EXPERIMENTS DEMONSTRATING THE UPTAKE, DISTRIBUTION AND ELIMINATION OF NITROUS OXIDE IN THE CONTEXT OF OUT-PATIENT ANAESTHESIA

PART II: NON-REBREATHING EXPERIMENTS AND EXPERIMENTS USING THE JERKIN PLETHYSMOGRAPH

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This series of ten dissimilar experiments, carried out on a single volunteer, was planned to illustrate some of the fundamentals of the uptake, distribution and elimination of nitrous oxide, in the context of out-patient anaesthesia. Three of the experiments are described in Part I and seven in Part II. Each experiment was designed to bring out particular aspects of the pharmacokinetics of nitrous oxide anaesthesia. The experiments were performed within a very limited period, so more emphasis was placed upon practical demonstration of the essential features of the subject than upon precision in measurement. Nonetheless, some of the results presented in Part II may be compared with a previous study of the uptake of nitrous oxide (Smith and Butler, 1964) because Subject B of that study was used as the subject throughout the present series.

The experiments are grouped under three main headings: (1) those in which a nitrous oxide and oxygen mixture was rebreathed from a spirometer (Part I); (2) those in which rebreathing was avoided by using a bag-in-a-box system (Part II); and (3) those in which a jerkin plethysmograph was used to detect changes in end-expiratory level and in trunk volume (Part II). The rebreathing experiments are comparable with systems in which the patient is allowed to rebreathe from a reservoir bag, while the non-rebreathing experiments relate to demand and continuous flow systems. Each experiment—its design, results and implications—is discussed in turn.

NON-REBREATHING EXPERIMENTS

Historical note.

T. W. Evans (1869) measured the uptake of nitrous oxide from a non-rebreathing system, by breathing from and into separate bell glasses over water. The first bell glass was filled with nitrous oxide and the volume inhaled was measured. The volume exhaled into the second bell glass was measured after absorbing carbon dioxide. He regarded the difference in volumes as showing “very nearly the actual amount of gas absorbed by the blood at the moment the inhalation was suspended”. He found that the uptake rarely exceeded 3 quarts (3,400 ml), but this figure would have included the oxygen uptake. The duration of inhalation in these experiments was not mentioned.

Donald and Christie (1949) used the uptake of nitrous oxide to demonstrate their bag-in-a-box system. They did not quote results, but their figures suggest that an uptake of about 230 ml/min ATP was obtained when a subject breathed 25 per cent nitrous oxide, and about 500 ml/min ATP when he breathed 50 per cent. No details of the subject were given. They noted that “Following 3 minutes exposure to 50 per cent nitrous oxide the subject became completely unaware of his surroundings and held his breath for some time. After this, although respirations were irregular and the total ventilation reduced, the rate of absorption increased. This was probably due to the apnoea and excitement of the first stage of anaesthesia causing an increase in cardiac output although changes in the respiratory quotient may also be involved.” They also commented that “When breathing the lower concentrations, total quantities of gas can be absorbed without ill effects that would cause unconsciousness if breathed in higher concentrations.”

Experiment 4 (fig. 6).

Demonstration of net uptake and elimination using a non-rebreathing system; and a comparison with results obtained (a) during rebreathing experiments, and (b) with previous experiments without rebreathing.

Apparatus.

The same basic apparatus was used as in Experiment 3, except that the rigid reservoir was discarded and two bag-in-a-box systems were added. One bag-in-box was used for breathing 80 per cent nitrous oxide with oxygen, and the other for breathing air.
The layout of the apparatus as shown to the left applies to Experiments 4 and 5 (see text). To the right, the upper box applies to Experiment 4 and the lower box to Experiment 5. The following are shown in each box, from above downwards: (1) spirogram; (2) percentage of nitrous oxide in the gases respired; (3) times at which the morse key was pressed; (4) times at which spoken numbers were played by the tape recorder. For convenience of illustration, (3) and (4) have been separated in the above figure, but during the actual experiments the signals from the morse key and the tape recorder were superimposed on the same channel of the ink writer, as in the previous study (Smith and Butler, 1964).

