When an inhaled anaesthetic agent is administered at a constant inspired concentration, its uptake in the body is conveniently studied by examining the rate of increase in the alveolar concentration of the anaesthetic towards the inspired concentration, and the changes in the body content of that agent. The various factors governing uptake under these conditions were formally described by Kety (1950, 1951). Important variables which influence the rate of increase in the alveolar concentration of an inhaled anaesthetic are the inspired concentration, alveolar ventilation, cardiac output and the solubility of the agent in body tissues, especially blood. Of lesser importance are the concentration effect, which relates the rate of increase of alveolar towards inspired concentration to the magnitude of the inspired concentration (Eger, 1963), and the second gas effect, which is concerned with the influence that the uptake of one gas in the alveolar space has on the uptake of other simultaneously administered gases (Epstein et al., 1964; Stoelting and Eger, 1969).

The factors influencing anaesthetic uptake have most commonly been evaluated using a constant inspired anaesthetic concentration. Some studies have considered uptake when alveolar anaesthetic concentration is maintained constant (Eger and Guardagni, 1963; Lowe, 1972, 1979). The factors governing uptake under these conditions do not differ from those described above. With a constant alveolar anaesthetic concentration, the amount of an agent taken up by the body per breath will be equal to the product of the inspired-to-alveolar anaesthetic concentration difference and the alveolar ventilatory volume per breath. If constancy of alveolar gas concentration is maintained by adjustment of the inspired concentration, then...
uptake is apparently independent of alveolar ventilation.

When anaesthetic agents are administered using a circle system, the inspired anaesthetic concentration is likely to vary throughout the administration. The factors influencing anaesthetic uptake under these circumstances were explored by Eger (1974). He showed that the rate of increase in the alveolar concentration of administered agents was influenced by the magnitude of the fresh gas flow to the circle system, and that the use of a circle system modified the effects of changes in ventilation and cardiac output on uptake.

The present study is an extension of that of Eger. It examines the uptake of three agents—nitrous oxide, halothane and methoxyflurane—in a model of a subject attached to a circle system and in relation to fresh gas flow and composition, the composition of gas in the system at the start of administration, the volume of the circle system, cardiac output and ventilation.

MATERIALS AND METHODS

The model used in these studies has been described previously (Conway, 1986a, b). The subject portion is based upon model P of the circulation–time models of anaesthetic uptake described by Mapleson (1973). This is a multi-compartmental model in which gas concentration and content in each tissue compartment are calculated at each heart beat, utilizing Henry’s law, the law of conservation of matter, an assumed tension equilibrium for each agent in the components of each compartment and the known solubilities of the agent in the various body tissues. It is assumed that all carbon dioxide entering the circle system is fully absorbed, and all fresh and expired gas in the system is uniformly mixed. Volatile agents are assumed to be administered by fully efficient vaporizers placed in the fresh gas flow line.

Except where otherwise stated, the fresh gas concentration of nitrous oxide was 60% and that of both halothane and methoxyflurane was 2%. The reference values of the relevant body and circle system variables are given in table I. Anaesthetic uptake has been evaluated by examining the changes in alveolar anaesthetic concentration and body anaesthetic content during simulated administrations of 30 min duration. The studies described here have been carried out both with the circle system initially free of anaesthetic agent and with the system initially filled with gas of the same composition as fresh gas. At the start of each study the subject model was assumed to be free of nitrogen. Body content of anaesthetic agent has been expressed at BTPD as the total amount present at the end of each breath, and equals the sum of the amount present in the functional residual capacity and the amounts dissolved in blood and body tissues.

The influence of fresh gas flow was determined by comparing uptake at fresh gas inflows to the circle system of 8, 4, 2, 1 and 0.5 litre min⁻¹ with uptake under non-rebreathing conditions. With halothane and methoxyflurane a fresh gas flow of 0.25 litre min⁻¹ was also used. These studies were performed with an initial circle volume of 6 litre and with the system both initially free of the agent being used and primed with gas of the same composition as fresh gas. The influence of the volume of the circle system was evaluated by repeating these studies with circle systems of initial volumes of 3 and 12 litre.

