UPTAKE OF NITROUS OXIDE DURING THE INDUCTION OF ANAESTHESIA

PART I: APPARATUS AND METHODS

BY

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SUMMARY

A method for measuring the breath-by-breath uptake of nitrous oxide during the induction of anaesthesia, using a non-rebreathing system, is described. The uptake of nitrous oxide is obtained from the difference between the quantities inhaled and exhaled. Pneumotachography is used for measuring respired volumes. The inspired concentration of nitrous oxide is controlled. Each complete successive expiration is collected in an individual bag and a gas chromatograph is used for gas analysis. The presentation of a fresh bag to the breathing system during each inspiration is achieved by a solenoid-operated mechanism. This is controlled by relays which are actuated by the pneumotachograph circuit. Correction factors, limitations and alternative possibilities are discussed.

The breath-by-breath absorption of nitrous oxide during the induction of anaesthesia has been estimated by measuring the quantities of nitrous oxide inhaled and exhaled and taking the difference. This article discusses the methods and apparatus used and some of their limitations. The experimental procedure and the results are discussed elsewhere (Smith and Butler, 1963).

The quantity of nitrous oxide inhaled during a single breath was given by the product of the tidal volume inspired and the concentration of nitrous oxide in the inspired mixture. The quantity of nitrous oxide exhaled was given by the product of the tidal volume expired and the average concentration of nitrous oxide in the expired gas. Subtraction of the quantity of nitrous oxide exhaled from that inhaled gave the quantity of nitrous oxide absorbed through the lungs during that breath, plus the quantity of nitrous oxide retained within the lungs.

A Vickers Research Ltd. flow transducer was used in conjunction with a Respiratory Analyser for the measurement of inspired and expired volumes. The nitrous oxide content of the inspired gas was controlled, a known mixture being inhaled from a Tissot spirometer. The average concentration of nitrous oxide in the expired gas was obtained by collecting each complete expiration in an individual bag and then measuring the nitrous oxide concentration by means of a gas chromatograph (Hill, 1962). A mechanism for automatically collecting each complete successive expiration in an individual bag was operated by solenoids. These were controlled by that voltage output from the Respiratory Analyser which corresponded to flow rate through the flow transducer.

THE BREATHING SYSTEM

The subject breathed into a non-rebreathing system through a nosepiece and a Vickers Research Ltd. flow transducer, as shown in figure 1. The apparatus deadspace, in addition to that contained in the nosepiece, was 60 ml. A tap in the inspiratory limb of the breathing system supplied either room air or a nitrous oxide and oxygen mixture which was stored in a Tissot spirometer. The expiratory limb of the breathing system was terminated by a short length of flexible tube so that the expiratory port could be raised and lowered through 3 mm. During expiration it was automatically lowered on to a bag in which the expired gas was collected through a non-return valve. During inspiration it was lifted clear so that a fresh bag could be presented.

THE MEASUREMENT OF RESPIRED VOLUME

The Vickers Research Ltd. flow transducer was used in conjunction with a Respiratory Analyser...
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Williams, 1960; Scott and Williams, 1960). The voltage output selected from the Respiratory Analyser was that corresponding to respired volume (i.e. “flow rate” voltages electronically integrated with respect to time; see Hill, 1959, and Woolmer, 1961). This was recorded continuously using an Ediswan pen recorder.

A difficulty encountered when using such a system for measuring respired volume is that if the volumes recorded as inspired are consistently different from those recorded as expired, the pen drifts towards one margin of the recording paper. This may occur if the balance of the electronic system varies or is not properly adjusted. It also occurs if there is a real difference between the volumes of gas passing through the flow transducer during inspiration and expiration. Such discrepancies may arise from leaks in the breathing system, from variations in the temperature, humidity and composition of the respired gases, and from differences between the quantities of gas actually inspired and expired. Some difference may be expected normally because the respiratory quotient is usually less than unity. During the induction of anaesthesia using nitrous oxide the volume expired may be considerably less than the volume inspired, due to the quantity of nitrous oxide absorbed.

