OUTPATIENTS expect to be able to walk into hospital and out again. They are usually unsedated and often apprehensive. When they are anaesthetized, induction must be rapid, depth of anaesthesia must be deep enough for the operative procedures performed—yet not so deep as to obtund protective reflexes—and prolonged recovery must be avoided. Many anaesthetic techniques are used with the aim of providing these conditions. Most of them make use of inhalational drugs. Whatever the technique, outpatient anaesthesia is associated with rapid changes in the depth of anaesthesia and in the respiratory and cardiovascular state of the patient. The so called "steady state" is unlikely even to be approached. These circumstances place the pharmacokinetics of outpatient inhalational anaesthesia into a special category.

It is not known how anaesthetics work. It can be assumed that for a given anaesthetic, depth of anaesthesia depends upon the number of anaesthetic molecules acting on cells in the brain. This in turn depends upon the partial pressure of the anaesthetic in the brain tissue fluid. An understanding of the factors affecting the partial pressure of an inhalational anaesthetic in this tissue fluid, therefore, is the key to an understanding of the control of inhalational anaesthesia. Two factors which are related to the partial pressure of an inhalational anaesthetic in nervous tissue are its uptake and elimination. The relationship is not a simple one. It cannot be appreciated without an understanding of the pharmacokinetics of inhalational anaesthesia, at least in general terms. That is why the first part of this article is taken up with a general description of inhalational anaesthesia.

No measurements of the uptake and elimination of inhalational anaesthetics during outpatient anaesthesia have been made, so the remainder of the article is concerned only with a discussion of possible approaches to the problem and with an outline of some preliminary laboratory measurements. If methods of measurement can be evolved, which are suitable for the special and difficult circumstances of outpatient anaesthesia, they may well find more general application.

INHALATIONAL ANAESTHESIA

General considerations.

If a patient were to breathe an inhalational anaesthetic at a constant inspired partial pressure for long enough, he would become saturated with it at that partial pressure. The partial pressure of the anaesthetic in the brain would then be the same as that in the alveoli. Its alveolar partial pressure, however, would be less than that in the mixture inspired from the mask, due to dilution with water vapour.

Theoretically it would take an infinite time to reach saturation, but it would be difficult to detect the difference between full saturation and, say, 97 per cent saturation. For practical purposes, therefore, one can assume that saturation can be achieved within a finite period, although not within the duration of an outpatient anaesthetic. The time taken to reach body saturation (or a given degree of saturation) with an inhalational anaesthetic, inspired at any constant partial pressure, depends: upon pulmonary ventilation; upon the solubility of the anaesthetic in blood; upon the pulmonary capillary blood flow; upon the distribution of arterial blood to the tissues; upon the solubilities of the anaesthetic in different tissues; and upon the different tissue masses.

Consider a hypothetical patient whose respiration and circulation remain steady under all circumstances, and let him inspire an inhalational anaesthetic at a constant partial pressure. The rate of saturation of his body would depend partly...
UPTAKE AND ELIMINATION OF INHALATION ANAESTHETICS

upon the concentration of the anaesthetic inspired (see the "concentration effect" below); but as a first approximation, the time taken to reach a given degree of body saturation would be the same for any constant inspired partial pressure used in clinical practice. The dose of anaesthetic required for a given degree of body saturation, however, would be greater for a high inspired partial pressure of anaesthetic than for a low inspired partial pressure. (Dose is taken here as synonymous with amount of inhalational anaesthetic taken up by the pulmonary capillary blood. It does not include any anaesthetic which is expired without having entered the circulation.)

These various relationships may be illustrated by considering what happens during the management of an inhalational anaesthetic using a non-rebreathing system. In practice the processes described are modified as a result of the effect of anaesthesia, and of surgical stimulation, upon respiration and upon the circulation.

INDUCTION OF ANAESTHESIA

The first inspiration.

The anaesthetic mixture inhaled at the first breath is diluted by the gases already in the lungs and by water vapour. The dilution depends upon the volume inhaled in relation to the anatomical deadspace and the functional residual capacity. Some of the anaesthetic reaching the alveoli is taken up into solution by the pulmonary capillary blood. The quantity of anaesthetic taken up depends upon its partial pressure in the alveoli, upon its solubility in blood and upon the pulmonary capillary blood flow. At the start of the first inspiration the partial pressure of the anaesthetic in the alveoli is zero. It rises to a maximum at the end of inspiration (Smith and Butler, 1963). The rate of uptake follows the same pattern. The changes in the alveolar partial pressure and in the uptake of anaesthetic, however, are pulsatile because of the pulsatile flow of the pulmonary capillary blood (Dubois and Marshall, 1957; Wasserman and Comroe, 1962).