The concentration effect was examined with fresh gas concentrations of 60 and 6% nitrous oxide, under non-rebreathing conditions and with fresh gas flows to the circle system of 0.5 to 8 litre min⁻¹. Second gas effects were examined by comparing the uptake of nitrous oxide and halothane when given separately and in combination. The effects of variations in cardiac output and ventilation were studied using values of cardiac output and minute ventilation of one-half, and double, the values of these variables shown in table I. These studies were performed under non-rebreathing conditions and with fresh gas flows of 1, 0.5 and (with the volatile agents) 0.25 litre min⁻¹. The nitrous oxide portion of this study was repeated with a fresh gas nitrous oxide.
concentration of 2%. The effects of changes in cardiac output and ventilation on halothane homeostasis were compared when this gas was given in oxygen, and in combination with 60% nitrous oxide.

RESULTS

The ratios of alveolar to fresh gas anaesthetic concentrations for the three agents under non-rebreathing conditions and with the circle system initially free of the agent in use and supplied with a range of fresh gas flows are shown in figure 1. The corresponding changes in body anaesthetic content are shown in figure 2, whilst the inspired anaesthetic concentrations during these studies when the circle system was in use are shown in figure 3. Figures 4 and 5 show the alveolar and inspired anaesthetic concentrations when these studies were performed with the circle system initially filled with fresh gas. Figure 6 shows the patterns of change in the gas concentrations of the three agents in the circle system when administered through systems of volumes of 3 and 12 litre, supplied with a fresh gas flow of 1 litre min⁻¹, and with the circle system initially both primed and unprimed with fresh gas. Figure 7 shows the related alveolar gas concentrations.

The effects of 10-fold changes in the nitrous oxide concentration of the fresh gas on the rate of increase of alveolar towards fresh gas concentration under non-rebreathing conditions and with fresh gas flows of 4 and 2 litre min⁻¹ are shown in figure 8. Figure 9 shows the rates of change of alveolar anaesthetic concentration when nitrous oxide and halothane were administered separately, and in combination, under non-rebreathing conditions and with a circle system supplied with fresh gas flows of 4 and 2 litre min⁻¹.

The effects of an increase and decrease in cardiac output on alveolar anaesthetic concentrations, both under non-rebreathing conditions and with the circle system supplied with a fresh gas flow of 1 litre min⁻¹, are shown in figure 10. The corresponding results of changes in ventilation are shown in figure 11. In figure 12 the effects of changes in cardiac output and ventilation under these conditions and at fresh gas flows of 0.5 and 0.25 litre min⁻¹ have been plotted as a histogram, to show for each agent the effects of changes in ventilation and cardiac output on alveolar anaesthetic concentrations as the percentage change from the control alveolar concentration at the end of 30-min administrations. Figure 13 compares, as a similar histogram, the effects of cardiac output and ventilation on alveolar nitrous oxide concentration when this gas was administered at fresh gas concentrations of 60% and 2%, whilst figure 14 shows the effects of changes in cardiac output and ventilation on alveolar halothane concentrations when 2% halothane was administered in oxygen and with nitrous oxide.

DISCUSSION

The fresh gas flows and compositions used in the studies described in this paper are unlikely to be followed in clinical practice. It is rare for the clinician to administer a fixed concentration of an inhalation agent, or to use a fixed low fresh gas flow throughout an administration. The rigidly controlled conditions that have been used here are necessary to elucidate the various influences of the use of the circle system on gas uptake.

The three agents used in these studies have been chosen as exemplifying agents of low, intermediate and high solubility in blood. Under non-rebreathing conditions the blood: gas partition coefficient of an inhaled anaesthetic agent markedly influences the course of uptake. The findings of this study demonstrate that the magnitude of the various influences of a circle system upon the uptake process are similarly affected by blood solubility.

Figure 1 shows that, compared with the non-rebreathing state, the rate of increase of alveolar anaesthetic tension is decreased during the use of a circle system. The magnitude of this reduction is a function of the solubility in blood of the agent being used, being least with nitrous oxide and greatest in the case of methoxyflurane. With halothane and methoxyflurane the rate of increase of alveolar anaesthetic concentration decreased as the fresh gas flow to the circle system was reduced. This was also true in the case of nitrous oxide early in its administration. With fresh gas flows greater than 1 litre min⁻¹, alveolar nitrous oxide concentration eventually increased to exceed fresh gas concentration. The modifications in the rates of increase of alveolar concentration for each agent are mirrored in the changes in body anaesthetic content (fig. 2) and are related to the change in circle system (and thus inspired) gas concentrations (fig. 3).

