BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Fifth Edition

Volume 3: Therapeutic Agents

Edited by

Manfred E. Wolff

Teshnipharm Consultants
Laguna Beach, California

A WILEY-INTERSCIENCE PUBLICATION

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Preface

This third volume of Burger's Medicinal Chemistry and Drug Discovery is concerned with two classes of medicines—CNS drugs and endocrine drugs. The advent, in the 1950s, of orally active agents for the treatment of mental illness and the control of human fertility brought about profound changes in everyday life in Western-type societies. The strides forward made in our understanding of the fundamental basis for the action of such compounds, as well as in increasingly rational methods for their design, is readily seen in the chapters in this volume. Today, CNS drugs represent a continuing, major area for drug discovery and drug design. In the endocrine sector also, entirely new areas such as the retinoid drugs have emerged.

Alfred Burger has had a lifelong interest in the discovery of CNS agents, and it is appropriate to give some details of his life in this preface. He was born September 6, 1905 in Vienna and entered the University of Vienna as a student of chemistry and pharmacy in 1923. Encouraged by his laboratory instructor, Erich Mosettig, he undertook chemical research on the benzyl isoquinoline alkaloids with Ernst Späth, and was awarded the Ph.D. degree in 1928. In 1929 he joined Mosettig at the Drug Addiction Laboratory of the National Research Council at the University of Virginia, where they collaborated on the chemistry of the morphine alkaloids. During his long career at Virginia he carried out extensive research in the synthesis of agents for the CNS and other areas, one of the fruits of this work being the antidepressant drug tranylcypromine. He became Professor of Chemistry in 1952. He founded this series in 1951, as well as the *Journal of Medicinal Chemistry* in 1959.

Alfred Burger's work resulted in about 160 papers, and was accomplished with the help of 42 graduate students and 36 postdoctorals, one of them being myself. All of us—students, friends, and associates—have been inspired by his warm concern for others, his enthusiasm for new ideas, and his courage in expressing himself and in beginning new ventures.

MANFRED E. WOLFF

Laguna Beach, California

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1 INTRODUCTION

It is now 150 years since the first public demonstration of ether anesthesia took place at the Massachusetts General Hospital in Boston. In that period, with the sole exception of the introduction of nonflammable agents, few major pharmacological improvements have been made in the volatile agents available to the anesthetist. The perspective is even worse when one considers that Paracelsus wrote in the sixteenth century of diethyl ether that "... it has an agreeable taste, so that chickens take it gladly, and thereafter fall asleep for a long time, awaking unharmed ... its use may be recommended for painful illnesses, and it will mitigate the disagreeable complications of them" (1). Whether, in fact, volatile agents more satisfactory than those employed today do await discovery is an open question. However, a sufficient understanding of the phamacokinetics, toxicity, and metabolism of general anesthetics has been achieved to allow new agents to be optimized for these properties. The outstanding problem today is to achieve a sufficient understanding of the mechanisms of action of general anesthetics so that new agents of improved specificity can be designed.

There are a number of characteristics of general anesthetics that have made them difficult to understand and dangerous to use. Prime among these is their relative lack of structural specificity. Within the constraint that lipophilicity is required, substances as disparate as xenon and certain steroids produce general anesthesia (Fig. 36.1). The conclusion that anesthetics do not interact with specific receptors is reinforced by the high concentration required for anesthesia, their lack of marked stereoselectivity and the absence of specific pharmacological antagonists. The implication that anesthestics are simple general cellular poisons is at least partially true, and the margin of safety between depressing consciousness and other vital functions, such as respiration, is small. Therapeutic ratios in the region of two to four are indeed normal. These characteristics, together with very steep dose–effect curves and the clinical need for rapid induction, place a high demand on the skill of the anesthetist. Fortunately these disadvantages are partially, and uniquely, offset by the mode of administration of the volatile agents. Thus it is possible to control precisely the concentration administered to the patient, and at least for agents with rapid pharmacokinetics, to reduce the level of anesthesia quickly should the need arise. This, of course, is not true of the intravenous agents and accounts for their lack of popularity for all but brief procedures.