The bags of the bag-in-box systems were 60-l. p.v.c. Douglas bags (0.47 cm thick) which were virtually impermeable to nitrous oxide. Each bag was enclosed in a rigid box of similar dimensions which was made of 18 gauge tinned sheet iron, reinforced diagonally by angle iron welded to the sides.

The arrangement of the breathing system is shown in figure 6. A spirometer was connected to each box. Breathing through non-return valves, the subject inhaled from the bag and exhaled into its box. The box being rigid, the volume of its contents, including the bag and its contents, remained constant; but the spirometer acted as a reservoir which allowed the capacity of the whole system to contract during inspiration, expand during expiration, and accommodate to changes in FRC and in the total volume of the apparatus plus subject’s lungs and airways (due to net gas exchange). In so doing the spirometer kept the system virtually at atmospheric pressure and the spirogram provided records of both the tidal flow between the subject and the apparatus, and of the net gas exchange. It must be acknowledged, however, that changes in thoracic blood volume may also be expected to show on the record. If pooling of blood in the lower parts of the body were to occur while the subject was in the sitting position, for example, the volume of blood lost from the thorax would be replaced...
by gas (unless there was a corresponding change in the end-expiratory level), and the movement of this volume of gas from the apparatus to the lungs would be recorded as if it were a net uptake.

Changes in FRC due to changes in posture may also be recorded.

Changes in the volume of the system may also be caused by small changes in the temperature of the bag-in-the-box system. Donald and Christie (1949) had expected errors from this source but in practice "owing to the length of the tubing, the size of the box and the passage of the expired air over the water seal of the spirometer, there was no significant rise of temperature in the box which remained at room temperature". The thermal conductivity and capacity of the box, which was made "of light metal with reinforcing struts" and was of 100 l. capacity (larger than the box used in the present experiments), were probably additional factors which helped to maintain the temperature of expired gases in the box at room temperature. The expired gases were not passed through the spirometer in the present experiments, but the tubing adjacent to the subject was made of brass.

Gases were humidified at room temperature by bubbling them through water while filling the bags. A two-position multiway tap was used for switching the subject's mouthpiece from one bag-in-box system to the other. (For simplicity this has been indicated as two separate taps in figures 6 and 7.)

The gas sample returned from the infra-red analyzer re-entered the breathing system in the expiratory limb between the mouthpiece and the multiway tap, so there was no need to reroute it when the subject changed from one bag-in-box to the other.

**Design of experiment.**

The subject breathed 80 per cent nitrous oxide with oxygen from one bag-in-box until the total net volume uptake was about the same as in Experiment 3. The subject then breathed air from the second bag-in-box. The procedure was otherwise the same as in Experiment 3.

**Results.**

Comparing the spirogram with that obtained in Experiment 3 (fig. 4), there are three striking differences: (1) the marked hyperventilation that occurred while rebreathing was not seen; (2) a definite, although small, net elimination was shown during the second part of the experiment; (3) the concentration of nitrous oxide in the end-expired gases continued to fall throughout the latter part of the experiment.

Because there was no rebreathing, the concentration of nitrous oxide reached a higher level (approaching 70 per cent) and, after the first three breaths, the end-expired concentration of nitrous oxide rose more quickly than in Experiment 3. Consciousness was lost sooner, after 75 seconds. The net volume uptake during the first minute was 1200 ml ATP. The subject was given air to breathe from the second bag-in-box after he had been breathing the nitrous oxide mixture for 135 seconds. By this time the total net volume uptake was 2500 ml ATP.

The concentration of nitrous oxide in the expired gases fell to 20 per cent after the subject had been breathing air for about 15 seconds, and thereafter it continued to fall. Normal responses were resumed after breathing air for 25 seconds. The net volume elimination after breathing air for 270 seconds (twice the time of uptake), however, was still only 800 ml ATP, or about one-third of the initial net uptake.

**Comment.**

(a) **Comparison with Experiment 3.** The quicker induction of anaesthesia, and the greater rate of net uptake in this experiment, compared with Experiment 3, may be accounted for by the more rapid rise in the concentration of nitrous oxide in the alveoli, and by the higher concentration inspired, when using a non-rebreathing system.

Although elimination was not impeded due to rebreathing (cf. Experiments 1 and 2), the rate of elimination was still considerably less than the rate of uptake, indicating that the partial pressure gradient driving nitrous oxide elimination was less than that driving its initial uptake, due to the redistribution in the body of the nitrous oxide taken up.

