THE RATE OF UPTAKE OF NITROUS OXIDE IN MAN [1]

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During inhalational anesthesia, an inert gas or vapor diffuses across the pulmonary membrane, dissolves in the blood and is carried by the circulation to all of the tissues of the body. The rate at which an anesthetic dissolves from the gaseous phase in the alveoli into the pulmonary capillary blood is termed the *rate of uptake* of that gas. The uptake of any inert gas continues for many hours at a slowly decreasing rate until the entire body is saturated with the gas at the inspired tension. For example, Behnke, studying nitrogen gas exchange, found that about 5 hours are required to reach 90 per cent of complete saturation at the inspired gas tension (1).

This slow process of body saturation should be differentiated from the process of saturation of the arterial blood, to which the depth of anesthesia is closely related. A normal denitrogenated subject, beginning to breathe air, requires about 3 minutes to reach 90 per cent of complete arterial saturation at the inspired nitrogen tension. If he breathes nitrous oxide, Kety showed that about 20 minutes are required to reach 90 per cent of complete arterial saturation at the inspired nitrous oxide tension (2). Both arterial and body saturation occur more rapidly with a relatively insoluble gas such as nitrogen, than with the soluble anesthetics, since large quantities of the soluble gases are carried away from the lung by the pulmonary blood, delaying the rise of alveolar gas tension.

As the anesthetic gas is taken up in solution in the blood, the resulting decrease in gas volume in a breathing reservoir can be measured by means of a spirometer, just as oxygen consumption is measured in the determination of basal metabolic rate. The method herein reported permits the determination of the volume rate of uptake of the anesthetic gas (in this case nitrous oxide), and oxygen, while maintaining a constant inspired tension of both gases.

The rate of uptake of an inert gas is of interest for the following reasons:

1) Kety and others have attempted to predict mathematically the rate at which soluble gases should be taken up by the body, but the only published experimental data were those in which the relatively insoluble gases nitrogen and helium were used (1, 3, 4). Kety's theoretical uptake curves, designed primarily to predict the course of arterial saturation, are not applicable to body saturation.

2) Behnke (1), Jones (3), and Stevens, Ryder, Ferris, and Inatome (4) independently have studied the nitrogen elimination rate on subjects breathing oxygen over long periods of time, and have concluded that the uptake or elimination rates of other inert gases can be predicted from their data, with certain corrections. Their predictions show a reasonably good correlation with the curves of uptake of nitrous oxide determined experimentally in the present report.

3) It had often been assumed that after 20 to 30 minutes of anesthesia, *all* the body tissues were nearly in equilibrium with the inspired tension of anesthetic gas. Foldes, Ceravolo, and Carpenter (5) describing a technique of nitrous oxide administration with low flow rates, stated that "after a comparatively short period no more nitrous oxide is removed from the administered gas mixture." The observations presented here indicate that nitrous oxide continues to be taken up for at least several hours.

METHOD

Six adult surgical patients without evidence of cardiac or pulmonary disease, were studied during prolonged surgical procedures. After topical application of cocaine, a cuffed endotracheal tube was inserted, through a previously prepared tracheotomy in three cases, and per-orally in the other three. Induction and supplementation of anesthesia were accomplished using intravenous thiopental. The residual nitrogen of the lung was re-

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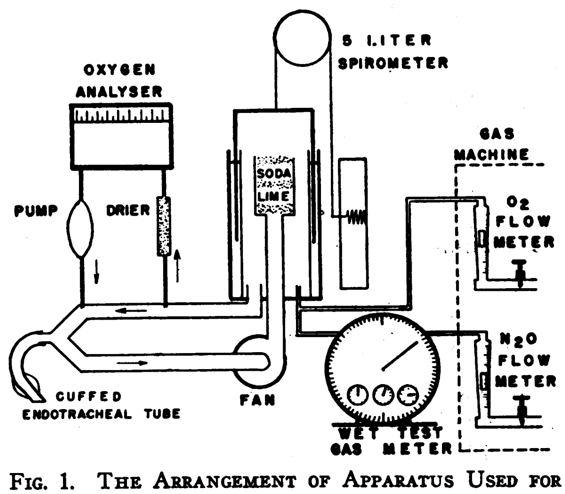