One final problem associated with general anesthetics stems from the high concentrations of these agents required. At the end of a prolonged operation a patient exposed to halothane may have absorbed more than a mole of the agent! Complete elimination of the anesthetic then requires days. The potential for toxicity resulting from such agents of their metabolites cannot be ignored.

The development of improved inhalation agents thus requires consideration of a number of factors. The most important requirements for these agents are

1. Sufficient specificity of action to spare the cardiac and respiratory systems at general anesthetic concentrations.
2. Rapidity of induction and recovery giving the anesthesiologist better control and the patient quicker recovery (the latter being

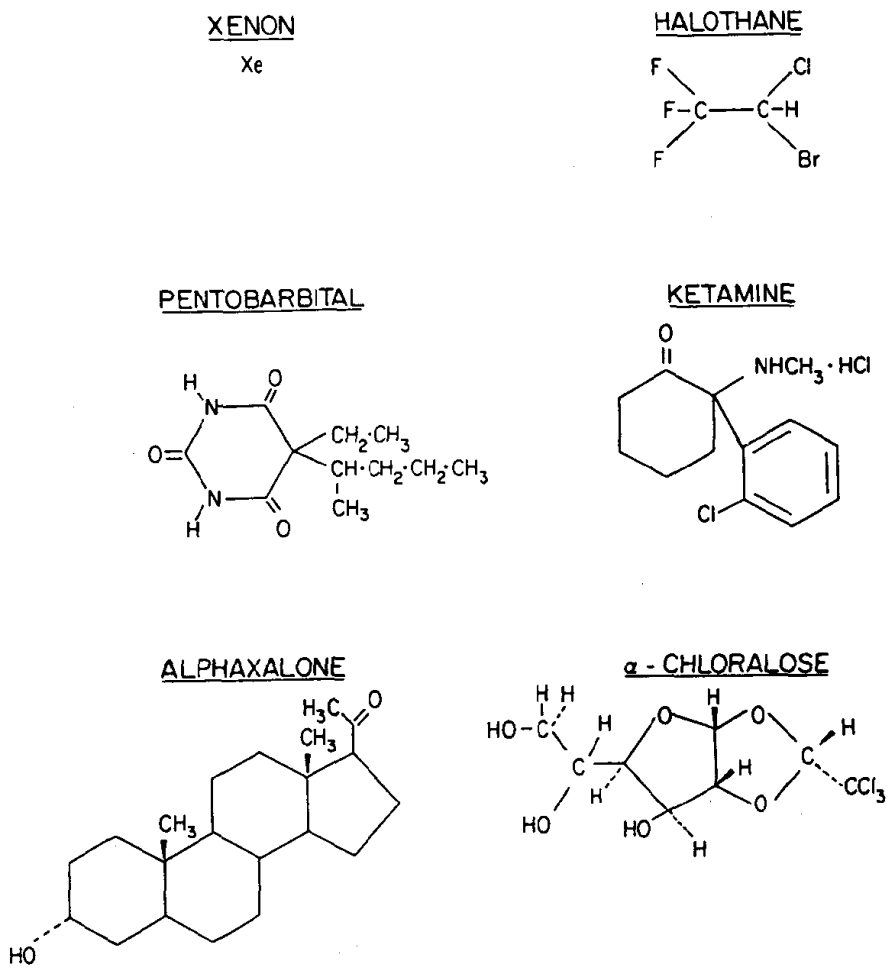


Fig. 36.1 The structures of some representative general anesthetics.

of economic as well as medical importance).

3. Chemical stability both *in vivo* and in the delivery system.

   For intravenous agents the second factor is the critical one and no agent lacking this property will be acceptable.

In seeking to design new agents, the traditional physicochemical approach (see Section 2) provides the best *a priori* way of predicting general anesthetic potency, which it does with considerable accuracy. It also leads to models of a biophysical nature which will be considered in Section 3. These models define the physical nature of the site of action even though its physiological nature is in doubt, a problem which is considered in Section 4. Finally, recent studies outlined in Section 5 seek to define the molecular mechanisms that general anesthetics exert on real physiological targets. These may help in defining more specific agents, although any relationship to the processes in the central nervous system which lead to loss of consciousness is unknown. Finally, a better understanding of the realms of pharmacokinetics and metabolism is considered.