Figures 1–3 show the time-course of events with the circle system initially free of anaesthetic
Fig. 1. Alveolar to fresh gas concentration ratios during 30-min administrations of 60% nitrous oxide, 2% halothane and 2% methoxyflurane. At the start of each administration the circle system was free of the agent being used. Note the different y-axis scaling factors. In this and succeeding figures the curves marked N refer to non-rebreathing conditions, whilst the figures against the other curves refer to fresh gas flows in litre min⁻¹.

Fig. 2. Total body anaesthetic content (V) (litre BTPD) associated with the administrations shown in figure 1.

Fig. 3. Inspired to fresh gas concentration ratios during the circle system administrations shown in figure 1.
agent. A somewhat different course of events occurs when, at the start of administration, the circle system contains some of the agent in use. Figures 4 and 5 show the changes in alveolar and inspired anaesthetic concentrations when the circle system is initially filled with gas of the same composition as fresh gas. Gas within the circle system acts as a reservoir which can, in part, satisfy the early uptake requirements of the subject. At the start of administration gas concentrations in the circle system decrease from their initial values, as uptake by the subject at this time exceeds the amount of agent entering the system in the fresh gas. The degree of this decrease increases as fresh gas flow is reduced, and also increases with increasing blood solubility of the agent. Later in the administration, as uptake requirements by the subject decrease, anaesthetic concentrations in the circle system increase towards the concentration in the fresh gas, and the rate of input of anaesthetic agent to the circle system equals and then exceeds its rate of removal. With nitrous oxide and with fresh gas flows of 1 litre min$^{-1}$ or more the gas concentration in the circle system at the end of a 30-min administration exceeds the concentration in the fresh gas.

The interactions between the inspired concentration of an anaesthetic, its alveolar concentration and its uptake by body tissues shown in these five figures demonstrate the overriding influence of the circle system on anaesthetic uptake. Uptake of an agent by a subject during the use of a circle system will, of necessity, reduce the amount of that agent remaining within the circle system, and tend to reduce the concentration of that agent within the circle system. The consequent diminu-
tion in inspired anaesthetic concentration will decrease the rate of uptake and limit the rate of increase of alveolar concentration. As the fresh gas flow to the circle system is diminished, so removal of anaesthetic by the subject has an increasing effect upon the residual concentration of that agent. With increasing blood solubility of an agent, increasing amounts are removed by uptake by the subject, and the effects of the circle system on gaseous homeostasis are correspondingly increased.

The changes in nitrous oxide concentration in the subject and in the circle system reflect an interplay between the uptake of this agent and oxygen uptake. In the early stages of administration the magnitude of nitrous oxide uptake commonly exceeds the magnitude of oxygen uptake. With the circle system primed with fresh gas, nitrous oxide concentration within the system decreases initially and oxygen concentration increases. Within a relatively short period of time, the rate of nitrous oxide uptake decreases, first to equal and then to be less than oxygen uptake. This explains the later increases in nitrous oxide concentrations shown in figures 4 and 5. If fresh gas composition is unchanged during the administration of nitrous oxide via a circle system, alveolar and inspired nitrous oxide concentrations will always eventually increase to exceed the fresh gas concentration. The final equilibrium under these conditions will be influenced by the fresh gas flow and the magnitude of oxygen uptake. In the examples shown here the inspired nitrous oxide concentration will eventually be slightly greater than the fresh gas concentration with a fresh gas flow of 8 litre min⁻¹. At a maintained fresh gas flow of 0.5 litre min⁻¹ of 60% nitrous oxide and with an unchanged oxygen uptake, inspired nitrous oxide concentration would, in theory, (but not in practice) eventually increase to 100%. These factors influencing nitrous oxide concentrations during administration via a circle system are also at play with the other two agents. Because these agents have a far slower time course of uptake than nitrous oxide, are administered with a high concentration of oxygen and have saturated vapour pressures considerably less than 1 atmosphere, it would require a very prolonged administration of a fixed fresh gas flow before inspired and alveolar concentration exceeded fresh gas concentration, and a potentially hypoxic gas mixture could not be present in the circle system. At a fresh gas flow of 0.25 litre min⁻¹ of 2% halothane and with the oxygen uptake as shown in table I, it can be predicted that, at equilibrium, inspired anaesthetic concentrations should exceed 14%. It would, however, require many hours of administration for such high inspired concentration to occur with halothane. Because of its low saturated vapour pressure, such a concentration could not occur with methoxyflurane.

