Inhalation anaesthesia may be viewed as the development of a series of tension gradients. The high partial pressures delivered by the anaesthetic apparatus progressively decrease on their passage through the circuit, from circuit to alveoli, from alveoli to bloodstream, and finally from circulation to brain or other tissues. The development of these gradients determines the course of anaesthesia. Some of these gradients are subject to manipulation by the anaesthetist while others are partially or completely beyond his control. The rational administration of inhalation anaesthesia requires an understanding of the factors governing these various gradients so that they may be accounted for or regulated.

FACTORS DETERMINING ALVEOLAR CONCENTRATION

In a patient who breathes an anaesthetic mixture of constant composition (constant inspired concentration), the initial alveolar concentration of agent is zero, but with the passage of time, inspired and alveolar concentrations approach each other. The rate at which this unification takes place is a function of three forces, each of which opposes or modifies the others. These are ventilation, uptake, and inspired concentration.

Ventilation. The rate at which normal ventilation introduces agent into the lung is extremely rapid. If this effect of ventilation were unopposed, the concentration of anaesthetic in the alveoli would rise from zero to 95 per cent of the inspired concentration within 2 minutes (Hamilton and Eastwood, 1955).

Uptake of anaesthetic vapour into blood. However, loss of anaesthetic to lung and blood occurs. This loss opposes or limits the rise in alveolar concentration consequent upon ventilation. The greater the loss—or uptake of anaesthetic agent—the lower the alveolar concentration relative to inspired concentration. Uptake of the agent is directly dependent on three factors.

(1) Blood solubility. The solubility of an anaesthetic in blood is an index of the capacity of blood to hold that anaesthetic. With greater blood solubility, a greater proportion of anaesthetic is distributed to blood at the expense of the concentration in the alveoli. Therefore, the greater the blood solubility, the lower the alveolar concentration relative to inspired concentration (Eger and Larson, 1964).

(2) Cardiac output. Since cardiac output determines the quantity of blood to which the alveolar gas is exposed per unit time, the higher the output, the larger the quantity of anaesthetic removed from the lungs. Therefore, increasing cardiac output lowers the alveolar concentration (Kety, 1951; Eger, 1963b; Mapleson, 1963a).

(3) Anaesthetic tension gradient between alveoli and pulmonary arterial blood. The amount of gas ("vapour" is included in the word gas) that may be removed by blood is limited by the amount already in the blood. If the tension in pulmonary arterial blood is identical to that in the alveoli, then no gas is taken up regardless of solubility or cardiac output. Conversely, the lower the blood tension relative to that in the lungs, the greater the uptake (Kety, 1951; Eger, 1963a).

Uptake of anaesthetic vapour into tissue. The tension in the returning venous and pulmonary artery blood is determined by the amount of anaesthetic removed by the tissues. Tissue uptake is directly related to the same three factors that determine uptake at the lungs, namely (1) the arterial-tissue tension gradient, (2) the blood flow per unit volume of tissue, and (3) the relative solubility of...
the agent in that tissue (Jones, 1950; Kety, 1951). Tissues such as brain, heart, liver, and kidney which are highly vascular (vessel rich group or VRG) rapidly (within 5 to 15 minutes) attain the same anaesthetic tension as exists in arterial blood. When this occurs, uptake of agent by these tissues becomes insignificant or ceases and the venous blood draining them possesses the same anaesthetic concentration as found in arterial blood. These tissues receive roughly 75 per cent of the cardiac output. Thus, as saturation at a given arterial tension occurs, 75 per cent of the venous blood no longer takes up agent from the alveoli unless the concentration in the alveoli rises further.

Tissues such as muscle (MG) and fat (FG) continue to absorb agent for prolonged periods because of their low blood flow per unit mass. Because of the high oil/blood partition coefficient of most anaesthetics, fat also has a great capacity or effective volume relative to blood flow. If alveolar or arterial anaesthetic tension remains constant, muscle continues to take up appreciable amounts of agent for 1 to 3 hours while fat absorption is maintained for hours to days. These tissues are supplied by 25 per cent of the resting cardiac output. Since the blood issuing from them is more or less cleared of anaesthetic for prolonged periods, 25 per cent of venous blood is capable of taking up further agent from the alveoli.