Whatever its cause, this drift of the pen used to record respired volume has two major disadvantages. Firstly, it necessitates repeated re-centering of the pen. Apart from the inconvenience, it is not easy to do this by hand precisely at the end of an inspiration or an expiration. Secondly, inspired and expired volumes have to be measured over different parts of the pen’s excursion. This makes measurement tedious. It also reduces accuracy since the calibration near maximum deflection of the pen is often different from that near its central position.

In order to overcome these difficulties, the pen which recorded respired volume was automatically returned to zero (i.e. the central position) at the end of each inspiration and expiration, so that all expirations were recorded above the base line and all inspirations below it. This facilitated measurement of the records and, since pen deflections were always measured from the base line, they were more accurate. The arrangement used is shown in figure 2. A polarized master relay (Carpenter Type 4 Mk II, one side stable, 750Ω + 750Ω) was used to detect the change of sign of voltage output.

FIG. 1

Right insert: The non-rebreathing system.
Centre: Outline diagram to show the tap in the inspiratory limb of the non-rebreathing system, and the relationship of the expiratory port to the mains relay, which moves it up and down, and the bags.
Left: Corresponding outlined photograph of the apparatus.
from the Respiratory Analyser, corresponding to the change of direction of flow through the flow transducer. The polarized master relay operated a slave relay and make-before-break contacts on the slave relay momentarily zeroed the "flow rate" integrator every time that the relay operated. Spare contacts were available on the slave relay for working any other apparatus (in this instance it was used for operating the solenoid sampling apparatus). The minimum flow rate required to operate the relay system depended upon the setting of the gain control on the amplifier which was connected between the Respiratory Analyser and the polarized master relay. The time delay inherent in the relay system at "make" of the slave relay was about 20 milliseconds and at "break" it was about 100 milliseconds. If shorter time delays were to be required they could be obtained by replacing the relay system by an appropriate electronic circuit.

**VOLUME CALIBRATION**

The above system for measuring respired volume was calibrated by using a 400-ml syringe to pass known volumes of gas through the flow transducer. The corresponding deflections of the appropriate Ediswan recorder pen were then noted. The calibration for inspired volumes presented no difficulty because the composition, temperature and pressure of the inspired gas were known and constant. Using the 400-ml syringe, known volumes of the gas mixture stored in the Tissot spirometer were withdrawn through the flow transducer and the corresponding pen deflections were recorded. The validity of this calibration was checked by comparing the sum of the individual inspired volumes measured during the induction of anaesthesia with the corresponding change in volume of the Tissot spirometer over the same period. There was close agreement. An example is given in table I.
The composition of expired gas, however, varied from breath to breath, and there was doubt as to the temperature of the expired gas during passage through the flow transducer. Because of these uncertainties it was originally planned to obtain the expired volumes by measurement of the volumes of the bags in which individual expirations were collected. Direct measurement in a spirometer and measurement by water displacement were tried, but both methods took too long to perform and the loss of nitrous oxide through the bag material during this measurement of volume became a factor of major concern (see below "Bag correction factors"). They were therefore abandoned. Instead, the flow transducer was calibrated for expired volumes by passing known volumes of room air through it, using the 400-ml syringe, and appropriate correction factors were determined.

The calibration of a flow transducer depends upon the relative viscosities, temperatures, pressures and humidities of the gases being measured and of the gas used for calibration. The correction factors for viscosity applicable to various mixtures of nitrogen with oxygen and of nitrous oxide with oxygen, for a Vickers Research Ltd. flow transducer calibrated with air, have been determined experimentally (Smith, 1961). These results could not be applied to the first few expirations because their nitrogen content was unknown. The majority of the expirations during induction, however, contained between 33 per cent and 40 per cent nitrous oxide and it so happens that the correction factor for viscosity is very near unity over this range. Corrections for viscosity, therefore, were not made in this instance.