**Influence of circle system volume**

Figures 1–5 demonstrate that the early course of anaesthetic uptake is influenced markedly by the composition of gas initially present within the circle system. A further factor which will influence the course of uptake is the initial volume of the circle system. This influence of circle system volume is illustrated in figures 6 and 7, which show circle system and alveolar anaesthetic concentrations during the use of circle systems of 3- and 12-litre volume and supplied with a fresh gas flow of 1 litre min⁻¹. These figures show the effects of having the system both initially free of agent, and primed with fresh gas. With the system unprimed with agent, circle system and alveolar anaesthetic concentrations increase more rapidly with the circle system of low volume. Conversely, when the system is initially primed with fresh gas, the initial decrease in circle system and alveolar anaesthetic concentrations are greatest with the smaller volume system.

With nitrous oxide delivered to the larger volume circle system initially free of this agent,
The concentration in the circle system at 30 min is about 80% of the fresh gas concentration. With the smaller volume circle system initially containing oxygen, and with both high and low volume systems when initially containing nitrous oxide, circle system concentrations at 30 min are slightly greater than the fresh gas concentration. With both volatile agents, circle system concentrations are nearly equal at 30 min, regardless of the composition of gas initially present in the circle system, but at a concentration considerably less than that in fresh gas.

Figure 7 shows the alveolar anaesthetic concentrations corresponding to the inspired concentrations of figure 6. As is to be expected, alveolar concentrations increase more rapidly when the system is primed initially with the agent in use. With the system initially free of fresh gas, alveolar concentrations follow a smooth curve, and increase more rapidly with the system of smaller volume. When fresh gas is initially present in the circle system, there is a sharp initial increase in alveolar concentration followed, in the case of the volatile agents, by a sharp decrease. Alveolar concentrations increase to a higher initial peak with the system of larger volume, but this initial rate of increase of alveolar concentration is less well maintained than with the system of smaller volume. In the case of nitrous oxide, and with the system initially primed with fresh gas, alveolar concentrations during use of a system of small volume exceed alveolar concentrations with the larger volume system after about 20 min. These changes reflect the changes in inspired concentrations under these conditions.

The volume of a circle system is large in relation to the magnitude of gas exchange, and may be large in relation to the magnitude of fresh gas flow. This relatively large volume gives the circle system some buffering properties, and reduces the rate at which the composition of gas within the system will change as a result of gas uptake, or a change in fresh gas flow or composition.

In a previous publication (Conway, 1981), the buffering properties were expressed in terms of a time constant of change. The magnitude of this time constant was given by:

\[
\text{Time constant} = \frac{\text{Circle system volume}}{\text{Fresh gas flow} - \text{net gas uptake}}
\]

where the term net gas uptake refers to the algebraic sum of all gas uptake with the exception of carbon dioxide. In the absence of gas uptake, the time constant reflects the wash-in or wash-out characteristics of the system. Thus with a circle system of 6-litre volume and a fresh gas flow of 8 litre min\(^{-1}\), the time constant is 45 s, whilst with the same circle system volume and a fresh gas flow of 0.25 litre min\(^{-1}\) the time constant is 24 min. Removal of gas from the system by uptake effectively diminishes the influence of fresh gas flow upon circle system gas composition and increases the time constant of change, so that (in theory) when fresh gas flow exactly balances uptake, the time constant is infinite.

This definition of a time constant disguises the influence on circle system and alveolar gas composition of ventilation by the subject. It is convenient to consider the volume uptake of inhaled anaesthetic gases as having two related components—gas taken up by solution in blood.
and body tissues, and gas added to the gas phase of the lung compartment. The quantity of gas taken up by solution will be predominantly influenced by alveolar gas concentration, cardiac output and the solubility of the agent in blood and body tissues. The amount of gas added to or removed from the gas phase of the lungs will depend mainly upon the inspired to alveolar concentration difference, lung volume and ventilation. At the start of the administration of an anaesthetic, addition to the gas phase is the predominant component of gas uptake and, thus, ventilation plays a major role in determining the rate of increase of alveolar concentration. Later in the administration, when alveolar concentration is changing more slowly, uptake by solution will predominate and ventilation will play a lesser role in determining alveolar concentration. It is for this reason that, in figure 4, where the circle system is in use and initially primed with fresh gas, alveolar concentrations of each gas increase in the first few minutes of administration at nearly equal rates regardless of fresh gas flow, and the rates are similar for each of the three gases. The time constant of change here is mainly related to circle system volume and lung volume, and these are the same in all the examples shown. Indeed, for the first few breaths of any of these administrations, the patterns of increase in alveolar concentration are closely identical regardless of whether or not the circle system is in use, and are determined mainly by lung volume and ventilation. After this initial period of mixing of gas within the lung compartment with that in the circle system, uptake by solution by the subject and the magnitude of fresh gas flow come to play a predominant role in determining inspired and, thus, alveolar gas concentrations.