At the same time as the inspired anaesthetic mixture is being diluted by the gases in the lungs, the nitrogen in the lungs is being diluted by the anaesthetic mixture. As a result, some of the nitrogen in the pulmonary capillary blood comes out of solution and passes into the alveoli. The volume of nitrogen released is usually negligible compared with the corresponding volume of anaesthetic taken up, because of the relatively lower solubility of nitrogen in blood. If the solubility of nitrogen in blood was the same as that of the anaesthetic it would no longer be permissible to ignore the nitrogen exchange. The volume of anaesthetic taken up by the pulmonary capillary blood would be exactly balanced by the corresponding volume of nitrogen coming out of solution. The "concentration effect" and "diffusion anoxia", which are discussed below, would not exist, and some of the methods used for estimating the uptake of nitrous oxide would not be possible. If the solubility of anaesthetic in blood was less than that of nitrogen, then the "concentration effect" and "diffusion anoxia" would be reversed, but the effect would be too small to be worth considering. Nitrogen exchange is ignored throughout the following arguments in order to simplify the description, but it does occur.

There is also a small difference between the volume of oxygen taken up and the volume of carbon dioxide eliminated. For the purpose of this discussion the respiratory exchange ratio has been taken as unity. The respiratory exchange ratio in the alveoli, however, may vary during the course of an anaesthetic and during a single respiratory cycle (Comroe et al., 1962). Oxygen uptake may also be reduced appreciably should hypoxic anaesthetic techniques be used in which the alveolar partial pressure of oxygen falls to levels corresponding with the steep part of the oxygen dissociation curve of haemoglobin.

The inspiratory flow of the anaesthetic mixture through the airways into the alveoli is generated by the pressure gradient between the mask and the alveoli. The expansion of the thorax is the main cause of the pressure gradient, but the extraction of anaesthetic by the pulmonary capillary blood also plays a small but definite part in reducing the intra-alveolar pressure. The volume of an anaesthetic mixture inspired, therefore, is equal to the volume increase in thoracic capacity plus the corresponding volume of anaesthetic taken up by the pulmonary capillary blood. The volume of anaesthetic taken from the alveoli is thus made good by the inflow of an equal volume of anaesthetic mixture.
The "concentration effect" during inspiration.

The extent to which this replacement volume helps to maintain the alveolar partial pressure of anaesthetic depends upon its concentration in the inspired mixture. If undiluted anaesthetic is inspired (e.g., 100 per cent nitrous oxide) then the anaesthetic taken up is replaced by an equal volume of undiluted anaesthetic and its alveolar partial pressure is fully maintained. The rate of anaesthetic uptake is high, both because its alveolar partial pressure reaches the highest level possible with that breath and because this partial pressure is maintained in the face of uptake by the pulmonary capillary blood.

If a mixture of anaesthetic and oxygen is inspired (e.g., nitrous oxide and oxygen) then the rate of anaesthetic uptake is both absolutely and relatively lower. The absolute reduction is because the alveolar partial pressure of anaesthetic after inspiring a given volume of anaesthetic mixture is less than that reached after inspiring the same volume of undiluted anaesthetic. The relative reduction is because the alveolar partial pressure is further reduced due to the replacement of the anaesthetic taken up by the inflow of a smaller volume of anaesthetic, the difference being made up by oxygen. This relative reduction in the alveolar partial pressure of anaesthetic is accompanied by a relative rise in the alveolar partial pressure of oxygen.

Expressed in another way, the time taken to reach a given degree of body saturation is increased slightly as the concentration of anaesthetic in the inspired mixture is reduced. This has been termed the "concentration effect" (Eger, 1963a, b, c). The contributory changes occurring during expiration are discussed below. The "concentration effect" has been analyzed mathematically (Eger, 1963b). The difference between the rates of body saturation when dogs are ventilated with anaesthetic and with sub-anaesthetic concentrations of nitrous oxide has also been demonstrated experimentally (Eger, 1963a).

Heller and Watson (1962) demonstrated a moderate rise in the partial pressure of oxygen in the arterial blood of man at the start of the induction of anaesthesia when using 79 per cent nitrous oxide with 21 per cent oxygen. When the inspired oxygen concentration was reduced to 14 per cent, they found a moderate drop in its arterial partial pressure. As the inspired concentration of oxygen is reduced its alveolar partial pressure falls. It may not fall quite as much as it would if the solubility of nitrous oxide was the same as that of nitrogen, but the absolute gain in the alveolar partial pressure of oxygen is not sufficient to justify the "effect" as a source of comfort to anyone making deliberate use of hypoxic techniques during the induction of anaesthesia.

If the volume of anaesthetic uptake is small, then the time taken to reach a given degree of body saturation can be considered as the same for any constant inspired partial pressure of anaesthetic—provided that the respiratory and the cardiovascular states are always the same.

The first expiration.

Recoil of the thorax causes a rise in the intra-alveolar pressure. The resulting pressure gradient between the alveoli and the mask generates the expiratory gas flow. While the expired gases are leaving the thorax, however, uptake of the inhalational anaesthetic continues according to its alveolar partial pressure. This tends to reduce the intra-alveolar pressure. The volume of gases expired, therefore, is equal to the volume decrease in thoracic capacity less the corresponding volume of anaesthetic taken up by the pulmonary capillary blood. The volume of anaesthetic taken up from the alveoli by the pulmonary capillary blood is thus replaced by the retention of an equal volume of alveolar gas.