An example of the uptake of halothane by various tissue when a 1 per cent concentration is inspired is shown in figure 1.* The uppermost graph is total uptake, while uptake by tissue groups is given in the succeeding curves. Lung tissue uptake is of consequence in the first minute only. Uptake by the vessel poor group or VPG (bone, cartilage, tendons, ligaments) is insignificant because of limited blood flow. The vessel rich group or VRG (brain, heart, kidney, hepatoportal system, endocrines), muscle group (MG), and fat group (FG) are the main determinants of uptake. The VRG dominates uptake during the first 10 minutes. Following this the MG is dominant for about 2½ hours. Fat (FG) continues to take up halothane after all other tissues have ceased doing so (Eger, 1963b).

The division of the body into four tissue groups (VRG, MG, FG, and VPG) is somewhat arbitrary. It assumes that the four groups can be separated on the basis either of blood flow per unit volume of tissue (this will apply to VRG, MG and VPG) or of tissue/blood solubility (this is important only in the fat group). It must be remembered that such separations allow a reasonable description of what actually is a nearly infinite variety of blood flows and tissue solubilities. In addition, as Perl (1963) has pointed out, this separation into tissue groups does not account for diffusion of anaesthetic from one tissue group to another, for example, from muscle to fat. Indirect evidence of such intercompartmental diffusion has been obtained by Rackow (personal communication). Despite these criticisms, use of the above concept of four tissue compartments allows one to predict anaesthetic uptake and alveolar concentration with reasonable accuracy (Eger, 1963a; Mapleson, 1963a).

It may be seen from the shape of the curves in figure 2 that the rise in alveolar concentration occurs in three or more phases. At first there is a rapid rise as ventilation moves agent into the lungs. As the alveolar tension rises, there is a concomitant rise in uptake until the ventilatory input of anaesthetic is matched by loss through uptake. Since uptake is directly proportional to solubility, the

---

*All the graphs used in this paper are derived from calculated data, except for figures 13 and 14. These calculated graphs have been substantiated for the most part by experimental observations.
UPTAKE AND DISTRIBUTION OF VOLATILE ANAESTHETIC AGENTS

The approach of alveolar to inspired anaesthetic concentration for five gases. The inspired concentration is noted on each curve. In all cases alveolar ventilation is 4 l./min, cardiac output is 6 l./min, and solubility is that given in the article on anaesthetic solubility in this journal. (Eger, 1963b, with the permission of the publisher.)

The relative alveolar concentration attained when uptake equals input is low with a soluble agent such as ether and high with a less soluble agent such as cyclopropane. The qualitative changes in alveolar tension for a fixed inspired concentration (i.e., the shape of the alveolar concentration curves) are the same for both gases. Balance between lung tissue uptake and input is reached within 1 minute, after which the alveolar concentration continues to rise but at a slower rate. The rate of rise following this initial bend in the graph is determined by the rate at which equilibration with the more vascular tissues (VRG) occurs. As equilibration with these tissues proceeds, uptake decreases; and the alveolar concentration rises in accordance with the balance between ventilatory input and uptake. Saturation of the vascular tissues occurs in about 10 minutes. After this time the alveolar concentration continues to rise but at a still slower rate. Rise in tension following this second bend in the graph is dependent on decreasing uptake by muscle and fat. Since saturation of these tissues is a process requiring hours to days, the final approach of the alveolar tension to that inspired is seldom seen in clinical anaesthesia except where the inspired concentration is high.

The course of events described above is best seen in figure 2 with halothane. There is an initial rapid rise in alveolar tension so that at 1 minute the alveolar tension is 25 per cent of that inspired. At this point (arrow 1 in fig. 2) ventilatory input and uptake are in balance and the first bend in the curve occurs. After this, alveolar tension rises at a slower rate determined by the saturation of the more vascular tissues. After 10 to 15 minutes, the anaesthetic tension in these tissues is essentially equal to the arterial tension to which they are exposed. At this point (arrow 2) when alveolar tension is about 50 per cent of inspired, the second bend appears. Uptake by muscle and fat continues at an appreciable rate throughout the remainder of the period described by the curves. Even at 50 minutes the alveolar tension has only risen to about 60 per cent of inspired. Were the curve extended over a long enough period, a third bend would be seen where muscle uptake ceases and only fat continues to extract a significant quantity of halothane.

Although the relative position of each graph in figure 2 is dependent in part on blood and tissue solubility, the general shape of the curves of alveolar tension changes with cyclopropane, halothane and ether are qualitatively the same and follow the course stated above for halothane. However, despite the similarity in the blood/gas partition coefficients of nitrous oxide and cyclopropane, both the shape and position of each are significantly different.