In order to determine the effects of the temperature and humidity of expired gas on flow transducer measurements, apparatus was arranged as shown in figure 3 (bottom right). The flow transducer was connected to a nosepiece as in the experiment, and this was applied to a hole in the side of a closed brass tank containing baffles. Plasticine was used to fashion an artificial nose and to provide an airtight seal between the nosepiece and the tank. The outlet from a Rotameter (calibrated for air) was connected to a second hole in the tank as shown. Apart from these two holes, the tank was completely closed. An inclined manometer was connected across the flow transducer. By passing air through the Rotameter at different flow rates and noting the corresponding pressure changes shown by the inclined manometer, the flow/pressure characteristics of the flow transducer were obtained for room air under ambient conditions. The results have been plotted thus ▲. The tank was then half filled with water which was heated, using a thermostat, so that the temperature of the humid air above the water remained between 37.5°C and 39°C. The experiment was
The flow/pressure characteristics of a Vickers Research Ltd. flow transducer using room air and after warming and humidifying room air. (The corresponding characteristics for a Fleisch No. 1 flow head, with the heater both on and off, are shown for comparison.)

Bottom right: Apparatus used for measuring the flow/pressure characteristics of a flow transducer under steady flow conditions.

Top left: Apparatus used for measuring the drift of a volume record under simulated respiratory conditions in which room air is "inspired" and warmed humid air is "expired". A record obtained is at top. (Read from right to left. The time signal returns the pen to the base line momentarily once per second. Automatic zeroing of the volume record with each "inspiration" and each "expiration" was not used in this instance.)
repeated and the results have been plotted thus ●. For a given flow measured at room temperature, the pressure was increased by a factor of 1.11. This result was consistent with the temperature within the flow transducer being the same as that within the tank, and with any change in viscosity resulting from the warming and the humidification of the air being negligible. In other words the volume of gas passing through the flow transducer was greater than that passing through the Rotameter by an amount to be expected from the temperature increase and from saturation with water vapour.

During respiration, however, warm saturated expired gas and colder unsaturated inspired gas alternate through the flow transducer. In order to simulate these conditions the experiment was modified as shown in figure 3 (top left). In place of the Rotameter, a tube was passed through and sealed into the hole in the tank. One end of the tube opened into the warm water. The other end of the tube was connected to a 400-ml syringe, and the tube and syringe were filled with water. By expelling water from the syringe into the tank, 400 ml of warm humid air were passed out of the tank through the flow transducer. On withdrawing

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**Fig. 4**

The measurement of temperatures in the breathing system, using a thermocouple, under steady flow and under cyclical flow conditions, the “expired” air being warmed and humid.
the plunger of the syringe, the volume of room air which was drawn through the flow transducer was that which would occupy 400 ml when fully saturated with water vapour and warmed to the temperature of the tank. An appropriate Vickers Research Ltd. pressure transducer was connected in place of the inclined manometer. A Respiratory Analyser and an Ediswan pen recorder were used in conjunction with it for recording the volumes passed through the flow transducer while the 400-ml syringe was repeatedly emptied and filled.

If the temperature of the air in the flow transducer had been the same as the tank temperature during "expiration", then recorded volumes "expired" would have been greater than those "inhaled" by a factor of 1.11 and the record would have drifted accordingly. A drift was recorded as shown in figure 3 (top left) but the factor was only a little over 1.05. This would have been consistent with a temperature within the flow transducer of about 29 °C during expiration.

It was thought advisable, therefore, to check the temperatures within various points of the breathing system under steady flow and under cyclical flow conditions. A copper-constantan thermocouple was used in conjunction with a potentiometric recorder. The sites at which the temperatures were recorded and the results are shown in figure 4. The results are entirely consistent with those of the foregoing experiments. It follows that if accurate results are required when using pneumotachography, the temperatures within the pneumotachograph during both calibration and measurement must either be the same or known. The results given here apply only to the Vickers Research Ltd. flow transducer under the circumstances described.