2 THE PHYSICOCHEMICAL APPROACH

2.1 Introduction

The physicochemical approach circumvents the lack of understanding of consciousness by determining the concentration of a wide range of agents that is sufficient to produce equal levels of general anesthesia and then comparing these concentrations to various

physical properties of the agents in order to provide both insight into the nature of the site(s) of action and useful predictive rules. The implicit assumption, often called the unitary hypothesis, is that all agents produce general anesthesia by the same mechanism.

General anesthesia is defined operationally by measuring, at a series of concentrations of anesthetic, the fraction of animals that fail to respond purposefully, not reflexively, to a well-defined stimulus. The quantal dose–response curves obtained vary with the exact end point used (see Fig. 36.2), indicating that the effective concentration required for lack of response varies with the intensity of the stimulus. Adjuvent drugs may thus change the apparent anesthetic potency by moderating the perceived strength of the stimulus. General anesthetic dose–response curves are generally steep and parallel, the latter observation supporting the null assumption. Unfortunately, one common end point, the minimum alveolar concentration (MAC), is defined in such a way that the slope of the underlying concentration–response curve is not apparent. The potency of many general anesthetics has been tabulated conveniently (2) and that of some representative agents are shown in Table 36.1. While these values are vital for comparing relative potency, it can be appreciated (Fig. 36.2) that they represent rather light anesthesia and levels employed in practice may be roughly twice as high.

2.2 The Traditional Solubility Theories

The objective of this approach is to find a model in which both the distribution of molecules surrounding the anesthetic molecule and the intermolecular forces between them resemble closely those between the anesthetic and its unknown physiological site of action. If the model fulfulls these conditions, a correlation between the anes-

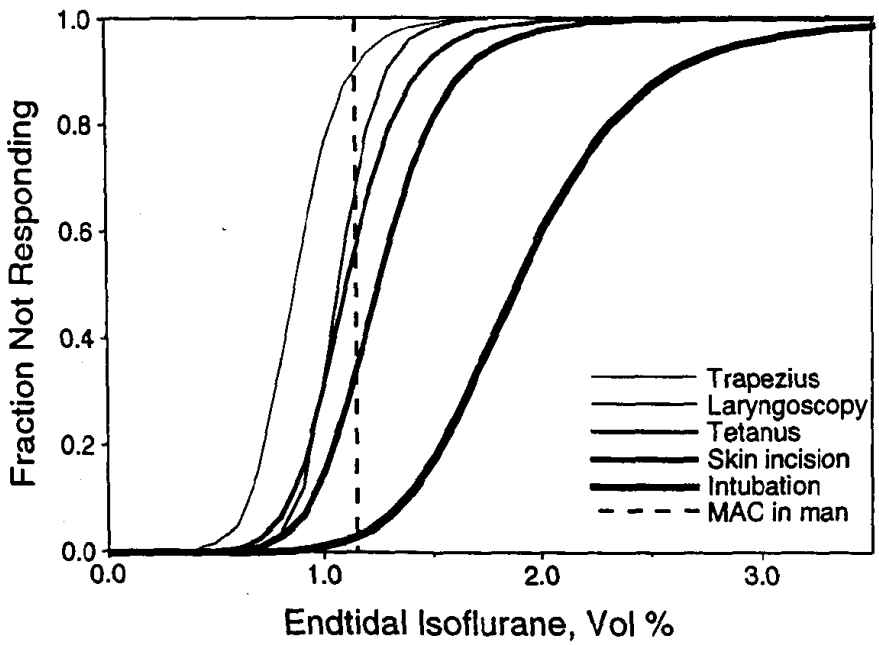
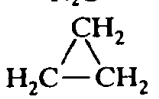


Fig. 36.2 The inspired volume percent required to abolish purposeful response to various clinical stimuli (indicated in the key) increases with their intensity. The end-tidal volume percent is plotted against the fraction of patients that do not respond. The 50% response concentrations range from 0.9 volume percent for a squeeze of the trapezius muscle to 1.9 for intubation and should be compared to a figure of 0.4 for response to voice command, a commonly used criterion for awaking from anesthesia. Adapted from Zbinden et al. (1994) with permission. The vertical dashed line is the MAC (minimum alveolar concentration) value in humans; no curve is given because the slope of the dose-response curve was not reported (data of Eger et al. taken from Ref. 2).