The "concentration effect" during expiration.

Even if undiluted anaesthetic is inspired, it is then diluted in the lungs, so that anaesthetic taken up during expiration is replaced by a smaller volume of anaesthetic which is retained in the alveoli. The difference is made up by the retention of oxygen and carbon dioxide according to their respective alveolar concentrations. This results in a reduction of the alveolar partial pressure of anaesthetic, and of its uptake, as expiration proceeds. The lower the partial pressure of anaesthetic inspired, the greater is the relative reduction in its alveolar partial pressure during expiration. While the alveolar partial pressure of anaesthetic falls, the alveolar partial pressures of oxygen and of carbon dioxide rise. After a short interval, depending
amongst other things upon the lung-to-brain circulation time, the rise in partial pressure of carbon dioxide can be expected to result in a central stimulation of respiration.

The distribution of anaesthetic taken up during the first breath.

The partial pressure of the anaesthetic in the arterial blood leaving the pulmonary capillaries is virtually the same as that in the alveoli (Forster, 1963). A proportion of this blood reaches the brain after a delay depending upon the lung-to-brain circulation time. At the brain, which is well perfused, there is a further drop in the partial pressure of the anaesthetic, due to its redistribution between the blood and the brain tissue. Some of the anaesthetic returns to the heart and lungs in venous blood at the reduced partial pressure. Similar exchanges happen throughout all the tissues of the body, although in some of the tissues they may not start until an appreciable time has elapsed since the first breath of the inhalational anaesthetic.

The second and subsequent breaths.

The dilution of the inspired anaesthetic mixture is less during the second breath because the lungs contain some anaesthetic left over from the first breath. Thus, at any instant during the second breath the partial pressure of anaesthetic in the alveoli is greater than at the equivalent time during the first breath. A similar argument applies between all successive breaths, so that the alveolar partial pressure of anaesthetic increases with each inspiration until body saturation is reached. This breath-by-breath increase in partial pressure, however, is not as great as it would be if none of the anaesthetic were extracted from the alveoli by the pulmonary capillary blood (Harris, 1951). The increase in the alveolar partial pressure of anaesthetic between successive breaths becomes progressively less as the induction of anaesthesia proceeds, provided that the alveolar ventilation and the pulmonary capillary blood flow do not change materially.

There is very little anaesthetic in the mixed venous blood returning to the lungs during the early stages of anaesthesia, because only the venous blood draining the tissues near to the heart contains any anaesthetic at all. As induction proceeds, blood containing anaesthetic returns to the lungs from more distant structures, and the partial pressure in venous blood coming from individual tissues rises as it rises in the tissues themselves. The partial pressure of anaesthetic in the mixed venous blood returning to the lungs thus rises, and this tends to reduce the uptake from the alveoli.

The inspired partial pressure of an inhalational anaesthetic and its induction time and dose.

Suppose the partial pressure of an anaesthetic in the inspired mixture is only a little more than that required in the brain to produce anaesthesia. Then anaesthesia is not achieved until the body is almost saturated with anaesthetic at this low partial pressure.

On the other hand, if a much higher partial pressure of the same anaesthetic is inhaled, anaesthesia is produced long before the body is saturated at this greater partial pressure. Induction time is thus quicker, and the total dose taken up at the end of induction is less than if the lower partial pressure is inhaled for longer. Recovery is therefore likely to be quicker.

MAINTENANCE OF ANAESTHESIA

When the partial pressure of an inhalational anaesthetic in the inspired mixture is only just enough to produce anaesthesia, then this partial pressure cannot be reduced without the risk of the patient waking up.

If anaesthesia of the same depth is induced by inhaling the same anaesthetic at a much higher partial pressure, then maintenance of this partial pressure results in progressively deeper anaesthesia until the body is saturated. If the maintenance of only a light level of anaesthesia is required, the partial pressure of the anaesthetic in the inspired mixture must be progressively reduced, until the body is saturated at the lower partial pressure required for this level of anaesthesia. The dose of anaesthetic taken up when the body is saturated at this low partial pressure is the same regardless of whether the anaesthetic is inhaled at the same partial pressure from the start, or at a higher partial pressure during the induction period. In the latter case, however, body saturation is reached sooner.

Some anaesthetic continues to be taken up even after body saturation has occurred, due to losses through the skin and through any operation sites.


## Recovery From Anaesthesia

The processes of elimination of an inhalational anaesthetic during the recovery period are the reverse of those of anaesthetic uptake during the induction of anaesthesia. Inspired air dilutes the anaesthetic in the alveoli. The alveolar partial pressure of anaesthetic (and also its arterial partial pressure) falls below that in the mixed venous blood returning to the lungs. Some anaesthetic comes out of solution and passes from the pulmonary capillary blood into the alveoli. This tends to delay the fall of its partial pressure in the alveoli, which in turn, tends to delay its subsequent elimination from the blood into the alveoli. At the same time some of the nitrogen in the inspired air is taken up into solution by the pulmonary capillary blood.