This early influence of ventilation upon anaesthetic uptake explains why, with a circle system initially primed with agent, alveolar anaesthetic concentrations follow the patterns shown in figure 7. In the first minute of administration the major changes that are occurring relate to gas in the subject's FRC mixing with gas in the circle system. With the circle system initially filled with anaesthetic agent, the amount of agent available to undergo mixing increases as the circle system volume is increased. With a large volume system a higher initial peak value will, therefore, be reached. With a smaller volume system the initial sharp increase in alveolar concentration reaches a lower value and is sustained for a slightly shorter period of time than with the larger volume system.

However, following the initial, mainly ventilation-dependent, phase of uptake, the shorter time constant of change of a 3-litre volume circle system results in alveolar concentrations at a more rapid rate than with the 12-litre system.

Concentration and second gas effects

The dependence of the rate of increase of alveolar nitrous oxide concentration upon the fresh gas concentration and the augmentation of these effects when a circle system is in use are illustrated in figure 8. Under non-rebreathing conditions alveolar concentration increases more rapidly towards inspired concentration when 60% nitrous oxide is in use than with 6% nitrous oxide. The difference becomes more marked with a circle system, with increasing augmentation of the effect as fresh gas flow is reduced.

The concentration effect reflects the influence of the initial concentration of a component of a gas mixture upon the effects of removing a proportion of that component from the mixture. If, for instance the nitrous oxide concentration in a nitrous oxide–oxygen mixture is 1%, removal of one-half of the nitrous oxide present reduces nitrous oxide concentration in the mixture to just over one-half of its initial concentration. If the initial nitrous oxide concentration is 50%, then removal of one-half this gas reduces the residual concentration to two-thirds of the initial value, whilst with 100% nitrous oxide, removal of one-half of this gas has no effect upon nitrous oxide concentration.

![Fig. 8. Alveolar to fresh gas concentration ratios during administration of 60% nitrous oxide (continuous curves) and 6% nitrous oxide (interrupted curves) under non-rebreathing conditions (NRB) and with the circle system supplied with fresh gas flows of 4 (VF4) and 2 (VF2) litre min⁻¹.](image-url)
The concentration effect is evident when an agent is used over a wide range of inspired concentrations, and when significant amounts of that agent are taken up by the body. Nitrous oxide is relatively insoluble in blood, but when it is used in an adult subject at an inspired concentration of 60%, uptake in the first few minutes usually exceeds 1 litre min\(^{-1}\), and throughout a 2-h administration its uptake in the body is unlikely to decrease to less than 100 ml min\(^{-1}\). Methoxyflu- ran, although taken up by the body in comparatively large amounts, is administered over a narrow inspired concentration range and, thus, exhibits an insignificant concentration effect. Halothane occupies an intermediate place between these two agents as regards both its blood solubility and potential inspired concentration range. A small concentration effect could be demonstrated when 10% halothane was administered. Within the conventional range of inspired concentrations, the concentration effect for halothane was negligible.

When a circle system is in use, the concentration effect will operate not only in the alveolar space, but also within the circle system (Conway, 1984). If the fresh gas concentration of an agent is high, removal of an agent by uptake will have a lesser effect upon the residual concentration of that gas within the circle system and thus in the inspired gas, than if fresh gas concentration is low. Because the influence of uptake upon circle system gas composition increases as fresh gas flow decreases, so the magnitude of the concentration effect also increases as fresh gas flow is reduced from high to low values. This influence of fresh gas flow is evident in figure 8.

The second gas effect results from the increase in concentration of one component of a gas mixture caused by removal of part of another component. Like the concentration effect, this phenomenon will influence circle system gas composition as well as acting in the alveolar space, and will have an increasing influence as fresh gas flow is reduced from high to low values. This effect is shown for halothane and nitrous oxide in figure 9. Under non-rebreathing conditions the second gas effect of halothane upon nitrous oxide is hardly discernible. With the circle system in use this effect is slightly more pronounced. Figure 9 shows that the absolute magnitude of the second gas effect of nitrous oxide upon halothane is approximately equal under non-rebreathing conditions and with the circle system in use. As alveolar halothane concentrations are less during circle system use, this implies an increase in the relative magnitude of this effect.