The concentration effect. These differences of shape and position are accounted for by the concentration effect by which the higher the inspired
concentration, the more rapid the approach of alveolar tension to that inspired (Eger, 1963b, c). When inspired concentration is 100 per cent, the approach of alveolar to inspired tension is most rapid and is identical for all gases, both soluble and insoluble. The influence of solubility (really, the influence of uptake, which is directly related to solubility) on the position and shape of the alveolar curves is eliminated when 100 per cent concentration is inspired and becomes manifest only as the inspired concentration is lowered. A crude explanation of this effect may be seen in a mythical lung filled with 100 per cent of any anaesthetic gas. No matter how little or how much of this gas is removed, that gas remaining is still at 100 per cent. Solubility or uptake do not affect the alveolar concentration (although they may decrease lung volume). Conversely, if this mythical lung is filled with less than 100 per cent of an anaesthetic gas then as some of this gas is removed by uptake, the concentration must fall. That is, the proportion of anaesthetic gas (falling) to diluent gas (constant) must decrease. Furthermore, the decrease is not proportional to the amount of gas taken up unless the initial concentration is low—another way of saying that the lower the inspired concentration, the more does solubility or uptake affect the alveolar concentration. A more complete explanation of the concentration effect with experimental confirmation may be found elsewhere (Eger, 1963c).

Figures 3 and 4 illustrate the concentration effect for nitrous oxide and for ether, respectively. The difference between curves with the same gas is greatest with ether. This must be so, since the curves for all gases are the same at 100 per cent inspired concentration but differ at lower inspired concentrations by virtue of their different solubilities—the greater the solubility, the slower the approach of alveolar to inspired concentration.

Clinically, anaesthetics exhibit the variation seen in figures 3 and 4 only when (1) they are used over a wide range of inspired concentrations and (2) they have an appreciable solubility. Such gases as nitrous oxide, cyclopropane, fluroxene, and ether meet these requirements, whereas gases such as halothane, chloroform, and methoxyflurane which are used only at low (10 per cent or less) inspired concentrations show little variation in the alveolar curves (for an individual gas).
The importance of inspired concentration may be seen in a comparison of the induction times with methoxyflurane and ether. These two anaesthetics have essentially the same solubility in blood (blood/gas partition coefficients of 13 and 12.1 respectively) but methoxyflurane is roughly 13 times as potent as ether. If the inspired concentrations of these agents were 26 per cent ether and 2 per cent methoxyflurane (a 13 to 1 ratio) the induction rate would be approximately twice as rapid with ether. That is, the rise of alveolar concentration to a given percentage of the inspired concentration would take half as long with ether despite the equivalence of the blood solubility. The difference between the induction rates is due to the difference in the inspired concentrations.

**EFFECT OF CHANGES IN CIRCULATION AND RESPIRATION ON ALVEOLAR CONCENTRATION**

As noted previously, the alveolar concentration is determined (in the absence of the concentration effect) by a balance between anaesthetic input by ventilation and anaesthetic loss by uptake. Anything which increases input in relation to uptake will increase alveolar concentration. An increase in ventilation, therefore, raises the alveolar tension (Yamamura et al., 1963). Similarly, a lower cardiac output decreases uptake and causes a rise in alveolar tension.

*Changes in cardiac output.* The more blood-soluble the agent used, the greater the variation in alveolar concentration caused by a change of cardiac output. Excitement, fever, and other hypermetabolic states may minimally influence the rate of induction with an agent such as nitrous oxide but may significantly slow induction with an agent such as ether. Conversely, an ether induction may be unexpectedly rapid in a patient in shock whereas the rate of rise of alveolar cyclopropane in the same patient may only be slightly more rapid than usual.