Table 36.1 Some Common Inhalation Anesthetics

Agent	Explosive?	Formula	Partition Coefficient, λ		Anesthetic Partial Pressure in Humans, P_{50} or MAC (Atm)	Concentration in Oil at Anesthetic Partial Pressure, λ(Oil/Gas) × P_{50}	Vapor Pressure at 26°C (Atm)
			Blood / Gas	Oil / Gas			
Nitrous oxide	*	N_2O	0.47	1.4	1.01	1.4	Gas
Cyclopropane	Y		0.5	12	0.092	1.1	Gas
Desflurane	N	$CHF_2-O-CHF-CF_3$	0.45	19	0.06	1.1	0.88
Diethylether	Y	$C_2H_5-O-C_2H_5$	12	65	0.019	1.2	0.70
Enflurane (Ethrane)	N	$CHClF-CF_2-O-CHF_2$	1.8	98	0.0168	1.6	0.28
Isoflurane (Forane)	N	$CF_3-CHCl-O-CHF_2$	1.4	98	0.0115	1.1	0.38
Halothane (Fluothane)	N	$CF_3-CHClBr$	2.3	224	0.0077	1.7	0.39
Methoxyflurane (Penthrane)	N	$CHCl_2-CF_2-O-CH_3$	12	970	0.0016	1.6	0.04
					Mean + S.D. =	1.4 ± 0.25	

*N_2O supports combustion, does not explode

thetic potency and the affinity of the anesthetic for the model is to be expected. A limitation of the method is that the intermolecular forces between unlike molecules tend to be systematically related to those between the two like molecules (3). Critically applied, however, this approach severely restricts the number of acceptable models (4), but even when successful such correlations can only be said to be consistent with the data; in no way is any model based on a correlation proved by it.

As originally proposed these theories referred directly to solubility in cell lipids, but they have also been taken to imply interaction with the hydrophobic regions of lipids. In this section, focus is on the traditional approach, leaving deductions about the nature of the site to the following section.

The most generalized form of the solubility theories, and the one used in the development of halothane, is that given by Ferguson (5), who noted that although the equilibrium concentrations of various anesthetics producing a given level of anesthesia vary widely, the corresponding thermodynamic activities lie in a relatively narrow range. The activity of a volatile anesthetic is defined as

$$a_{50} = \frac{P_{50}}{p^\circ} = \frac{EC_{50}}{C_{Sat}} \qquad (36.1)$$

where a_{50} is the thermodynamic activity at the anesthetic partial pressure P_{50} at which half the subjects are anesthetized, and p° is the saturated vapor pressure of the pure liquid anesthetic. In aqueous concentrations, EC_{50} is the corresponding anesthetic concentration and C_{Sat} is the saturated concentration of the anesthetic. The thermodynamic activity a_{50} is found to be approximately equal to 0.01–0.04 for many anesthetics (6, 7; Fig. 36.3), so that the anesthetic partial pressure of any other agent may be predicted by Ferguson's principle. Since many empirical rules have been developed for the prediction of vapor pressure (9), this is quite a useful relationship. However, from the foregoing discussion one limitation should be immediately apparent. Only the derived quantity a_{50} contains any information about the anesthetic site; p° is a property dependent only on the agent's own intermolecular forces. Thus, the estimate is reliable only to the degree that the intermolecular forces between the unknown agent and the site of action of anesthesia are related to the intermolecular forces between molecules of the agent itself. Thus the highest degree of accuracy is obtained when an additional member of an homologous series is considered, whereas low reliability may be expected with highly fluorinated agents which exhibit anomalously weak intermolecular forces with hydrocarbons.