**Influence of ventilation and cardiac output upon uptake**

The effects of a doubling and halving of cardiac output upon the rates of increase in alveolar anaesthetic concentration, under non-rebreathing conditions and with a circle system supplied with a fresh gas flow 1 litre min\(^{-1}\), are shown in figure 10. The corresponding effects of similar changes in ventilation are shown in figure 11. These
Fig. 11. Alveolar to fresh gas concentration ratios during administration of nitrous oxide (N), halothane (H) and methoxyflurane (M) under non-rebreathing conditions and with a circle system supplied with a fresh gas flow of 1 litre min\(^{-1}\). The continuous lines relate to the model having a minute ventilation of 6 litre min\(^{-1}\). The interrupted lines relate to a halving, and the dotted lines to a doubling of minute ventilation.

These effects, together with the effects at different fresh gas flows, are shown as a histogram in figure 12. A decrease in cardiac output results in a lesser amount of agent being removed from the alveolar space by blood perfusing the lung, and the increase in alveolar tension that this produces is associated with a reduced rate of uptake of anaesthetic agent by the subject. An increase in ventilation results in a greater amount of agent being available for uptake from alveolar gas into pulmonary capillary blood, and thus an increase in both the rate of increase in alveolar concentration and the rate of uptake into body tissues. The effects of changes in both cardiac output and ventilation are least with nitrous oxide. Whilst the changes with halothane are larger in the absolute sense than those with methoxyflurane, figure 12 shows that, in terms of percentage change from control, the reverse is true.

The right-hand portion of figure 10 shows the effects of changes in cardiac output during the use of a circle system. It is apparent that, when the circle system is in use, the influences of cardiac output on alveolar nitrous oxide concentration are enhanced. The influences of cardiac output upon the two volatile agents are less obvious, but figure 12 shows that the effect of a circle system is to enhance the influence of cardiac output with all agents. Figure 11 shows that, with a circle system in use, the effects of ventilation on alveolar concentrations of all three gases have been considerably limited.

These effects of a circle system result from changes in circle system, and thus inspired, gas concentration, as a result of the influence of cardiac output and ventilation upon uptake. A

Fig. 12. Histogram to show the effects of doubling and halving cardiac output (left hand panel) and ventilation (right hand panel) upon alveolar anaesthetic concentrations. In this and the succeeding histograms, alveolar concentrations at the end of 30-min administrations for each cardiac output and ventilation value are expressed as the percentage difference from the alveolar concentrations at the end of a 30-min administration with the control values of cardiac output and ventilation. The solid bars refer to the non-rebreathing state, horizontal hatching refers to a fresh gas flow of 1 litre min\(^{-1}\), vertical hatching refers to a fresh gas flow of 0.5 litre min\(^{-1}\) and diagonal hatching refers to a fresh gas flow of 0.25 litre min\(^{-1}\).
reduction in cardiac output and the consequent reduced rate of removal of agent from alveolar gas into pulmonary capillary blood will, during circle system use, be associated with a reduced amount of agent being removed from the system. The resulting increased inspired gas concentration will tend further to increase alveolar gas concentration. An increase in ventilation will increase the amount of an agent removed from the system and thus reduce inspired concentration. This will oppose the effects of ventilation upon alveolar concentration. The magnitudes of the augmentation of the effects of changes in cardiac output and the reduction of the effects of changes in ventilation increase as fresh gas flow is reduced towards basal values. This is because removal of a given amount of agent from a circle system will have a greater effect upon the residual concentration when fresh gas flow is low than when it is high.

These modifications, by a circle system, of the effects of ventilation upon the uptake process confirm those which Eger and his associates derived from a simple analogue model (Eger et al., 1973; Eger, 1974). These workers also showed that the use of a circle system augmented the effects on alveolar anaesthetic concentration of changes in uptake by the subject, but did not differentiate between changes in uptake as a result of alterations in cardiac output and those from changes in blood solubility.