This may be seen in figure 5 where nitrous oxide, halothane, and ether are compared. The curves for nitrous oxide are altered over a small range by changes in output except for the first few minutes where a more sizeable change is seen. The limited range with nitrous oxide, despite a nine-fold increase in cardiac output, may be related to the relatively small proportion of nitrous oxide taken up regardless of cardiac output. In addition, at the concentration inspired (75 per cent), the effect of uptake is partially negated (concentration effect). Cyclopropane, a drug with proportionately similar uptake, should show a slightly larger range at a lower inspired concentration commonly used. An increase in cardiac output produces a considerable reduction in alveolar halothane concentration. With ether, increase in cardiac output results in the greatest relative reduction in alveolar concentration. For example, at 20 minutes the difference in alveolar ether concentration is threefold at the extremes of cardiac output cited (18 and 2 l./min). For halothane a twofold difference is seen, while for nitrous oxide the difference is negligible.
Changes in ventilation. The more blood-soluble the agent used, the greater the variation in alveolar concentration caused by a change of ventilation. Accordingly, if ventilation is increased, as often occurs when respiration is changed from spontaneous to controlled, little change in anaesthetic depth (i.e., little hazard) will be seen if an agent such as nitrous oxide or cyclopropane is used; but a profound and potentially dangerous change may be seen if the anaesthetic is halothane or ether.

Figure 6 illustrates the effect of altered ventilation on alveolar tension. With increase in ventilation there is an increase in alveolar concentration. Except for the first few minutes, the effect with nitrous oxide is minimal. This is to be expected because uptake with nitrous oxide is small relative to its alveolar concentration (except initially), and because of the negation of the effect of uptake by the high inspired concentration. Uptake removes a significant proportion of the halothane introduced by ventilation. A change in ventilation, therefore, produces a considerable change in the alveolar curve with this agent. Uptake relative to ventilatory input is greatest with ether and the greatest relative changes in the position of the alveolar curve at different minute volumes are seen with this agent. At 20 minutes, for example, over a threefold increase in alveolar tension is seen when ventilation is 8 l./min as compared to 2 l./min. At the same time, comparable halothane curves show but a twofold increase, while the nitrous oxide curves change by an insignificant amount.

THE EFFECT OF FLUCTUATIONS IN PHYSIOLOGICAL PARAMETERS

The previous discussion and graphs are based on an assumed constancy of cardiac output and respiration throughout the course of administration of any one anaesthetic. That is, a curve describing the alveolar tension rise of halothane with a cardiac output of 6 l./min and an alveolar ventilation of 4 l./min does not allow for any fluctuations in these parameters (although separate curves may be made at a different cardiac output or ventilation). As pointed out by Landahl (1963), this is a more or less incorrect assumption since anaesthetics themselves alter respiration and cardiac output. Many anaesthetics initially stimulate circulation and ventilation, and all anaesthetics when given in sufficient concentration produce depression of these parameters. Any accurate prediction of alveolar or brain anaesthetic tension must take into account this variable depression. The problem is further complicated by the altered patterns of perfusion and ventilation produced by anaesthetics (Nunn and Hill, 1960). Blood flow to one group of organs may increase at the expense of another. Uneven perfusion and ventilation (vide infra) occurs. Vascular shunting may develop. Changes in solubility may result from local alterations in temperature (in the skin and subcutaneous tissues for example). General hypothermia, by increasing blood and tissue solubility, may double the anaesthetic capacity of the body. All of these things alter the
picture of uptake and distribution to as yet an unpredictable degree. Fortunately, at light levels of anaesthesia the alterations in these parameters are limited, as evidenced by our ability to predict anaesthetic uptake with reasonable accuracy (Eger, 1963a; Mapleson, 1963a).

EFFECT OF UNEVEN VENTILATION-PERFUSION ON END-TIDAL AND ARTERIAL TENSION

Thus far the non-existence of abnormalities of ventilation and perfusion of the lung has been assumed. In this case, the anaesthetic tension in the lungs was considered to equal the tension in arterial blood.

However, uneven ventilation-perfusion does commonly exist. Emphysematous patients, patients with atelectasis, or patients with a right-to-left shunt are examples. Anaesthesia itself is associated with uneven ventilation-perfusion as evidenced by an alveolar-arterial carbon dioxide gradient (Nunn and Hill, 1960). Under these circumstances, the alveolar (or end-tidal) anaesthetic tension is higher than the arterial tension, the size of the gradient being related to the magnitude of the alveolar deadspace and the right-to-left shunt. Although the size of the gradient is relatively the same for all anaesthetics, the form it takes varies with the blood solubility of the anaesthetic (Eger and Severinghaus, unpublished data).