Figure 36.3 shows that although the fully fluorinated gases show marked deviations, most common liquid anesthetics have a potency that is well within an order of magnitude of that predicted. Thus, if the underlying physical shortcomings of Ferguson's approach are recognized, it provides a reliable first estimate of an agent's potency even before that agent is synthesized.

Ferguson's approach is classified as a solubility theory because $(1/p^\circ)$ is the ideal (or statistical) solubility predicted by Raoult's law (3). An obvious improvement would be to substitute for ideal solubility the solubility in a solvent which closely resembles the site of action of anesthetics. Historically, such an approach preceded Ferguson's; the well-known correlation of anesthetic potency with lipid (usually olive oil) solubility proposed by Meyer and by Overton at the turn of the century provides in fact a much more accurate method for predicting anesthetic potency even for the fluorinated gases (Figure 36.3, Table 36.1).

The model based on this correlation is that anesthesia "occurs when a certain molar concentration is attained in the lipids of the cell." For mice this concentration is ~0.06 *M* (Table 36.1), a rather high figure, which serves to emphasize the dangerously nonspecific nature of general anesthetics.

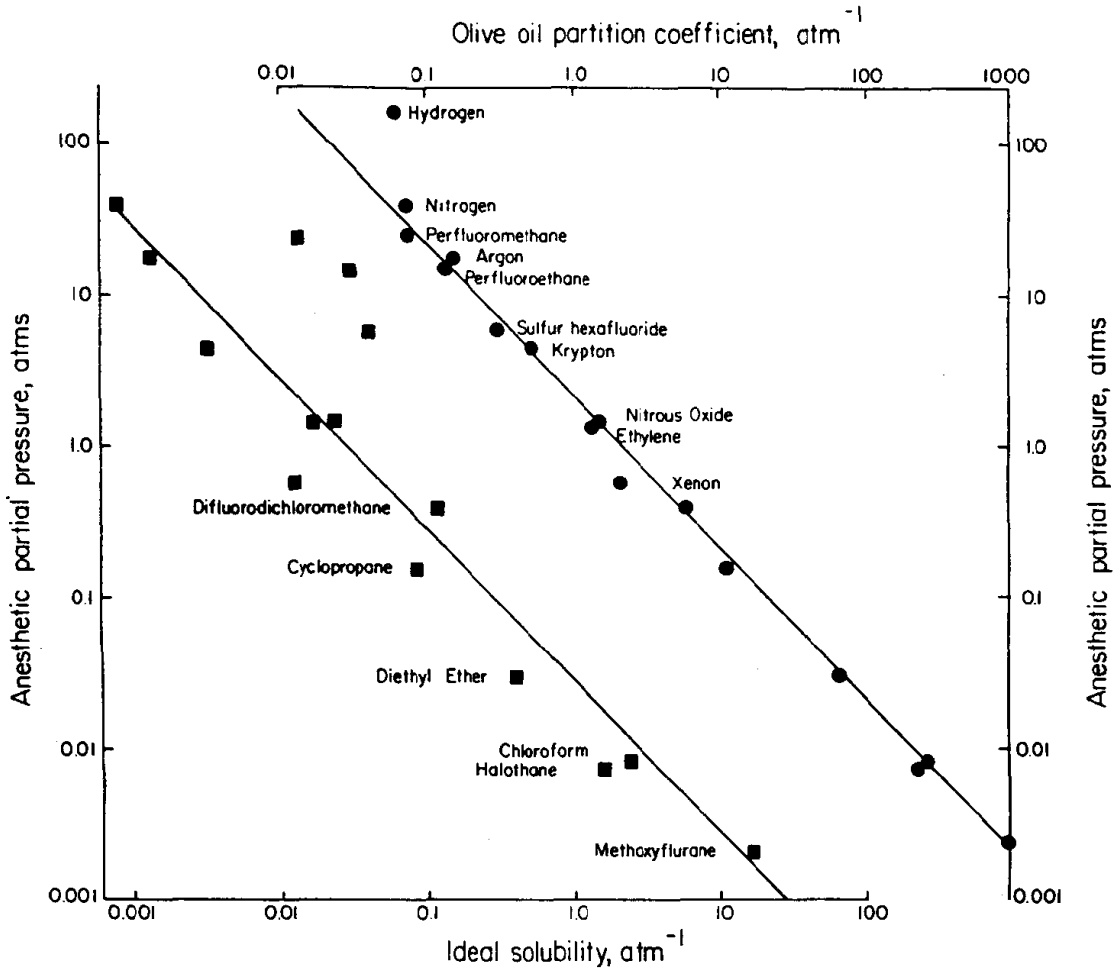


Fig. 36.3 A comparison of the correlation of anesthetic potency with ideal solubility $\left(\frac{1}{p}\right.$, Ferguson's Rule$\left.\right)$ (■) and with olive oil solubility (●). The lines are drawn with unit slope as required by Equations 36.1 and 36.2. The physical data at 37°C are from Ref. 3 and the anesthetic potency in mice from Ref. 8.

The Meyer-Overton hypothesis may be written

$$P_{50} \cdot \gamma_{o/g} = EC_{50} \cdot \gamma_{o/w} = \text{constant} = C_{50} \tag{36.2}$$

where $\gamma_{o/g}$ is the oil/gas partition coefficient of the anesthetic in olive oil at a partial pressure of 1 atm and, alternatively, EC_{50} is the aqueous anesthetic concentration bathing the animal (for example, a tadpole) or isolated preparation and $\gamma_{o/w}$ is the oil/water partition coefficient of the anesthetic. Equations 36.1 and 36.2 provide useful predictive rules that are not improved on by more complex models in practice although octanol may provide a more convenient solvent than olive oil (see below for a more systematic approach for choosing solvents). Two physicochemical refinements of the Meyer-Overton rule are worth mentioning.

First noted by Mullins (10), the importance of the general anesthetic's volume forms the basis of the critical-volume hypothesis developed to explain the phenomenon of pressure reversal of anesthesia. While the hypothesis provides a remarkably self-consistent model for these effects, especially for gases, and has been useful in the development of inert gas mixtures for deep diving (11), it has not lead to insights that are likely to be useful in the design of general anesthetic agents and a detailed description will not be given here. However, it is worth noting that the studies of pressure–anesthetic inter-

