish the role of GABA\textsubscript{A} receptors in tadpole righting reflexes, and for enantiomers of anaesthetics.

**Conclusion**

Clinical outcome from different anaesthesia procedures (such as perioperative awareness, postoperative pain, emesis or recovery from surgery) cannot be compared unless there are ways to quantitatively establish that these different procedures were identical in the level of anaesthesia they provided. Before anaesthesia monitors can be constructed it must be clear what anaesthesia-related quantities they should measure and what the underlying mechanisms of anaesthesia are. Clinical and experimental functional endpoints have to be clearly and quantifiably defined before they can be meaningfully measured and compared. Otherwise, the pursuit of anaesthesia mechanisms will remain one of ‘the most controversial, emotive and subjective aspects of our discipline’, involving ‘philosophical exchanges instead of thoughtful scientific analysis’.

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