Figure 12 shows that the diminution of the effects of changes in ventilation on alveolar gas concentration that occur with the circle system become more marked as the blood solubility of the agent used increases. At a fresh gas flow of 0.5 litre min\(^{-1}\), a doubling of ventilation has, in the case of nitrous oxide, an effect which is 63% of the effect seen under non-rebreathing conditions. The corresponding figures for halothane and methoxyflurane are 14% and 6.5%, respectively. Conversely, with a circle system in use, the augmentation of the effects of changes in cardiac output on alveolar anaesthetic concentration is greater with agents of low as opposed to high blood solubility. At a fresh gas flow of 0.5 litre min\(^{-1}\) the effect of halving cardiac output is, in the case of nitrous oxide, more than 12 times the effect under non-rebreathing conditions. With halothane the effect is 140% greater, and with methoxyflurane only 40% greater than in the non-rebreathing state. Whilst under non-rebreathing conditions the effects of changes in both cardiac output and ventilation on alveolar gas concentration are approximately twice as great for methoxyflurane as for halothane, with the circle system supplied with a fresh gas flow of 0.5 and 0.25 litre min\(^{-1}\) the influences of both these variables on the two agents are approximately equal. Indeed, at the lowest fresh gas flows, the effects of doubling or halving ventilation upon alveolar concentrations of all three agents used are slight and of the same order of magnitude.

These modifications by a circle system of the effects of changes in ventilation and cardiac output upon the uptake process reflect the interrelationships between inspired gas composition and gas uptake inherent in the use of a circle system. Use of a circle system will augment the effects of a decrease in cardiac output because of a concomitant increase in circle system, and thus inspired, gas concentration. This increase will tend to promote uptake and oppose the primary influence of the reduction in cardiac output. The opposing influence will be greater with agents of high blood solubility which are taken up in large rather than small amounts, and will have a greater influence as the flow of fresh gas is reduced from high to low. Limitation of the effects of ventilation results from a reduction in inspired anaesthetic concentration. The degree of attenuation of the effects of an increase in ventilation will depend on the amount of agent removed from the circle system, and this amount will again be greater with agents of high rather than low blood solubility. The effect of the removal of the agent on gas concentrations in the circle system will increase as fresh gas flow is reduced from high to low. Similar reasoning can be used to explain the effects, during the use of the circle system, of reductions in ventilation and increases in cardiac output.

These effects of changes in ventilation during the use of the circle system differ from the effects of changes in ventilation on the depth of anaesthesia that occur when a vaporizer is used within a circle system. In the studies described here, vaporization of volatile agents has been performed outside the circle system and is uninfluenced by ventilation. With a vaporizer within the system, ventilation would be the major determinant of vaporization and, thus, of the composition of the inspired and alveolar gases.

The reduced influence of ventilation shown here also differs from the situation that arises when, during circle system use, a constant alveolar anaesthetic concentration is maintained by manip-
ulation of the amount of anaesthetic added to the system and, hence, of the inspired gas concentration. Under these conditions the amount of agent present in the alveolar space remains constant, and the uptake of the agent by solution in the blood perfusing the lung is controlled by the amount of agent added to the lungs in the inspired gas—the product of inspired concentration and alveolar ventilation. If this control is effected purely by manipulation of the inspired gas concentration, changes in ventilation will be compensated for by the changes in the inspired concentration and will not influence the uptake of the anaesthetic.

In evaluating the effects of cardiac output and ventilation, changes in alveolar gas concentration have been compared at the end of 30-min periods of administration. This is a convenient but arbitrary criterion. It is not completely satisfactory to use this criterion in comparing the effects of blood flow and ventilation on nitrous oxide with those on the two volatile agents, as with nitrous oxide there is a more rapid increase in alveolar towards the equilibrium concentration. Cardiac output and ventilation will influence the rate of increase of alveolar gas concentration, but will not influence the final equilibrium concentration. The effects of cardiac output and ventilation on the uptake process will diminish as equilibrium is approached. The criterion used here has been chosen to illustrate qualitative differences of the effects of cardiac output and ventilation on the three agents used, and is not intended as a quantitative index of these differences.

Nitrous oxide has been used in these studies at a much higher concentration than the two volatile agents. Figure 13 compares the effects of changes in cardiac output and ventilation when nitrous oxide is supplied at fresh gas concentrations of 60% and 2%, under non-rebreathing conditions and with fresh gas flows to the circle system of 1 and 0.5 litre min⁻¹. This figure shows that, both under non-rebreathing conditions and with a circle system, the effects of cardiac output and ventilation on alveolar anaesthetic concentrations are concentration-dependent, being greater when 2% nitrous oxide is being administered than with 60% nitrous oxide. This influence of administered gas concentration on the effects of cardiac output and ventilation can be explained in a way similar to the concentration effect. If the alveolar concentration of a gas is 100%, it will not be influenced by changes in cardiac output and ventilation. As alveolar concentration is reduced, so alterations in the amount of gas removed by uptake have an increasing influence on the residual gas concentration.