actions have provided strong evidence for multiple sites of action of anesthetics in the central nervous system (see Section 4.1). In particular, the site at which general anesthetics protect against convulsions, which is indistinguishable on the basis of solubility properties from that which causes general anesthesia, may none-the-less be distinguished by its response to pressure (12).

The second refinement of the solubility theory was also introduced by Mullins (10). He analyzed the action of general anesthetics on various physiological end points in terms of the solubility parameter, δ. This parameter derived from Regular Solution Theory (6), distinguishes solvents from each other and predicts that the mutual solubility of two liquids will be greatest when the difference between their solubility parameters is least. In general, the forces between solvent molecules increase as the solubility parameter increases and solvents with high solubility parameter values tend to be more polar. Solubility of a solute in a solvent increases as the difference in their solubility parameters decreases.

Mullins (10) applied this analysis to the inhibitory action of alcohols on the perfused stellate ganglion of the cat (7) and obtained $\delta = 11.5$ and 10 $(cal/cm^3)^{1/2}$ for the nonsynaptic and synaptic sites, respectively, implying a less polar or cohesive environment in the latter case. Thus, ethanol with a δ of 13 selectively blocks the nonsynaptic pathway (at concentrations lower than those required to block the synaptic pathway); butanol with an intermediate δ of 11 blocks both pathways at similar concentrations, whereas octanol with a δ of 9 blocks the synaptic pathway selectively. This reflects the relation of the solubility of the agents at each site to the difference between their solubility parameter and that of the site (6, 13). At a given partial pressure, the concentration of octanol is higher at the synaptic than at the nonsynaptic site and, other things being equal, this explains its selectivity. Thus, in general agents with δ greater than 11.5 depress the nonsynaptic pathways selectively, whereas, those with δ less than 10 are selective for synaptic pathways. Apolar compounds, such as general anesthetics, generally have δ values less than nine, and thus, are predicted to be selective for synaptic pathways, as is found to be the case. Indeed, analysis of the general anesthetic potency data for mice suggests that the best correlations are obtained with nonpolar solvents having $\delta = 10$–11 (8, 12), consistent with the notion that general anesthesia results from synaptic block.