In order to be able to apply these results to the conditions of a nitrous oxide uptake experiment, information was required as to the temperature at which air is expired from the nose. A thermocouple was therefore inserted into a nostril while the subject breathed in through the mouth and out through the nose. A temperature of 33.7 °C was recorded. The corresponding mean temperature of the air within the flow transducer during expiration was estimated from figure 4 by proportion. For a room temperature of 23 °C, for example, the mean temperature within the flow transducer during expiration was estimated to be 27.5 °C.

FIG. 5
The apparatus for collecting each complete expiration in an individual bag.
FIG. 6
An outlined photograph of the solenoid mechanism, and the corresponding circuit diagram, showing the state of the components during expiration. The bags are stationary.

FIG. 7
Outlined photographs of the solenoid mechanism, and corresponding circuit diagrams, showing the operation of the component parts at the start of inspiration. A bag containing an expiration is being removed from the expiratory port and a fresh bag is being presented in its place.
THE COLLECTION OF EXPIRED GAS

A solenoid mechanism presented a fresh bag to the expiratory port of the breathing system during each inspiration. The bags were 30-gram meteorological balloons. These were suspended from brass mounts (wardrobe rod supports) into each of which was inserted a non-return valve (Siebe-Gorman 6D/650, 29). The mounts were linked by open hooks and they were supported on two brass rails on which they could slide. The rails were tilted in order to reduce the effect of friction.

An overall view of the apparatus is shown in figure 5. It was suspended from the ceiling and counterpoise weights were used so that the tilt of the rails and the height of the nosepiece could be adjusted to the subject. Forty-two bags were usually accommodated on the rails, the lengths of which were 8 feet. The two weights dangling from the top end of the train of bags acted as brakes which prevented the last few bags from overshooting the solenoid mechanism. The two angled pieces beneath the lower end of the rails were for catching the bags.

THE SOLENOID MECHANISM

The expiratory port of the breathing system was attached to the arm of a mains relay as shown in figure 1. Throughout expiration the mains relay was energized so that the expiratory port was held down by the relay arm to form an airtight seal with a bag mount. During inspiration the expiratory port was lifted clear. The contacts on the mains relay were used for controlling the solenoid mechanism which presented a fresh bag to the expiratory port during each inspiration.

The component parts of the solenoid mechanism and the circuit diagram are outlined in figures 6, 7 and 8. While the expiratory port was applied to a bag mount during expiration, a solenoid-operated stop prevented the bags from sliding down the rails, and a "return" solenoid held the transport arm in the "re-
turn” position ready for the next inspiration. The state of the apparatus during expiration is illustrated in figure 6. Figure 7 indicates the changes which occurred at the start of inspiration. The mains relay was open-circuited and the expiratory port was raised clear of the bags. The “stop” was released in order to allow the bags to move on. The “return” solenoid was open-circuited and then the “drive” solenoid came into operation to drive the transport arm. The bags moved. As each bag mount moved clear of the “stop”, the following bag mount closed “feeler” contacts which brought the “stop” solenoid back into operation in anticipation of the end of the stroke. At the end of the stroke the transport arm closed “end-stroke” contacts momentarily, as shown in figure 8. These, by operating a relay, caused the “drive” solenoid to be open-circuited and the “return” solenoid to come back into operation. The end of the transport arm was hinged so that it could ride over the bag mounts during the return stroke.

Such a mechanism must take a finite time to operate. A spirometer was used to determine the amount of the expired sample lost through delay in descent of the expiratory port. The spirometers obtained are shown in figure 9. A 400-ml syringe connected directly to the spirometer gave the calibration spirogram A. The 400-ml syringe was then connected to the nosepiece of the non-rebreathing system (fig. 1) and the spirometer was connected to a valve mount held beneath the expiratory port. When the expiratory port was held down, the relay mechanism being switched off, and the syringe was emptied and filled at a rate of 13 per minute, spirogram B was obtained. There was a loss of 1.5 per cent due to incompetence of the inspiratory valve of the non-rebreathing system. Spirogram C was obtained under similar conditions except that the mains relay was allowed to operate and move the expiratory port up and down. The additional loss was 1.5 per cent. When the syringe was operated at a rate of 31 per minute as shown in spirogram D, there was, in this instance, an additional loss of about 10 per cent.