If recovery starts when the body is saturated with anaesthetic, then the partial pressure gradients between all the tissues and the capillary blood perfusing them are the same. If recovery starts soon after the end of induction, then well perfused tissues, such as the brain, may be nearly saturated while poorly perfused tissues, such as fat, may be very far from saturated and may at first continue to take up anaesthetic while the more saturated tissues are releasing anaesthetic.

The elimination of anaesthetic from the pulmonary capillary blood into the alveoli continues throughout the respiratory cycle. During inspiration the volume of anaesthetic released from the pulmonary capillary blood helps to fill the increased lung capacity due to the expansion of the thorax. The volume of air inspired, therefore, is equal to the volume increase in thoracic capacity less the corresponding volume of anaesthetic eliminated into the alveoli. The volume of gases expired is equal to the volume decrease of the thorax plus the corresponding volume of anaesthetic eliminated into the alveoli.

"Diffusion anoxia."

The volume of anaesthetic eliminated during inspiration prevents an equal volume of air from entering the alveoli. The volume of anaesthetic eliminated during expiration causes an equal volume of alveolar gas to be displaced from the alveoli. The situation is the reverse of that described under the heading of "concentration effect" during the induction of anaesthesia. The fall in the alveolar partial pressure of oxygen seen during recovery from nitrous oxide and oxygen anaesthesia has been termed "diffusion anoxia" (Fink, 1955). Rackow (1963) has suggested that the corresponding fall in the alveolar partial pressure of carbon dioxide may aggravate "diffusion anoxia" by causing a central depression of respiration. During outpatient anaesthesia patients are not usually saturated with nitrous oxide, so the rate of its elimination is relatively low. "Diffusion anoxia" is therefore of little importance in this context.

The "equivalence" of the patterns of anaesthetic uptake and elimination.

In the hypothetical patient with unchanging respiration and circulation, who is breathing a constant anaesthetic mixture, the pattern of anaesthetic elimination with respect to time would be the mirror image of the pattern of anaesthetic uptake during the induction of anaesthesia—provided that recovery starts from a state of full body saturation. Under these circumstances it can be said that anaesthetic elimination is "equivalent" to anaesthetic uptake.

In outpatient departments, inhalational anaesthetics are usually withdrawn before body saturation has been reached. Under these clinical conditions, therefore, the quantitative rate of elimination of anaesthetic is less than the corresponding rate of uptake. Some modification of the qualitative pattern of elimination can also be expected as a result of the partial redistribution of anaesthetic in the body at the start of the recovery period. Far greater discrepancies between the patterns of uptake and elimination can be expected to arise from the changes in respiration, cardiac output and the distribution of the circulation occurring during clinical anaesthesia (Salanitre et al., 1962).

### Inhalational Anaesthetic Techniques Used in Outpatient Departments

Most of the inhalational anaesthetics have been used for outpatient anaesthesia. Rather than attempt to describe all the techniques and agents which have been employed, two basic techniques and one specific technique will be discussed.

The first basic technique entails the maintenance of a steady level of anaesthesia following induction. When an anaesthetic is used which has
to be inspired at a high partial pressure in order to produce anaesthesia (e.g., nitrous oxide), there is no call to reduce the partial pressure of anaesthetic inspired once anaesthesia has been induced, unless to avoid hypoxia. When an anaesthetic which is capable of producing anaesthesia at a low partial pressure (e.g., halothane) is administered at a much higher partial pressure in order to accelerate the induction of anaesthesia, its inspired partial pressure must then be reduced progressively if a steady level of anaesthesia is to be maintained.

The second basic technique entails the induction of anaesthesia to a depth greater than that required for the surgical procedures. The anaesthetic (e.g., cyclopropane, ethyl chloride or divinyl ether) is then withdrawn and the operation is carried out during the recovery period. Using this technique there is no definable period of maintenance. It implies the use of an anaesthetic capable of producing anaesthesia at a low inspired partial pressure.

The specific technique to be discussed is that recommended for use with the Medrex anaesthetic apparatus (Marrett, 1963). It is an example of the second type of basic technique, and it has been chosen because it is the most recently published outpatient anaesthetic technique and because its analysis presents a formidable challenge. The essentials of the apparatus are indicated schematically in figure 1. A face mask, an expiratory valve, a standard length of corrugated tubing, a halothane vaporizer and a reservoir bag are connected in series. Fresh gases from Rotameters enter the system between the corrugated tubing and the vaporizer. The vaporizer can be partially or completely bypassed. The anaesthetic technique uses flows of 1 l./min of oxygen and 5 l./min of nitrous oxide through a well-fitting face mask for the first five breaths of the induction, the vaporizer being turned three-quarters on according to the dial. The nitrous oxide supply is then turned off and the vaporizer is turned full on, the flow of oxygen remaining at 1 l./min. Induction is continued until the eyelash reflex is abolished or until the jaw is relaxed. The mask is then removed and the operation is carried out during recovery. The description thus far presents enough problems for the purposes of the present discussion. The original article should be consulted for further details of the apparatus and the technique.