Attempts have been made to rationalize the balance of excitation and depression found in many volatile agents on the basis of their solubility parameters (13). The observation is that many convulsant gases have $\delta \leq 7$ whereas many general anesthetics fall in the range 7–9. This is consistent with inhibitory synapses having lower solubility parameters than excitatory synapses, but whether this is the case remains to be demonstrated. In general, most general anesthetics do cause excitation at subanesthetic partial pressures, hence the desirability of rapid induction, so that the solubility parameter approach may be inadequate.

2.3 Limitations of the Solubility Models

Various deviations from the classical theory suggest ways in which it may be developed to be more comprehensive.

2.3.1 THE ANESTHETIC CUT-OFF. In many homologous series of anesthetics, higher members lack anesthetic activity. For example, the anesthetic potency of 1-alkanols increases roughly logarithmically with the addition of successive methylene groups up to dodecanol (14). At that point, the addition of a single methylene groups leads to a complete loss of anesthetic activity even at the highest obtainable concentrations. This behavior has been termed "anesthetic cut-off." The reason that tridecanol and higher homologues are not anesthetics is not failure to

reach their physiological target (15), nor a lack of solubility because their partition coefficients increase logarithmically with the number of carbons (16). Thus, they represent a failure of the solubility model.

A cut-off exists for the normal hydrocarbons (17), but they provide a much more instructive example. All smaller alkanes, including octane, cause anesthesia, but nonane and decane are not general anethetics when applied at the highest obtainable partial pressures. However, at these partial pressures they do decrease the partial pressure of isoflurane required to cause anesthesia. They, therefore, contribute an anesthetic action without being capable of producing full anesthesia and are termed *partial anesthetics.*

By their nature, partial general anesthetics must reach their site of action. Therefore, they might fail to cause anesthesia either because their saturated solubility is too low or because their efficacy is weak. Intrinsic efficacy can be defined as the ability per molecule of agent interacting with the site of general anesthesia to perturb that site. Then the solubility rule can be rewritten as

$$\text{Efficacy} \cdot (P_{50} \times \gamma_{o/g}) = \text{constant} \tag{36.3}$$

where Efficacy = 1 for normal agents and zero for nonanesthetics such as tridecanol, undecane, and their higher homologues. The partial anesthetics, nonane and decane, must have intrinsic efficacies of the order of 0.1 because their anesthetic potencies, extrapolated from additivity studies, are an order of magnitude below those expected from the Meyer-Overton solubility rule. Thus, higher concentrations must be achieved at the site of action to compensate for the low efficacy value (Equation 36.3). It is possible for full general anesthetics to have lower than usual efficacy and, therefore, higher than expected P_{50}s. For example, the higher normal alcohols and hydrocarbons deviate increasingly from the Meyer-Overton prediction with increasing molecular weight and it follows that their intrinsic efficacies must be declining systematically. Thus, cut-off arises in the cases of the normal alcohols and hydrocarbons because eventually one cannot deliver a sufficiently high concentration to offset the decline in efficacy.

Thus, Equation 36.3 provides that an agent may fail to be a general anesthetic either because the product $(P_{50} \times \gamma_{o/g})$ cannot achieve a sufficiently high value (a solubility limited agent), or because its Efficacy is too low (an efficacy limited agent). In the latter case low efficacy can be counteracted by elevated P_{50} up to a point. In the former case, the agent cannot cause anesthesia by itself but may contribute a certain fraction towards reducing the concentration of a second agent that is required to cause anesthesia. This follows from the fact that the potency of volatile agents is generally simply additive (4).