![Spirometer tracings obtained in order to check sampling losses due to mechanical delays.](https://academic.oup.com/bja/article-abstract/35/4/224/255370)

**Fig. 9**

A. Spirometer calibration ±400 ml.
B. A 400-ml syringe was connected to the nosepiece and emptied and filled while the spirometer was connected to a bag mount held below the expiratory port. The relay mechanism was switched off and the expiratory port was held down.
C. As B, but the relay mechanism was switched on and the expiratory port was allowed to move up and down at a rate of 13/min.
D. As C, but at a rate of 31/min.
BAG CORRECTION FACTORS

When the 30-gram meteorological balloons were emptied completely and then allowed to hang free, they took in a variable amount of air not exceeding 400 ml. Before an experiment, therefore, each bag was emptied and then filled with 400 ml of air. This known dilution was allowed for in the final calculations. The bags were bunged until just before the experiment began in order to guard against any reduction in this volume due to incompetence of the non-return valves in the bag mounts.

A major disadvantage of the 30-gram meteorological balloons was that nitrous oxide passed through their walls. The extent of this loss is shown in figure 10. Five balloons were filled with 2000 ml of 80, 70, 60, 50 and 40 per cent nitrous oxide respectively. The concentration of nitrous oxide within each bag was measured at intervals using a gas chromatograph (Hill, 1962). These measured concentrations were then expressed as percentages of the initial concentrations and plotted against time. It can be seen that for a given volume of balloon contents the proportion of nitrous oxide lost in a given time was constant. Eleven balloons were then filled with different volumes of 80 per cent nitrous oxide and the experiment was repeated. The rate of proportionate loss from each balloon was plotted against its starting volume, and the curve obtained was used for correcting the percentages of nitrous oxide expired as determined by gas chromatography.

At the end of an experiment the contents of each balloon were bottled under water. It was anticipated that some nitrous oxide would go into solution during the bottling process, but this loss was found to be too small to measure by the methods used. It was therefore ignored. The time interval between the filling of a balloon with expired gas and the bottling of the contents was known. The initial volume of the balloon contents was 400 ml plus the expired volume. The concentrations of nitrous oxide in the bottled samples were determined by gas chromatography. Using

**FIG. 10**

The loss of nitrous oxide from the meteorological balloons by diffusion. The proportionate loss plotted against time for a number of bags, each filled with the same volume of different concentrations of nitrous oxide, is shown on the left. The rate of proportionate loss is plotted against the initial volume for a number of bags, containing different volumes of the same concentration of nitrous oxide is shown on the right.
the curve shown in figure 10 it was then possible to estimate the concentrations of nitrous oxide in the expired gas at the times of expiration. Unfortunately the tidal volumes frequently coincided with the steep part of the curve so that errors may still have been large even after application of the correction factors.

By suitable choice of bag material it may be possible to reduce or avoid this serious loss of nitrous oxide.

DISCUSSION

Using the apparatus described it has been possible to demonstrate an approach to the problem of measuring the uptake of an inhalational agent during the induction of anaesthesia, and to apply it to the estimation of the uptake of nitrous oxide under laboratory conditions. Apart from the unsatisfactory bag material used, the apparatus is too cumbersome for clinical use and it can be used only with a non-rebreathing system.

An alternative approach would be to withdraw only small representative samples of each expiration instead of collecting complete expirations. If representative samples of each inspiration were also collected, it would not matter if the concentration of the inhalational agent in the inspired gases varied. Gas chromatography could be used for analysis of the samples as in the present experiment. If the samples were to be kept sufficiently small relative to the volume of the breathing system plus the residual volume of the subject, it should be permissible to withdraw them from any type of breathing system—at least for short periods.