During the first five breaths, nitrous oxide, oxygen, and a completely unknown concentration of halothane are respired, and there is some rebreathing. During subsequent breaths there is considerable rebreathing, the nitrous oxide supply is turned off and an unknown, but greater, concentration of halothane is respired. The combined deadspace of the patient's airways, of the mask and of the corrugated tubing is large compared with a normal tidal volume. If the first breath happens to be less than this deadspace plus the volume of fresh gases entering the system, then no freshly vaporized halothane reaches the alveoli. Carbon dioxide accumulation due to rebreathing soon results in deeper breathing so that halothane gets to the patient, but it is delivered at full concentration only towards

![Figure 1](https://example.com/fig1)

Schematic representation of the essentials of the Medrex apparatus—as described in the text.

(Details of the vaporizer control are not shown.)
the end of inspiration. As the induction of anaesthesia proceeds, the increasing depth of anaesthesia tends to reduce tidal volume so that the amount of halothane inspired is reduced. Measurement of the peak concentration of halothane inspired would give no indication of its “effective” inspired partial pressure. It would be more relevant to know what constant concentration of halothane would have to be inspired in the same tidal volume in order to inspire the same mass of halothane, or, in other words, the “mixed inspired concentration” (Nunn and Newman, 1964).

APPROACHES TO THE MEASUREMENT OF THE UPTAKE AND ELIMINATION OF INHALATION ANAESTHETICS

Ways of expressing the uptake and elimination of inhalational anaesthetics.

The uptake of an inhalational anaesthetic is expressed as a dose in units of mass or volume. The rate of uptake is expressed as the dose taken up per unit time. For purposes of comparing one series of measurements with another and in order to allow for changes in the concentration of anaesthetic inspired, rate of uptake has also been expressed in units of mass, time, body surface area and inspired anaesthetic concentration (Butler, 1962). This may be the only way to allow for changes in the inspired concentration, but it should be remembered that different inspired concentrations of anaesthetic may have relatively different effects upon respiration and upon circulation.

It is useful to have some measure of the degree of body saturation with an anaesthetic inspired at a given partial pressure. An obvious way of expressing this would be to give the dose taken up as a fraction of the dose required to saturate the body at that partial pressure. This is not in general use and, furthermore, the dose required for body saturation is usually unknown. Instead, the end-expired partial pressure of anaesthetic (as representative of the alveolar partial pressure) is expressed as a fraction of its partial pressure in the inspired mixture, either as a percentage or as a decimal fraction. This does not necessarily give the same information. If inhaled anaesthetics were always at the same partial pressure throughout the body as in the alveoli (this in fact occurs only at body saturation), then these two measures of the degree of saturation would be identical. The difference between them may prove to be small, but their relationship is neither simple nor obvious.

Rate of saturation can be expressed as the change in degree of saturation per unit time. In this context the degree of saturation may be taken as synonymous with the degree of equilibration between the anaesthetic in the inspired mixture and the anaesthetic in the body.

The same units are used for expressing the elimination of an inhalational anaesthetic.

The pertinence of different expressions of uptake and elimination to the induction, maintenance and recovery periods of inhalational anaesthesia.

Induction. Anaesthesia may be induced to a given depth by administering an inhalational anaesthetic at a low partial pressure for a relatively long time or at a high partial pressure for a relatively short time. The more rapid induction is associated with a lower induction dose of anaesthetic, with a lesser degree of body saturation and with a greater rate of uptake. The expressions of anaesthetic uptake which give the best indication of speed of induction are the rate of uptake and the rate of saturation. If the partial pressure of the anaesthetic in the brain required to produce anaesthesia and the partial pressure of anaesthetic in the inspired mixture are known, then knowledge of the rate of saturation is particularly informative.

When using the Medrex apparatus, however, it is difficult to define degree of saturation. Saturation can be defined only in relation to a given partial pressure of anaesthetic, and using this apparatus the mixed inspired concentration of halothane (or the “effective” partial pressure) varies with the tidal volume, and this changes from breath to breath.

Maintenance. If anaesthesia is being maintained with an inhalational anaesthetic which must be administered at a high partial pressure (e.g., nitrous oxide) then knowledge of its uptake during the maintenance period adds little to the understanding of the changes in its partial pressure in the brain, except in so far as the total dose taken up during the induction and maintenance periods affects the recovery period.

When a high partial pressure of anaesthetic has
been administered in order to produce a rapid induction of anaesthesia, measurement of the changes in saturation during the maintenance period is not possible because the partial pressure of the inspired anaesthetic is not kept constant (see the second basic technique above). It would be of considerable interest to know how the inspired partial pressure of anaesthetic would have to be manipulated in order to keep its partial pressure in the brain constant, but this information cannot be derived from the measurement of uptake alone.

Changes in the rate of uptake which are not attributable to changes in the inspired partial pressure of the anaesthetic or to the steady saturation of the body, would reflect changes in respiration or circulation.