Consider a lung, half of which is ventilated with the same volume as normally respired by the whole lung. The other half-lung is unventilated but has

The effect of uneven ventilation-perfusion on the approach of end-tidal (broken lines) and arterial (continuous lines) cyclopropane tensions to inspired tension. \( \text{PET} \) signifies tension of cyclopropane in end-tidal gas, \( \text{Pa} \) is tension in mixed arterial blood, and \( \text{Pi} \) equals tension in inspired gas. Perfusion (\( Q \)) to each lung is noted and is constant and equally divided for all curves. Ventilation (\( V_A \)) to each half-lung is altered as noted. The centre curve, where broken and continuous lines overlap, represents the normal approach of alveolar (equals arterial in this case) to inspired tension. (From Eger, E. I. (it), and Severinghaus, J. W., to be published.)
no reduction in gaseous volume (i.e., no reduction in functional residual capacity). Both parts of the lung are equally perfused. If this abnormal lung is now ventilated with a relatively insoluble gas such as nitrous oxide or cyclopropane, the alveolar tension rapidly rises in the ventilated portion while no rise occurs in the unventilated half until the blood returning to it contains anaesthetic. The mean arterial tension in the blood leaving this abnormal lung must lie midway between the tension in the ventilated and unventilated parts. Since the rapid rise in the ventilated portion can be only slightly in excess of the rapid rise that normally occurs in the absence of uneven ventilation perfusion (see variation in nitrous oxide curves in fig. 6), the arterial tension must be lower than normal while the end-tidal (alveolar) tension is essentially unchanged (fig. 7).

Consider that the above mythical lung is now ventilated with a highly soluble agent such as ether. Again the respiring half-lung will receive the total minute volume (i.e., twice its normal volume). Accordingly, the tension in this lung rises to nearly double the tension found when the same ventilation is divided between the two parts of the lung (see the ether curves in fig. 6). This doubling of the normal end-tidal tension also doubles the arterial concentration issuing from that half-lung. Even if no ether is found in the blood leaving the unventilated lung, the mean arterial tension must be close to that occurring if there were no uneven ventilation-perfusion (fig. 8).

Uneven ventilation-perfusion produces an almost equal deviation of both alveolar and arterial tensions with halothane, an anaesthetic of intermediate solubility (fig. 9).

Since the course of an anaesthetic induction is related to the rise in arterial tension, uneven ventilation-perfusion as occurs with emphysema, atelectasis or right-to-left shunting may markedly affect the required inspired concentration of cyclopropane but little affect that required of ether. If half the cardiac output flows through unventilated lung, then the inspired cyclopropane concentration must be raised almost 50 per cent to achieve the same rate of induction as normally obtained. That

![Diagram](image_url)

**Fig. 8**

The effect of uneven ventilation-perfusion on the approach of end-tidal (broken lines) and of arterial (continuous lines) ether tensions toward the inspired tension. Only one curve in which an abnormality exists (0/4 ventilation) is drawn for arterial blood, since even with this extremely uneven ventilation-perfusion the deviation of arterial from the normal curve (overlapping broken and continuous lines) is slight. Compare these curves with those in figures 7 and 9. (From Eger, E. I. (11), and Severinghaus J. W., to be published.)
The effect of uneven ventilation-perfusion on the approach of end-tidal (broken lines) and of arterial (continuous lines) halothane tensions toward the inspired tension. (Compare with figures 7 and 8. (From Eger, E. I., and Severinghaus, J. W., to be published.)

is, if 20 per cent cyclopropane were previously required for a 5-minute induction, then 30 per cent cyclopropane would be required for the same rate of induction in the presence of a shunt of half the pulmonary blood flow. Under the same circumstances the ether concentration must be raised slightly if at all.

The statements above consider the effect of variation in ventilation relative to perfusion, but in all cases the ventilated portion of lung is also perfused. When ventilation occurs without perfusion, this increases deadspace and hence reduces alveolar ventilation relative to total ventilation. This, also, introduces an end-tidal to arterial anaesthetic tension difference. However, if alveolar ventilation is maintained at normal levels by increase in ventilation to the remaining perfused portion of lung, then rise in arterial anaesthetic tension in the normal subject and in the subject with increased deadspace will be identical.

This description assumes that these abnormal states (emphysema, atelectasis, or right-to-left shunts) alter the distribution but not the total quantity of ventilation and circulation. Obviously this is not the case. Ventilation is reduced in severe emphysema while atelectasis or right-to-left shunts are often associated with an increase in cardiac output. These changes cause a greater reduction in the arterial tension of soluble as opposed to insoluble anaesthetics (see figures 5 and 6). The overall effect of uneven ventilation-perfusion may therefore be to slow the rate of induction with both soluble and insoluble agents.