The total net volume uptake in this experiment was marginally less than during Experiment 3 (2,500 ml ATP as against 2,700 ml ATP in Experiment 3), but the anaesthetic mixture, which retained its original composition, was breathed for longer while the patient was unconscious (62 seconds as against 46 seconds in Experiment 3). The recovery time, however, was slightly shorter (25 seconds as compared with 32 seconds in Experiment 3). In this experiment, both the redistribution of nitrous oxide in the body and the continued washout of nitrous oxide from the lungs would have combined to lower the tension of nitrous oxide in the brain.

(b) **Comparison with previous study** (Smith,
The subject's time to "no-response" of 75 seconds found in this experiment is consistent with the times observed during the previous study in which the uptake of nitrous oxide was measured by pneumotachography.

The rate of uptake found in this experiment, however, is only about half that found in the previous study. It was appreciated, and stated at the time (Smith and Butler, 1964), that the values for uptake obtained previously seemed rather high and that this may have been due to errors inherent in the system used. It was appreciated, for example, that a small error in the measurement of the tidal volume would account for a considerably greater error in the determination of net uptake (Smith, 1964b) but quite such a large discrepancy was not anticipated. Although precision in measurement was to a certain extent sacrificed during the present experiments, the potential sources of error were considerably less than in the previous study. In the first part of that study (Smith, 1964b) many of the potential sources of error were described. Perhaps the main virtue of the second part of the study (Smith and Butler, 1964), apart from some incidental observations, was to emphasize the reality and the magnitude of those errors and difficulties. A previous regret may be repeated: "It is unfortunate that circumstances did not permit the simultaneous use of a well tried bag-in-a-box system as a check on the accuracy of pneumotachography" (Smith, 1964a). It is probable, however, that by the application of modern technology to the instrumentation, a considerable improvement could be made on previous efforts. Furthermore, not all applications of pneumotachography have such exacting requirements.

Experiment 5 (fig. 6).

The effect of exercise on the net uptake and elimination of nitrous oxide, using a non-rebreathing system.

Apparatus.

Exactly the same apparatus was used as in Experiment 4.

Design of experiment.

Out-patients are often apprehensive, and stimulated surgically under light anaesthesia, but there are obvious objections to reproducing these conditions in a volunteer in order to measure their effects. Exercise was therefore used as an alternative.

Whereas Experiment 4 was carried out after the subject had been engaging in normal activity in the laboratory, Experiment 5 was carried out immediately after the subject had walked up and down the stairs. In all other respects the designs of Experiments 4 and 5 were identical.

Results.

The subject's minute volume during the induction of anaesthesia was 19.8 l./min ATP, compared with 11.6 l./min ATP in Experiment 4. The concentration of nitrous oxide in the expired gases rose more rapidly and reached a higher value (nearer 80 per cent than 70 per cent) within the time of the experiment. Consciousness, however, was lost slightly later, after 82 seconds. The net volume uptake in the first minute was 1,500 ml ATP, a 25 per cent increase over the net rate of uptake in Experiment 4. The subject was given air to breathe from the second bag-in-box after 90 seconds, by which time the total net volume uptake was 2,200 ml ATP (compared with 2,500 ml ATP in Experiment 4).

The concentration of nitrous oxide in the end-expired gases fell to 20 per cent after the subject had been breathing air for about 26 seconds. The morse key was pressed 34 seconds after starting to breathe air but regular responses were not resumed until after 52 seconds. Although the total net volume uptake was less than during Experiment 4, the initial rate of elimination appeared to be more rapid, the spirogram showing a net elimination of 800 ml ATP after only 150 seconds (compared with the same net elimination after 270 seconds in Experiment 4), and 1,050 ml ATP after 270 seconds.

Comment.

One might expect hyperventilation to flush anaesthetic into the lungs, and so raise its alveolar and arterial tensions more rapidly towards its inspired tension, and hasten induction. On the
other hand, one might expect increased pulmonary blood flow to remove anaesthetic from the lungs more rapidly and so, according to its solubility in blood, lessen the rise in alveolar tension due to hyperventilation. One would also expect that hyperventilation and increased pulmonary blood flow would both tend to increase the rate of anaesthetic uptake.