Recovery. Recovery from anaesthesia depends upon the reduction of the partial pressure of anaesthetic in the brain due to its redistribution within the body and due to its elimination through the lungs. The amount of redistribution taking place is related to the degree of body saturation at the partial pressure prevailing in the brain at the end of anaesthesia. If the body is saturated at that partial pressure, then there will be no redistribution. If the anaesthetic is inspired at a constant partial pressure throughout the induction and maintenance periods, then a measure of the degree of body saturation at the start of the recovery period should be relevant to the amount of redistribution taking place.

The time taken to eliminate the anaesthetic in the body is related to its total dose. Consciousness will be regained long before this has all been eliminated, especially if much redistribution takes place. Subsequent changes in local perfusion, as a result of exercise or change of posture, might mobilize sufficient anaesthetic to cause momentary impairment of attention or of muscular co-ordination. This might be of clinical importance in relation to the safe use of inhalational anaesthetics in outpatient departments, particularly if anaesthesia should be prolonged.

The prediction of the uptake and elimination of inhalational anaesthetics in relation to outpatient anaesthesia.

Mathematical theory and analogue computers have been applied to the prediction of the uptake and the elimination of inhalational anaesthetics; but these treatments are based upon assumed values for the relevant respiratory, cardiovascular and tissue parameters. If changes in ventilation or cardiac output are considered, they are usually introduced as sudden changes. The inspired anaesthetic is usually taken to have a constant partial pressure. During outpatient anaesthesia both the respiratory and cardiovascular states may be liable to gradual and to acute changes which have been inadequately defined and which would be difficult to allow for in any theoretical treatment. Even if this were not the case, measurements of actual uptake would be required in order to test the validity of the theoretical analyses.

THE MEASUREMENT OF THE UPTAKE AND ELIMINATION OF INHALATIONAL ANAESTHETICS DURING OUTPATIENT ANAESTHESIA

General considerations.

Volunteers can be anaesthetized in the laboratory using techniques commonly employed in outpatient departments, but it is not so easy to reproduce the normal clinical environment and circumstances, complete with lesions and their surgical treatment. As these factors may have considerable influence on the management and course of anaesthesia, anaesthetics given in the laboratory cannot be regarded as strictly comparable with those given in outpatient departments. The aim should be to measure the uptake and the elimination of inhalational anaesthetics under clinical conditions. The value of such measurements would be limited unless related to simultaneous observations on respiration, on the circulation and on clinical changes during and following anaesthesia. Apparatus used would have to be such that it neither increased the apprehension of patients nor interfered with clinical routine. In view of the brevity of the procedures and the rapid changes in the variables to be measured, as near continuous recording as possible should be attempted.

In the casualty department, using a well-fitting face mask, it should be possible to measure uptake during the induction and maintenance of anaesthesia, and perhaps elimination during the start of the recovery period.

In the dental chair, using a nosepiece, measurements would be possible only so long as nasal respiration was maintained without any leak through
the mouth. This would probably limit observations to the start of the induction period. The use of a well-fitting mask should permit measurements to be continued up to the end of the induction period.

Methods used for the measurement of the breath-by-breath uptake of inhalational anaesthetics during outpatient anaesthesia could be adapted for use during longer procedures in the operating theatre.

The measurement of anaesthetic uptake from the difference between the quantities inhaled and exhaled.

It is impracticable to measure the mass of anaesthetic taken up by weighing the patient. An alternative is to measure the masses of anaesthetic inhaled and exhaled with each breath and to take the difference. The mass of anaesthetic inhaled or exhaled is given by the products of the appropriate tidal volume and the corresponding mixed anaesthetic concentration in the respired gases. The breath-by-breath anaesthetic uptake measured in this way includes anaesthetic retained in the lungs as well as that taken up by the pulmonary capillary blood. The accuracy of this method is least when it is used for measuring the uptake of the less soluble inhalational anaesthetics (e.g., nitrous oxide) after the initial induction period, because body saturation is approached rapidly and after a short while the mass of anaesthetic taken up with each breath is small compared with the mass of anaesthetic inspired. With more soluble anaesthetics (e.g., halothane) body saturation is slower and during brief anaesthetics the mass taken up remains relatively large. Accurate measurements of the elimination of inhalational anaesthetics following outpatient anaesthesia are likely to be very difficult, not only because of the technical problems, but also because few patients are likely to approach saturation, and the quantities excreted with each breath are likely to be very small.

The measurement of respired volumes.

Respired volumes can be measured by spirometry. Recording Tissot spirometers, or the bag-in-a-box system of Donald and Christie (1949) for which an accuracy of within ½ per cent is claimed, can be used with non-rebreathing systems. The method of Nunn (1956), for which an accuracy of within 2 per cent is claimed, can be used with rebreathing systems. Spirometry might be difficult to manage under routine clinical conditions.

Pneumotachography is an alternative which could be used in any breathing system. There are difficulties, such as increased deadspace, variation in calibration with changes in the composition of respired gases, variation in the temperature of respired gases and electronic drift. These problems and steps taken to overcome them have been discussed elsewhere (Smith, 1963, 1964).

The measurement of "mixed respired anaesthetic concentrations": complete and proportional sampling.