THE EFFECT OF THE ANAESTHETIC SYSTEM

Interposition of an anaesthetic system between the anaesthetic source and the patient introduces several obstacles to the development of the anaesthetic state.

Increase in gas volume. The volume of an anaesthetic system acts as a buffer to changes in anaesthetic tension. The larger the gas volume of the system, the more slowly does change occur. An illustration of this effect is given in figure 10 for nitrous oxide, halothane, and ether. The delay in rise of alveolar tension appears greatest with nitrous oxide and least with ether. However, in
The effect of increasing the volume of the total gas phase from 2.7 to 10 litres as occurs with interposition of an anaesthetic circle system between patient and gas source. In this case no anaesthetic tension gradient exists between the alveoli and the anaesthetic system (i.e., ventilation is "infinite") and the differences between the two curves for each gas are due entirely to the buffering effect of the increased gaseous volume. Gas is flowing into the circle (gas phase 10/1.) at 4 l./min. When the gas phase equals 2.7/1., alveolar ventilation is 4 l./min. Nitrous oxide, 75 per cent, inspired (top two curves); halothane, 1 per cent (middle two); and ether, 10 per cent (lower two) are compared. (Eger, 1963a, with the permission of the publisher.)

either case a significant difference occurs only during the first 5 to 10 minutes.

Inflow and ventilation as determinants of alveolar tension. Both inflow to the system and ventilation of the patient are vital to the development of an alveolar anaesthetic concentration (Hamilton and Eastwood, 1955; Eger, 1960, 1963b; Severinghaus, 1963; Mapleson, 1963a). Obviously, if ventilation is zero, no anaesthetic reaches the lungs, regardless of inflow. Similarly, no anaesthetic can be extracted from a zero inflow, regardless of ventilation. Each of these factors set a limit on the effectiveness of the other in altering alveolar concentration. The limiting effect of inflow is illustrated for nitrous oxide in figure 11. Inflow to an 8-litre circle system is fixed at 4 l./min. As ventilation increases the rate of rise of alveolar concentration becomes more rapid, but even at infinite ventilation does not exceed the rate of rise when respiration is 4 l./min (the same as the inflow rate) from a non-rebreathing system. Similarly, if ventilation is fixed, then no matter how great the inflow to the anaesthetic system, the alveolar concentration can never exceed that obtained with a non-rebreathing system (fig. 12).

A rapid induction of anaesthesia requires that both inflow and ventilation be adequate to raise the alveolar tension, as quickly as is safe, to that required for anaesthesia. In the case of the less potent agents (nitrous oxide, ethylene) the inflow
The limiting effect of inflow on rate of rise of alveolar nitrous oxide tension towards inflowing tension at alveolar ventilation of 1, 2, 4, 8, 16 l./min and infinite (indicated on each curve). Inflow rate is 4 l./min. The uppermost graph (broken lines) represents alveolar rise when ventilation is 4 l./min from a non-rebreathing system (NRB). (Adapted from Severinghaus, 1963, with the permission of the publisher.)

Fig. 11

The limiting effect of ventilation on rate of rise of alveolar nitrous oxide tension towards inflowing tension at inflow rates of 1, 2, 4, 8, and 16 l./min (indicated on each curve). Alveolar ventilation is 4 l./min. The uppermost curve represents alveolar rise when ventilation is from a non-rebreathing system (NRB). This curve would overlie the curve given by an infinite inflow rate. (Adapted from Severinghaus, 1963, with permission of the publisher.)

Fig. 12
should be in excess of 8 l./min (Eger, 1960). With the more potent anaesthetics, the effect of low inflows may be counteracted by increasing the inflowing concentration (for example, 50 per cent cyclopropane at 2 l./min inflow or 10 per cent halothane at 1 l./min inflow). It must be remembered that if these inflow concentrations are maintained beyond the induction period, they may produce potentially lethal alveolar concentrations.

Anaesthetic uptake by rubber. The rubber in an anaesthetic system also opposes the development of an alveolar anaesthetic concentration by absorbing a portion of the anaesthetic introduced (Eger, Larson and Severinghaus, 1962; Eger and Brandstater, 1963). The rubber-solubility of the anaesthetic is the dominant factor in determining the amount absorbed. Of the anaesthetics in use, trichloroethylene, methoxyflurane, chloroform, and halothane are significantly rubber-soluble. Induction with these agents is slowed by rubber uptake. Similarly, rubber saturated with these agents may release anaesthetic to the system when an attempt is made to reduce the agent concentration in the system. Recovery thus may also be delayed.