A possible method for collecting representative samples would be to use a separate glass syringe for each individual inspiration and expiration. The plunger of each syringe would need to be withdrawn at a rate directly proportional to the instantaneous flow rate of the gases being expired or inspired. This could be achieved by using a servo mechanism to withdraw the plunger of each syringe in turn. Such a servo mechanism could be operated by voltages proportional to respired flow rate, as derived from a pneumotachograph, in which case it would control the rate of withdrawal of the plunger of the syringe. Alternatively it could be operated by voltages proportional to respired volume, as derived by electronic integration of "flow rate" voltages, in which case it would control the position of the plunger at any instant relative to the corresponding volume at that instant. The latter would probably be preferable. Problems of sample losses due to diffusion should be overcome by using such an apparatus. The size of the apparatus needed in the immediate vicinity of the breathing system should also be reduced sufficiently for uptake measurements to be possible under both clinical and laboratory conditions.

With some breathing systems it may be permissible to withdraw a continuous sample from the airway for instantaneous measurement of anaesthetic concentration, and to return it to some other part of the system—provided that the sampling rate is kept low. Usually the analyzed sample would need to be returned "downstream" from the sampling point. A solenoid device could be operated from the slave relay shown in figure 2 so as to direct the returned gases to each side of the sampling point in turn, according to the direction of flow during inspiration and expiration respectively. Rapid infra-red gas analysis would be appropriate. Voltages proportional to the rate of mass flow of anaesthetic could be derived using electronic multiplication of a voltage proportional to the anaesthetic concentration (derived from an infra-red gas analyzer) by a voltage proportional to the simultaneous respired flow rate (derived from a pneumotachograph). Electronic integration of this product would give a voltage proportional to the mass of anaesthetic passed. Such a system would have very attractive possibilities since it could be arranged to provide for continuous recording of respired volume, anaesthetic concentration and mass of anaesthetic. Automatic zeroing of the type described above, would be advantageous for the record of anaesthetic mass as well as that for respired volume.

ACKNOWLEDGMENTS

The apparatus was constructed at short notice for use in a class experiment during a course on "Measurement in Anaesthesia" held at the Royal College of Surgeons (March 26-31, 1962). Time was not available for rehearsals and both the apparatus and the methods used were modified several times during the course. None of the five experiments carried out during that week was completely successful, but the forbearance and generous co-operation of all the participants certainly contributed to the later experiments. Their assistance is gratefully acknowledged, as is that of the late Professor R. Woolmer for providing every facility and for his interest and encouragement.
throughout. Mr. S. Mable gave helpful advice with regard to choice of relays for the automatic volume zeroing circuit. The work was carried out while holding a Wellcome Research Fellowship at the Research Department of Anaesthetics of the Royal College of Surgeons. The Wellcome Trust also purchased the Respiratory Analyser.

REFERENCES

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SOMMAIRE

L’auteur décrit une méthode permettant de mesurer pendant l’induction d’une anesthésie l’absorption d’oxyde nitreux par chaque inspiration — sans emploi d’un système de re-respiration. On obtient le taux d’absorption d’oxyde nitreux par la différence entre les quantités inspirées et expirées. La pneumotachographie sert à mesurer le volume respiré total et d’autre part à contrôler la quantité inspirée d’oxyde nitreux. Chaque expiration successive est recueillie dans un sac “individuel” qu’un chromatographe à gaz analyse. La présentation d’un nouveau sac au système respiratoire pendant chaque inspiration est réalisée par un mécanisme solénoïde contrôlé par des relais actionnés par le circuit du pneumotachographe. L’auteur discute les facteurs de correction, les limites naturelles d’emploi et la série des mesures alternatives possibles.

ZUSAMMENFASSUNG


THE FACULTY OF ANAESTHETISTS OF THE ROYAL COLLEGE OF SURGEONS IN IRELAND

ANNUAL SCIENTIFIC MEETING

A symposium on Respiratory Insufficiency will be held in the Royal College of Surgeons in Ireland on June 8, 1963, commencing at 10 a.m.  
All anaesthetists are eligible to attend. A fee of one guinea will be charged which will include morning coffee, buffet lunch, and afternoon tea.  
The annual dinner for Fellows and guests, including ladies, will be held in the College on the same evening at 7.45 p.m.  
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