Ferguson suggested that loss of efficacy occurs when the anesthetic assumed a similar size to its site of action (5). Recently, sterically constrained alcohols have been used to explore which aspect of size is important (17a). The cycloalkanemethanol series was compared to the 1-alkanols. The highest homologue in each series to be a full anesthetic was cyclododecanemethanol and dodecanol, respectively, leading to the conclusion that exceeding a critical volume rather than a critical length leads to loss of efficacy. However, when other series are considered the case for a size limit is not so clear cut. For example, the normal hydrocarbons larger than decane lose activity (17), as do the fluorocarbons larger than perfluoromethane or perfluorocyclobutane (18) (the exact point is open to question, but in any case the volumes are not comparable to dodecanol's). A better understanding of the loss of efficacy must await Section 3, in which, specific models are considered.

Finally, there are agents that do not obey Equation 36.3. The clearest examples arise when the contribution of lipid soluble, receptor targeted drugs are examined. Thus, mor-

phine initially decreases the anesthetic partial pressure of halothane (19), but higher concentrations fail to cause further decreases. Since the concentration of morphine in lipid increases linearly with its free concentration, it is probable that its contribution to general anesthesia results from a receptor-targeted action on a neural pathway involved in the stimulus–response chain rather than from a nonspecific action at the site of general anesthesia. In such a case, the assumption that equal degrees of anesthsia are reflecting equal physiological states is no longer valid; that is, the null hypothesis has broken down.

2.3.2 PRESSURE REVERSAL. Although xenon, krypton, and argon fit the Meyer-Overton rule (Fig. 36.2), neon and helium are omitted from the correlation because they do not cause anesthesia in the tolerable pressure range. Hydrogen, with an anesthetic partial pressure of over 100 atmospheres, is much less potent than predicted.

The reason these light gases deviate lies in the high pressures involved. Hydrostatic pressure "reverses" anesthesia; the ED_{50} of an anesthetic increases when it is measured at a series of increasing pressures (20). In the case of hydrogen in mammals, its lipid solubility is just high enough to overcome the effect of pressure, but with helium this is not so. However, helium is sparingly lipid-soluble and it is possible to demonstrate that it makes a contribution to anesthesia by comparing the effect of hydrostatic and helium pressure on the ED_{50} of another anesthetic (20).

Thus, it is not necessary to propose that the light gases possess unusual efficacies; the failure of the solubility theory lies in its neglect of the role of pressure.

2.3.3 STEREOSELECTIVITY. The solubility theory predicts that enantiomers should be equipotent. Interest in this prediction goes back many years. Early work in rats suggested that the enantiomers of secondary alkanols caused general anesthesia selectively, but careful study ruled this out (21). Nor was stereoselectivity found in a large cohort study using small tadpoles, an experimental model with a venerable history that allows rapid equilibration of the biophase with the bathing medium (14). More recently, evidence that the enantiomers of isoflurane differ in potency has been advanced. Groups of six rats were examined and MAC determined. The (+)- and (−)-enantiomers had MACs of 1.06 ± 0.07 and 1.62 ± 0.02%, respectively (22). Reanalysis shows that the concentration–response curves were not parallel. Furthermore, in a study of 200 tadpoles the concentration–response curves showed no differences in EC_{50} or slope (23). Clearly a more detailed study in mammals is needed because the level of confidence cannot be high until the statistical problems are dealt with. In any case, the small difference in potency in the rat study (~50%) is not sufficient to indicate much about the site of action. However, because the therapeutic indexes of general anesthetics are so small, even a small stereoselectivity might be beneficial if the respiratory and cardiac side effects prove unselective. Thus, a more systematic investigation of these compounds would seem to be in order (24).

It is commonly observed that the degree of stereoselectivity in a series of drugs increases with their potency. Thus, the more potent intravenous agents might be better candidates than the volatile agents. Early research implicated stereoselectivity in the action of the barbiturates. However, the interpretational difficulties posed by differential metabolism led to these observations being discounted (25). More recently, systematic studies have been undertaken with the enantiomers of pentobarbital which suggest that there exists true stereoselectivity of action. In one study in mammals, the authors demonstrated stereoselectivity in volume of distribution, clearance rate and plasma protein binding, but these were insufficient to account for differences in anesthetic potency