UPTAKE AT A CONSTANT ALVEOLAR CONCENTRATION
The previous discussion has assumed a constant inspired or inflowing anaesthetic concentration. This must represent a constantly changing depth of anaesthesia with continual deepening until equilibrium between alveolar and inspired concentration is reached. This is contrary to the usual practice of rapidly attaining a certain depth of anaesthesia which is maintained thereafter at roughly the same level. A closer approximation to this usual practice may be made by holding constant the alveolar rather than inspired tension. Inflowing and inspired concentrations then must be constantly changing (decreasing) until equilibrium is attained.

It has been suggested that even a constant alveolar tension does not represent a constant anaesthetic depth since the tension in the brain must lag behind that in alveoli and arterial blood (Mapleson, 1963b). However, the instantaneous production of an adequate brain anaesthetic tension would initially require a very high alveolar concentration. Although this might produce a constant brain tension, the tension to which other vital tissues are exposed might be excessively high.

Therefore, a constant alveolar concentration is probably the best practical approach to a constant anaesthetic depth, since with this technique the maximum tissue tension is limited.

Essentially, no difference in anaesthetic uptake exists between the two techniques (constant inspired versus constant alveolar concentration) when the less soluble gases are respired, since here the alveolar and inspired concentrations are essentially identical (fig. 2). However, as anaesthetic solubility increases, an appreciable difference in uptake is found. This may be seen in figures 13 and 14 for halothane and for methoxyflurane respectively. When a constant inspired concentration is inhaled, uptake changes less with time than when the alveolar concentration is constant. This difference is more apparent for methoxyflurane which is highly blood-soluble than for halothane which is only moderately soluble in blood. Less change in uptake is seen with a constant inspired mixture because as the tissues become saturated at one alveolar tension the tension is free to rise further.
UPTAKE AND DISTRIBUTION OF VOLATILE ANAESTHETIC AGENTS

since it is far below that inspired. The increased alveolar tension maintains the tension gradient from arterial blood to tissue and therefore maintains uptake. On the other hand, when the alveolar concentration is held constant, there can be no compensatory rise in arterial tension as tissues become saturated. Hence, uptake continues to fall as more and more tissues equilibrate with the arterial concentration.

Uptake of soluble agents at a constant alveolar concentration differs in two other respects from uptake at a constant inspired concentration. By definition, changes in ventilation have no effect on uptake at a constant alveolar concentration since ventilation can effect uptake only by changing the alveolar concentration. However, uptake at a constant inspired concentration is profoundly altered as illustrated for ether in figure 15. When alveolar ventilation is increased from 2 to 4 to 8 to 16 l./min, uptake at induction shows a proportionate, sixfold variation when inspired concentration is held at 10 per cent. When the alveolar concentration is constant (4 per cent in this case), uptake does not vary despite similar changes in ventilation.

In a converse fashion, changes in cardiac output have little effect on uptake at a constant inspired concentration. As Kety (1951) has noted, uptake of soluble agents is limited by ventilatory input of agent. Since almost all of that which is inspired is taken up, any increase in uptake by increased cardiac output must be small. On the other hand, when alveolar concentration is constant, an increase in cardiac output results in a significantly greater uptake initially but a more rapid fall in uptake with time. This is seen for ether in figure 16.

When a constant inspired concentration of 10 per cent is respired, uptake varies by no more than 55 per cent despite a ninefold increase in cardiac output from 2 to 18 l./min. However, when alveolar concentration is constant at 4 per cent and
Ether uptake at a constant inspired concentration of 10 per cent (broken curves) versus a constant alveolar concentration of 4 per cent (continuous curves). Cardiac output (l./min) is indicated on the respective graphs. Alveolar ventilation is 4 l./min. (Adapted from Eger, 1963a, with the permission of the publisher.)