In this experiment, breathing 80 per cent nitrous oxide (nitrous oxide has about one-fifth the solubility in blood of halothane), the end-expired concentration of nitrous oxide did rise more rapidly after exercise than after normal activity. The initial net volume uptake was also more rapid.

In the light of these observations it may seem surprising that consciousness was not lost sooner in this experiment than in Experiment 4, rather than slightly later. Speed of induction, however, depends also upon cerebral perfusion, and upon the tension of anaesthetic in the brain required to produce anaesthesia, and this may vary, for example, with the subject’s composure. No attempt was made to measure or to assess such factors.

A detailed analysis of this spirogram would be inadvisable without further data, because the effect of exercise upon the respiratory exchange ratio and oxygen uptake in this particular experiment is unknown. Furthermore, although an increased cardiac output may be assumed during the first part of the experiment, the extent to which it may have decreased following the induction of anaesthesia is open to question. The effects of exercise may also have contributed to a delay in the subject’s appreciation of the significance of the spoken numbers during the recovery period.

Experiment 6 (fig. 7).
Demonstration of the effect of halving the concentration of nitrous oxide inspired upon its uptake and elimination.

Design of experiment.

Instead of breathing 80 per cent nitrous oxide from the bag-in-box, the subject breathed 40 per cent nitrous oxide with 60 per cent oxygen. He changed from this nitrous oxide and oxygen mixture to air from the second bag-in-box when the total net volume uptake had reached about the same value as in Experiments 3, 4 and 5.

Results.
The net volume uptake after breathing 40 per cent nitrous oxide for 1 minute was 600 ml ATP. The net volume elimination after breathing air for 270 seconds was 800 ml ATP (compare with Experiment 4).

Comment.

The initial net rate of uptake while breathing 40 per cent nitrous oxide in this experiment was half that found when the same subject breathed 80 per cent nitrous oxide in Experiment 4. The pattern of elimination in the two experiments, however, was almost identical. In other words, the rate of uptake depends largely upon the concentration of nitrous oxide inspired whereas the pattern of elimination depends largely upon the total uptake, which may be more after prolonged inhalation of analgesic concentrations than after brief inhalation of anaesthetic concentrations. The maximum possible uptake, of course, increases with the concentration inspired.

Experiment 7 (fig. 7).
Demonstration of the effect of voluntary hyperventilation upon uptake.

Apparatus.

In addition to the apparatus used in Experiment 6, a jerkin plethysmograph was employed in order to check that the end-expiratory level did not change while the subject voluntarily hyperventilated. The jerkin plethysmograph is described in more detail in relation to the next experiment. It was used with the second spirometer.

There are no technical objections to using the same spirometer with both bags-in-boxes, but as time was limited it was found expedient not to use the second bag-in-box in this experiment, so no record of the net elimination of nitrous oxide was obtained.
The apparatus used for Experiments 6 and 7 (see text). The upper spiogram and record of percentage nitrous oxide apply to Experiment 6. The lower records, which include also a jerkin plethysmogram, apply to Experiment 7. The jerkin plethysmogram shows that during hyperventilation the trunk always returned to the same volume at the end of expiration. The jerkin plethysmograph is described in the text under the heading of Experiment 8, and it is illustrated in figure 8.

**Design of experiment.**

The subject breathed 40 per cent nitrous oxide with 60 per cent oxygen as in Experiment 6, except that he voluntarily hyperventilated.

**Results.**

A minute volume of about two and a half times that in Experiment 6 was achieved without altering the end-expiratory level. The concentration of nitrous oxide in the end-expired gases rose more rapidly than in the last experiment and the net uptake in the first minute was 700 ml ATP.

**Comment.**

The net rate of uptake was greater in this experiment than in Experiment 6 but relatively less than in Experiment 5. This appears to be in accord with the commentary on Experiment 5 but the result should be interpreted with caution in the absence of data on the net exchange between oxygen and carbon dioxide in this experiment. One would expect the respiratory exchange ratio to have been greater in this experiment than during Experiment 6 and the oxygen uptake to have been little different, in which case the uptake of nitrous oxide during the first minute may have been greater than the net uptake of 700 ml ATP would suggest.
EXPERIMENTS USING THE JERKIN PLETHYSMOGRAPH

Experiment 8 (fig. 8).