If a non-rebreathing system is supplied with a constant anaesthetic mixture, there is no limitation on the methods which can be used for measuring this inspired concentration. The measurement of mixed expired concentrations, even in a non-rebreathing system, is not so easy. It is possible to collect and analyze each complete expiration. This has been tried in the laboratory (Smith, 1963; Smith and Butler, 1963) but the method is unsuitable for clinical circumstances.

A method is required for measuring mixed respired anaesthetic concentrations which can be used with any breathing system (this means that only small samples can be withdrawn) and for both phases of respiration. It is not permissible to withdraw a continuous sample at a steady rate because analysis of the samples withdrawn from each tidal volume would only give the required answer if the flow rate of the respired gases remained constant throughout respiration. If a continuous sample could be withdrawn in such a way that the sampling rate would be a given small fraction of the simultaneous respiratory flow rate, then analysis of the complete sample withdrawn during each phase of respiration would give the true mixed respired anaesthetic concentrations. The volume of the sample withdrawn during each phase of respiration would be proportional to the corresponding tidal volume. This could be achieved by servo-control of a sampling syringe from voltages derived from a pneumotachograph. A device based on this principle is being designed (Bookallil, 1963, personal communication). Separate sampling systems could be used alternatively for inspiration and expiration. The samples could be passed directly into a rapid analyzer or they could be stored in suitable
containers for analysis at leisure. Stored samples, if kept small enough, would permit complete breath-by-breath analysis, not only of the inhalational anaesthetics used, but also of nitrogen washout, oxygen uptake and carbon dioxide exchange, using, for example, mass spectrography or gas chromatography. Such a system could be used for analyzing the anaesthetic technique advocated for use with the Medrex anaesthetic apparatus (Marrett, 1963).

The measurement of anaesthetic uptake using pneumotachography, continuous gas analysis and electronic computation.

The principle of this proposed method is illustrated in figure 2, nitrous oxide being chosen as the anaesthetic in this instance. At top left is illustrated a pneumotachogram during a single breath (flow rate of mixed respired gases with respect to time). At top centre is illustrated a corresponding record of the concentration of anaesthetic in the respired gases. (An infra-red analyzer or mass spectrometer having a rapid response time would be required.) At any instant during that breath the mass flow rate of anaesthetic contained in the respired gas mixture is given by the product of the flow rate of the mixed respired gases and the concentration of anaesthetic in those gases. A plot of mass flow rate with respect to time, so derived, is illustrated at top right. The area between this curve and the baseline gives a measure of the mass of anaesthetic respired. The integration of mass flow rate with respect to time (to get this mass of anaesthetic respired) is illustrated at bottom right. In terms of electronics: voltages proportional to the flow rate of respired gases could be obtained by using pneumotachography; voltages related to anaesthetic concentration could be obtained from an infra-red analyzer, although special circuitry might be required to make this relationship linear.

The principle of the measurement of nitrous oxide uptake using pneumotachography, continuous gas analysis and electronic computation.

Fig. 2
Electronic integrators and multipliers are available. In practice there is an inevitable delay in obtaining measurements of anaesthetic concentration using infra-red analysis, due to the time taken for the sample to travel from the sampling point to the measuring apparatus. The same delay would have to be introduced before presentation of the pneumotachograph voltages to the electronic multiplier. This could be done by storing the information (e.g., on magnetic tape) for the necessary delay period. The sampling rate would have to be kept low when low-flow anaesthetic systems are used. A high sampling rate used when sampling from the Medrex anaesthetic apparatus (Marrett, 1963), for example, would of itself affect the concentration of anaesthetic delivered.

The estimation of anaesthetic uptake from measurements of respired volumes.

If the difference between the volumes of oxygen taken up and of carbon dioxide excreted during the induction of anaesthesia is accepted as small compared with the volume of anaesthetic taken up, if the solubility of anaesthetic in blood is accepted as high compared with that of nitrogen, and if the anaesthetic is inspired at a high concentration, then the volume uptake of anaesthetic can be estimated by taking the difference between the inspired and expired tidal volumes (at b.t.p.s.). This is applicable to the uptake of nitrous oxide. The estimated nitrous oxide uptake does not include the nitrous oxide accommodated in the lungs because this displaces an equal volume of nitrogen, which is expired. The method gives an estimate of the uptake of anaesthetic by the pulmonary capillary blood. Fink (1955) using spirometry during recovery from nitrous oxide anaesthesia, noted differences between the inspired and expired tidal volumes, but he made no quantitative estimates of nitrous oxide elimination.

The measurement of “degree of saturation”.

If end-expired anaesthetic concentration (expressed as a fraction of the inspired anaesthetic concentration) is accepted as a measure of the degree of saturation or of the degree of equilibration, then this is probably the easiest measurement to make. An infra-red analyzer can be used. It should have a rapid response even with a low sampling rate. High sampling rates would not be permissible with low-flow systems such as the Medrex (Marrett, 1963). In some circumstances it may be permissible for the analyzed sample to be returned (downstream) to the breathing system. Frumin et al. (1962) and Salanitre et al. (1962) have used infra-red analyzers for the measurements of degree of saturation with nitrous oxide.