In general, uptake at a constant alveolar tension is of the same qualitative form for all anaesthetics (fig. 17). This form relates to the saturation of tissue groups. Since all tissues are initially unsaturated, uptake is highest at this point. During the first 5 to 15 minutes, the well-perfused tissues approach saturation at the alveolar tension. The rate at which saturation of these tissues occurs is inversely proportional to the tissue/blood partition coefficient. Brain saturation with halothane, which is more soluble in brain as opposed to blood takes longer than with ether (brain/blood coefficient equals about 1). In any event, in the more vascular tissues, equilibration between alveolar and tissue tension occurs within 15 minutes. During this time uptake rapidly falls to about 30 per cent of that found initially. Note that this 70 per cent reduction corresponds to the fraction of the cardiac output directed to these tissues. After 15 minutes, uptake continues to decrease slowly as muscle and fatty tissues contain more and more agent and the arterial-tissue anaesthetic gradient falls. From these data one may predict what concentration must be inspired to maintain the alveolar tension (Eger and Guadagni, 1963).
where $C_{IN8}$ is the inspired anaesthetic concentration, $C_A$ is the alveolar concentration, $V_U$ is uptake, and $V_A$ is alveolar ventilation.

Figure 18 shows the inspired concentration of halothane required to maintain an alveolar concentration of 0.8 per cent. The general pattern of each curve follows the pattern of decrease in uptake. It follows from the above equation that the required inspired concentration is greatly dependent on ventilation. Hyperventilation decreases the concentration required. For example, increasing ventilation after 1 hour of anaesthesia from 2 to 8 l./min decreases the required inspired concentration from 1.7 to 1 per cent. Care must be taken to reduce the inspired tension when increasing ventilation, otherwise anaesthetic depth will also increase.

When an anaesthetic system is inserted between the halothane source and the alveoli, then a second equation may be used to predict the inflowing concentration required to maintain the alveolar tension at 0.8 per cent:

$$C_{INF} = C_A + V_U / V_A$$

where $C_{INF}$ is the anaesthetic concentration in the gas flowing from the anaesthetic machine, and $V_{INF}$ is the inflow rate of that gas.

Inflow concentration varies not only with uptake and ventilation but also with inflow rate. This is seen for halothane in figure 19. Variations in inflow rate may produce a doubling or tripling of the required inflowing concentration. For example, at a 1 l./min inflow the initial concentration must be about 10 per cent, while in a non-rebreathing system only 3 per cent is required. Since uptake is
a factor in determining the gradient between inspired and alveolar tensions, gases of greater solubility than halothane require a proportionately greater inflow relative to alveolar concentration. Conversely, the inflow concentration of gases of lesser solubility need not greatly exceed the alveolar concentration even at low inflow rates.

From the above it may be seen that although the concentration of anaesthetic vapour flowing into a system may be accurately controlled, the alveolar concentration is subject to considerable variation. There is no rigid correlation between the percentage administered and that found in the alveoli. The latter is also determined by inflow rate, by ventilation, and by uptake.

CONCLUSION

In summary the concentration of anaesthetic agent found in the alveoli is determined by a balance between ventilatory input and loss through uptake. The effect of uptake is decreased as the inspired concentration is raised, such that at 100 per cent inspired concentration the alveolar concentration is determined solely by ventilation (concentration effect). At constant inspired concentrations of less than 100 per cent, alterations of anaesthetic input to and loss from the lungs change the alveolar concentration. Increase in ventilation or decrease in cardiac output both cause the alveolar concentration to rise. As the tissues of the body become saturated with anaesthetic, uptake falls; and accordingly, the alveolar concentration rises. The initial decrease in uptake is rapid for the less soluble agents and falls roughly 70 per cent in the first 10-15 minutes to about 30 per cent of the initial uptake. Thereafter uptake continues slowly to decrease so that after 2 hours it reaches 15 per cent of initial uptake. In contrast to this, uptake of soluble agents at a constant inspired concentration does not decrease greatly with time.

Changes in respiration and circulation exert opposite effects on uptake of soluble anaesthetics at a constant alveolar as compared to uptake at a constant inspired concentration. Ventilatory changes markedly affect uptake at a constant inspired concentration but have no effect on uptake at a constant alveolar concentration. In contrast, uptake at a constant alveolar concentration is markedly affected by variation in cardiac output while uptake at a constant inspired concentration is not.

No absolute prediction of the brain anaesthetic tension may be made from knowledge of the inflowing or inspired tension. The tension in the brain is also determined by inflow rate, by ventilation, by uptake, and by perfusion.

ACKNOWLEDGMENTS

The author wishes to acknowledge the valuable assistance in the preparation of the manuscript given by Drs. Stuart C. Cullen and Harry C. Churchill-Davidson. Figures 7, 8, 9 and 14 are taken from papers which have been accepted for publication in Anesthesiology and appear with the permission of the editor of that journal.
REFERENCES