The jerkin plethysmograph: its calibration and its application in the investigation of nitrous oxide uptake.

Apparatus.

One spirometer was used for rebreathing either air or 80 per cent nitrous oxide with oxygen. The other spirometer was used with the jerkin plethysmograph.

The jerkin plethysmograph (Vickers Ltd.) is a double-layered garment containing air between its inner and outer walls (see figure 8). It is worn so as to enclose the trunk and it is laced under the crutch in order to prevent it riding up the body. In these experiments two fixed armrests (not shown in the diagram) kept the subject's arms at right angles to the body, and these, together with the mouthpiece and the seat of the chair, helped to fix his position. As used originally (Heaf et al., 1961) the mass of air contained between the walls of the jerkin was kept constant and the changes in its pressure were measured as an index of corresponding changes in trunk volume. In the present experiments, however, the jerkin was connected through wide-bore tubing (two lengths of 28-mm corrugated tubing in parallel) to a spirometer, on to the bell of which were placed weights to a total of 378 g. These maintained the pressure within the jerkin at about 1.3 cm H₂O, and the air moved between the jerkin and the spirometer according to the changes in trunk volume.

On the left: the jerkin plethysmograph and the way in which it was used in these experiments. In the middle: the calibration of the jerkin plethysmograph. On the right: spiromgrams and plethysmograms obtained when rebreathing 80 per cent nitrous oxide with oxygen (see Experiment 8).
Design of experiment.

The jerkin was first calibrated. The subject rebreathed air from one spirometer while the second spirometer recorded the corresponding displacement of air from and into the jerkin. Tidal volumes increased automatically as carbon dioxide accumulated in the spirometer during rebreathing. In order to calibrate the jerkin for encroachments upon the expiratory reserve, the subject, watching the spirogram, kept his end-inspiratory position constant, and so automatically used his expiratory reserve as ventilation increased. The middle section of figure 8 shows the spirograms and plethysmograms used in one complete calibration run, those used for calibration below the resting expiratory level being on the left. The subject then rebreathed 80 per cent nitrous oxide with oxygen, as in Experiments 1 and 2. Finally he rebreathed 80 per cent nitrous oxide, but deliberately filled the spirometer to the same level at the end of each expiration, as shown on the extreme right of figure 8.

Results.

The net uptake shown by the spirogram when rebreathing 80 per cent nitrous oxide in the usual way was 750 ml ATP in 1 minute. When he repeated this experiment, but always filled the spirometer to the same level at the end of each expiration, he encroached upon his expiratory reserve to the extent of 800 ml.

Comment.

Plots of inspired volume against volume displacement from the jerkin, obtained from several calibration runs, indicated that, for a given set of conditions, the relationship was consistently linear when the subject breathed normally. When he encroached upon his expiratory reserve, however, the scatter was greater and the relationship no longer linear, except, perhaps, for small displacements. The simple explanation would be that this is a function of the characteristics of the jerkin plethysmograph and that breathing into the expiratory reserve is likely to be associated with some change of posture. Another possible explanation is that blood as well as gas may be "squeezed" out of the trunk during encroachment upon the expiratory reserve. This explanation would fit both with the greater scatter and with the direction of the deviation from linearity.

In view of the scatter of the calibration points below the resting expiratory level, the extent to which the subject encroached upon his expiratory reserve in the final experiment must be regarded as essentially the same as the net uptake shown by the spirogram when he rebreathed the same amount of nitrous oxide in the usual manner.* It could be argued, however, that one might expect the net uptake to be slightly greater in the final experiment because the ventilation over the first minute of rebreathing was greater by a factor of \((13.7/11.6) = 1.2\), and the volume of the lungs in use would have been reduced progressively with the encroachment upon the expiratory reserve.

Experiment 9 (fig. 9).

Demonstration of net gas exchange during breath holding: an indication of the significance of nitrous oxide uptake during respiratory obstruction.

Apparatus.

Exactly the same apparatus was used as in Experiment 8.

Design of experiment.