THE MEASUREMENT OF THE UPTAKE OF NITROUS OXIDE DURING THE INDUCTION OF ANAESTHESIA

Measurements using rebreathing systems.

Davy (1800) measured the uptake of nitrous oxide during the induction of anaesthesia while rebreathing nitrous oxide from a counterpoised bell-jar-upon-mercury air holder. He noted the reduced volume at the end of the experiment and analyzed the remaining gases. The purity of nitrous oxide used is not known and the methods of gas analysis would not be accepted today. The rate of uptake over two experiments was about 2,300 ml/min, but it is difficult to assess these results. In the first experiment the air holder held 1,670 ml of nitrous oxide which contained 1/50 common air. In the second experiment the airholder contained 2,980 ml of nitrous oxide mingled with 40 ml of common air. He was his own subject and his functional residual capacity, as measured by rebreathing hydrogen, was 1,935 ml.

Severinghaus (1954) determined the rate of uptake of nitrous oxide by measuring the rate at which it had to be replaced in a closed breathing system to keep the composition and the volume of the respired gas mixture constant. Engström, Herzok and Norlander (1960) used the same principle to measure nitrous oxide uptake during controlled ventilation. Neither method would be appropriate for use during outpatient anaesthesia.

Measurements using 80 per cent nitrous oxide in a non-rebreathing system and collecting each complete successive expiration.

Measurement of the breath-by-breath uptake of nitrous oxide by the lungs and the pulmonary capillary blood during the induction of anaesthesia, from the difference between the quantities inhaled and exhaled, has been attempted in the laboratory (Smith, 1963; Smith and Butler, 1963). Respired volumes were measured by pneumotachography. Voltages derived from the pneumotachograph circuits were also used to control a solenoid mechani-
ism which operated a system for collecting each complete successive expiration in an individual bag. The contents of the bags were analyzed by gas chromatography. Only one complete experiment was reported. The measurement obtained implied an improbably high cardiac output. The most likely source of error was nitrous oxide leakage through the bag material. The experiment served as a preliminary indication of the possibilities and the limitations of such methods.

**Estimations using 80 per cent nitrous oxide in a non-breathing system and measuring the respired volumes.**

The difference between inspired and expired tidal volumes has been measured in the laboratory for the breath-by-breath uptake of nitrous oxide by the pulmonary capillary blood during the induction of anaesthesia. Pneumotachography was used for measuring tidal volumes. It is unfortunate that circumstances did not permit the simultaneous use of the well-tried bag-in-a-box system as a check on the accuracy of pneumotachography. Seven determinations were made with each of two male subjects of similar predicted body surface area but different body build and age. The results will be reported in detail elsewhere (Smith and Butler, 1964). An uptake of nitrous oxide of 2.3 l. (s.t.p.) over the first minute can be taken as representative for both subjects.

**The simultaneous use of pneumotachography and trunk plethysmography.**

As a preliminary to the last study, trial experiments were carried out using a jerkin plethysmograph (Heaf et al., 1961) and pneumotachography in order to obtain simultaneous measurements of respired volume and of changes in thoracic capacity. If changes in intragastric pressure, and changes in the distribution of the circulation between the trunk and the periphery are ignored, then trunk volume changes are synonymous with changes in thoracic capacity. The difference between the respired volume and the corresponding change in thoracic capacity during a single breath gives an estimate of the uptake of nitrous oxide by the pulmonary capillary blood over the same period. As with the last study, the method does not allow for nitrogen exchange, nor for any changes in the respiratory exchange ratio. The jerkin plethysmograph was calibrated against the pneumotachograph while the subject breathed air prior to the induction of anaesthesia. Curves of the uptake of nitrous oxide were obtained, but the method was abandoned because it was considered that the advantages to be gained by attempting to measure the uptake of nitrous oxide during each phase of respiration were negligible compared with the additional inaccuracies and experimental complexities introduced. It does serve, however, to illustrate the description of the processes of uptake given earlier in this article.

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**REFERENCES**


CAMBRIDGE UNIVERSITY MEDICAL SCHOOL

Symposium on Instrumental Measurements in Clinical Anaesthesia

At Addenbrooke's Hospital, Saturday, May 9, 1964

**Morning Session**

10.45 **The Use of Simple Instruments and the Six Senses**

Dr. R. E. Loder (Peterborough).

11.30 **Measurements of Respiratory Function**

Dr. R. I. Bodman (London).

12.15 **Discussion**

To be opened by Dr. A. Crampton Smith (Oxford).

These meetings are open to Anaesthetists of all grades and any members of other departments who are interested. Course fee £1 1s. Charge for buffet lunch (1 p.m.) at the hospital 5s. 6d.

Those intending to attend are asked to notify the Secretary of the Medical School, Tennis Court Road, Cambridge, before Saturday, May 2, 1964, stating whether lunch is required and enclosing the appropriate fee.

**Car Parking.** Please do not park in the hospital forecourt. There is a public car park in Brookside, near the junction of Lensfield Road and Trumpington Street.