Similar effects take place within the circle system, so that the influence of factors modifying uptake will increase as fresh gas concentration is reduced.

Given that the magnitude of the influences of cardiac output and ventilation upon alveolar anaesthetic concentrations are influenced by the alveolar concentration of an agent, it can be predicted that, because of the second gas effect, cardiac output and ventilation will have a slightly lesser effect on alveolar anaesthetic concentrations when agents are given in combination than when given separately. That this is so is shown in figure 14, which compares the influences of cardiac output and ventilation on alveolar halothane concentration when 2% halothane is administered with oxygen, and with 60% nitrous oxide. Both under non-rebreathing conditions and with the circle system in use, the influences of cardiac output and ventilation are greater when halothane is being given with oxygen than when nitrous oxide is present, although the differences are less than those seen with high and low concentrations of nitrous oxide.

CONCLUSIONS

As stated previously, the patterns of fresh gas flow and composition used in these studies have not been intended to follow those used during clinical
anaesthesia, but have been rigidly controlled so as to demonstrate the various aspects of the uptake of anaesthetic gases that are influenced by the use of a circle system. The findings relate to the behaviour of a mathematical model, and should be taken as a guide to the pattern of anaesthetic uptake and, thus, the course of anaesthesia when the circle system is in use, rather than as predictions of absolute behaviour. In these studies the influence of nitrogen has been ignored. In practice, nitrogen initially present in the lungs and tissues of the subject would dilute the contents of the circle system, and slow down the course of anaesthetic uptake. This effect would be slight except at fresh gas flows close to the basal value.

The only direct way in which the presence of a circle system can influence gas uptake is by a modification of the inspired gas concentration. Because gas concentration within a circle system is itself influenced by the uptake of gas by the subject, there are complex interrelations between fresh gas flow and composition, inspired and alveolar gas concentration, and the uptake of gas by the subject. The effects of factors known to alter the course of uptake, such as changes in ventilation and cardiac output, may be influenced considerably by these interrelations.

Of the three agents chosen to illustrate the findings of this paper nitrous oxide was the least, and methoxyflurane the most affected by the presence of a circle system. The effects on halothane, a gas of intermediate blood solubility, were of intermediate magnitude.

Halothane, enflurane and isoflurane are the most widely used volatile anaesthetic agents. The performance of the model with these last two agents in the studies described in this paper is broadly similar to that of halothane. A major reason for the popularity of these agents is their relatively low solubility in blood. When these agents are used under non-rebreathing conditions an adequate depth of anaesthesia can be attained fairly rapidly, and can be controlled readily by adjusting the inspired concentration. When these agents are used with a circle system and a low fresh gas flow, this does not apply. The alveolar concentration of the anaesthetic will now increase towards the fresh gas concentration in a manner more closely resembling that seen with highly blood soluble agents. With a circle system used in the ways used in this study, attainment of adequate brain concentrations of volatile agents would be a lengthy process, and changes in the fresh gas anaesthetic concentration would take a considerable time to influence the depth of anaesthesia. In practice, the administrator has to take steps to overcome this debasement, such as priming the system with a high concentration of anaesthetic agent, commencing administration with a period of high fresh gas flow, or increasing fresh gas flow at times when it is necessary to alter the depth of anaesthesia.

The paradoxical concentration and second gas dependence of the effects of cardiac output and ventilation on gas uptake is unlikely to be of major clinical significance. The overall influence of a circle system in augmenting the effects of changes in cardiac output and limiting the effects of changes in ventilation is of some importance and, in one way, can be seen as a potential disadvantage of circle systems. In the studies described, cardiac output and ventilation were maintained constant throughout each study. In clinical practice cardiac output will tend to decrease as the depth of anaesthesia increases and, in spontaneously breathing subjects, this reduction in cardiac output will commonly be associated with a decrease in ventilation. A decrease in cardiac output will result in a greater increase in alveolar anaesthetic concentration when a circle is in use than under non-rebreathing conditions, and the increased depth of anaesthesia will tend to reduce cardiac output further. Since the effects of a decrease in ventilation are attenuated when a circle system is
in use, these potentially progressive effects of cardiac output would not be opposed by any coexistent respiratory depression.

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