The subject hyperventilated on room air, then, by turning a tap, he connected his mouthpiece to the spirometer, which was filled with air, and held his breath. First, while watching the spirogram, he kept his trunk fixed and his glottis open; then he repeated the whole experiment, except that he kept his glottis closed and made no effort to fix his trunk.

The spirometer was then filled with 80 per cent nitrous oxide with oxygen. The above experiment was repeated, except that this time, between hyperventilation and breath holding, he

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* The rate of uptake of 750 ml/min ATP found in this experiment is little different from the 800 ml/min ATP found in Experiments 1 and 2; but it may be mentioned that the spirometer was filled initially to 4 l, in this experiment, whereas in Experiments 1 and 2 it was filled initially to 5 l. In all three experiments the spirometer bell communicated also with the Pulmotest fan chamber (the fan was not used), the other outlet from which was occluded by means of a rubber bung.
took three 1-litre breaths from the spirometer, breathing out into the room after each breath.

\textit{Results.}

When the trunk was fixed, air flowed through the open glottis from the spirometer at a rate of 100 ml/min ATP. When the glottis was closed, the trunk contracted at about the same rate, after a delay of 15 seconds.

When three breaths of 80 per cent nitrous oxide were interposed between hyperventilation and breath holding, flow through the open glottis when the trunk was fixed was about 1 litre ATP in 1 minute. With the glottis closed, the trunk contracted by about 550 ml in 1 minute. Duplicate records are shown in figure 9.

\textit{Comment.}

In the first experiment the flow of air through the open glottis would have arisen from the difference between the rate of uptake of oxygen and the rate of elimination of carbon dioxide. The initial delay in the corresponding contraction of the trunk might have been due to the first 25 ml of net gas uptake being made good by a net flow of about 25 ml of blood into the trunk. A similar explanation might partly account for the trunk contraction in the final experiment being less than the corresponding flow through the open glottis when the trunk was fixed. The alveolar gases were probably also at a subatmospheric pressure in the final experiment and, as no nitrous oxide could flow into the lungs to replace

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{Spirograms and plethysmograms obtained when breath holding, keeping the trunk fixed and the glottis open, and keeping the glottis closed but not fixing the trunk. Each experiment was preceded by hyperventilating on room air. The duplicate records shown on the right were obtained when three breaths of 80 per cent nitrous oxide with oxygen were interposed between hyperventilation and breath holding (see Experiment 9).}
\end{figure}
the nitrous oxide taken up, the concentration of nitrous oxide in the lungs, and presumably the net uptake, would have fallen progressively (the total volume of gas in the lungs would have fallen at the same time).

It is well known that after nitrogen washout, postobstructive absorption of oxygen may result in atelectasis. Uptake of nitrous oxide, however, may reach five times that of oxygen, and these experiments emphasize the possibility of nitrous oxide uptake contributing to alveolar collapse in the event of respiratory obstruction or aspiration during the early stages of an anaesthetic.

Experiment 10 (fig. 10).

Demonstration of the effect of nitrous oxide uptake upon the concentration of oxygen in a system containing both gases.

Apparatus.
The experimental set-up used for Experiments 8 and 9 was supplemented by a Beckman D.2 paramagnetic oxygen analyzer and a metronome.

Design of experiment.
The subject rebreathed air from the spirometer, regulating his respiratory rhythm in time with the metronome, and his tidal volume by watching the jerkin plethysmogram. After taking eight 2-litre breaths in 64 seconds, the spirometer was closed to atmosphere and to the subject by turning a tap, and its contents were analyzed for oxygen.

The procedure was then repeated while rebreathing the same volume of 79 per cent nitrous oxide with oxygen in the same manner. (This mixture was prepared by filling the spirometer from Rotameters and then adjusting the content of oxygen or nitrous oxide until the same reading was obtained on the oxygen analyzer as with air.)

Results.
After rebreathing air the final concentration of oxygen in the spirometer was about 15.5 per cent. After rebreathing 79 per cent nitrous oxide in the same way the final concentration of oxygen was about 17 per cent.

Comment.
The Beckman D.2 oxygen analyzer was not the ideal instrument to use for this purpose, but the experiment was repeated a number of times and the change was always in the same direction and of about the same magnitude. On the assumption that the oxygen uptake was essentially the same in the two parts of the experiment, the quantity of oxygen contained in the total capacity of the apparatus plus subject's lungs and airways would have been the same after breathing either air or the nitrous oxide and oxygen mixture. In the latter case, however, the total volume of all the gases at the end of the experiment would be less, due to the loss of the nitrous oxide taken up, so the proportion of oxygen would be greater. (The subject breathed into the spirometer through tubing having a dead-space of about 300 ml, but there would also have been considerable mixing with the deadspace of the fan chamber, although the fan of the Pulmotest was not switched on. If a total deadspace of about 3 l. be assumed, then the above difference in oxygen concentration would be consistent with an FRC of just over 4 l.)

This experiment illustrates the fact that nitrous oxide uptake may influence alveolar oxygenation, and it is sometimes suggested that this is important in the context of out-patient anaesthesia. This is unlikely.

Nitrous oxide uptake does tend to conserve the amount of oxygen contained in the alveoli, even when a non-rebreathing system is used. Only about one-fortieth of the volume of nitrous oxide taken up is replaced by nitrogen eliminated, due to the relative solubilities of the two gases in blood. The remaining thirty-nine-fortieths are made good by additional gases drawn into the lungs during inspiration and by the retention of alveolar gases during expiration, and they both contain oxygen. The effect, however, is insufficient to justify the administration of hypoxic mixtures.

Fink (1955) described the reverse effect of hypoxia during recovery from anaesthesia, due to large volumes of nitrous oxide diluting the alveolar gases, but, as has been demonstrated in this series of experiments, large volumes of nitrous oxide are not eliminated after short anaesthetics.
The jerkin plethysmograph and the metronome were used to enable first air and then 79 per cent nitrous oxide to be rebreathed in a standard manner. The oxygen analyzer was used to measure the concentration of oxygen remaining in the spirometer in each case (see Experiment 10).

From above downwards: duplicate records of pulse, blood pressure and respiration, obtained when a dog was given first nitrogen to breathe, and then, after recovery, nitrous oxide (Rottenstein, 1880).
Historical note.

John Snow (1847) thought that an inspired oxygen concentration of 16 per cent would asphyxiate—probably because he had previously carried out a series of experiments using small birds which are notably susceptible to hypoxia (Snow, 1839)—but he surmised that ether did not cause asphyxia because it was absorbed as fast as it reached the air cells, and that substitution of hydrogen or nitrogen in the same proportion would cause asphyxia. Snow appreciated that anaesthetic solubility in blood and uptake of anaesthetic could be relevant to alveolar oxygenation.

The records of pulse, blood pressure and respiration shown in figure 11, taken from Rottenstein (1880), may also illustrate the point, although there is no guarantee of the purity of the gases used at that time. A dog was given first nitrogen to breathe, then, after recovery, nitrous oxide. Signs of severe anoxia took about 10 seconds longer to develop when the dog breathed nitrous oxide.

ACKNOWLEDGEMENTS

I am greatly indebted to Mr. H. G. Lumby and Miss R. Bailey, of the Department of Medical Illustration, University of Leeds, for preparing the final diagrams without which this work could not have been presented in the time available. I would also like to thank Mr. A. L. Pegg, of the Department of Medical Photography. Several colleagues helped with the experiments from time to time, including Dr. R. Dobson, Dr. M. Hargreaves and Dr. G. R. Kelman; and I would particularly like to acknowledge the assistance given by Dr. Greenbaum who helped with the greatest number, often at inconvenient times. Professor J. F. Nunn provided the stimulus which led to this study being undertaken, and I am extremely grateful for his careful perusal of the manuscript and helpful suggestions for its final presentation.

REFERENCES


— (1847). On the Inhalation of the Vapour of Ether in Surgical Operations: containing a description of the various stages of etherization, and a statement of the results of nearly eighty operations in which ether has been employed in St. George's and University College Hospitals. London: John Churchill.


BOOK REVIEW


One of the features of scientific medicine has been the publication of lists of references in which are included virtually all the material concerning some limited subject. This paperback volume is such. In order to facilitate reference the material is presented under some 20 headings all reflecting different aspects of the effects of hyaluronidase. The author index facilitates reference to any particular article. For anyone who seeks information on this drug, this is a most useful volume.

A. R. Hunter