FIG. 1. THE ARRANGEMENT OF APPARATUS USED FOR DETERMINING THE NITROUS OXIDE UPTAKE RATE

An anesthesia gas machine was modified to permit the flow of N_2O to be measured with a wet-test gas meter before mixing it with O_2. The O_2 analyzer pump was a hand bulb. The flow rates of N_2O and O_2 were adjusted to keep the end expiratory spirometer volume constant, and the inspired O_2 concentration at 20 per cent.

placed with oxygen administered in an open circuit (no rebreathing) for at least 10 minutes. The endotracheal tube was then connected to a spirometer containing a circulating fan and CO_2 absorbent (Figure 1). The total

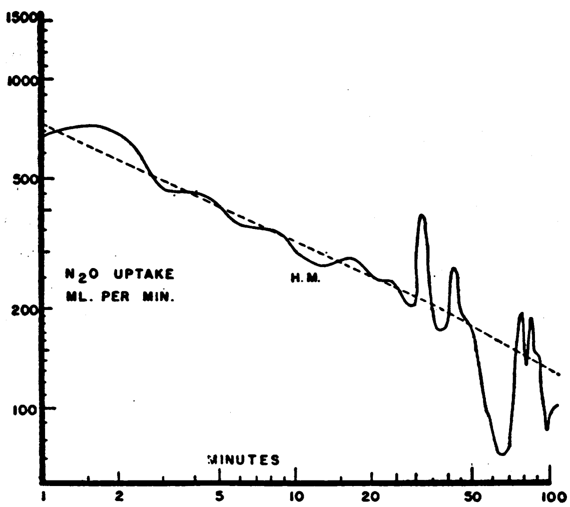

FIG. 2. AN EXAMPLE OF THE OSCILLATIONS IN UPTAKE RATE DUE TO VARIATIONS IN THE INSPIRED CONCENTRATION OF N_2O IN ONE PATIENT DURING 100 MIN. OF ANESTHESIA

On log-log coordinates the curve of uptake rate *vs.* time was most nearly a straight line. This allowed the best estimate of the N_2O uptake which would occur if inspired concentration were held constant, by visually selecting a line to average out the oscillations.

gas capacity of the spirometer and tubing was 12 liters consisting of a 5 liter bell and 7 liter residual volume. It had been filled to 10 liters with 100 per cent nitrous oxide (in 2 cases 90 per cent N_2O, 10 per cent O_2). The respiration of the subject then mixed the lung gas, oxygen, with the spirometer nitrous oxide. Normally at the end of expiration the lungs contain 2 to 3 liters of gas (the functional residual capacity). As this volume of oxygen mixed with 10 liters of N_2O, the O_2 concentration in the spirometer rose, and at the same time, the alveolar O_2 concentration fell. The inspired oxygen tension was measured with a Pauling type oxygen analyzer [3] so arranged that the analyzed gas samples were returned to the system. Nitrous oxide was added to the spirometer through a wet-test gas meter which indicated the total volume of flow. The flow rates of both O_2 and N_2O were controlled with the needle valves and rotameters on a conventional anesthesia machine. The method required that one observer continuously monitor both the inspired O_2 concentration and the end-expiratory spirometer volume. He adjusted the rates of flow of both O_2 and N_2O to hold the inspired O_2 concentration at 20 per cent and the volume constant. If these criteria were achieved, then both O_2 and N_2O were added to the system as rapidly as they were taken up in solution by the body. At one minute intervals, a second observer recorded the total volume of N_2O that had been added through the wet-test gas meter, and the inspired oxygen concentration.

The inspired N_2O concentration was calculated to be 100 per cent minus the inspired O_2 concentration. Actually, there was always a small gradual rise in the N_2 concentration as it diffused outward from the tissues of the body, in one case (R. E.) amounting to 7 per cent after 65 minutes. It follows that both the N_2O concentration and its rate of uptake decreased slowly during the experiment. The resulting inspired N_2O concentration at the end of the experiment was probably between 70 per cent and 75 per cent when the O_2 concentration measured 20 per cent.

It was usually not possible to keep the inflow of nitrous oxide exactly equal to the rate of uptake by the patient. A correction was made in calculating the uptake rate based on the changes in spirometer volume and O_2 concentration from minute to minute.

RESULTS

The rate of uptake of N_2O tended to oscillate (Figure 2) as a result of concentration changes in the alveolar gas. The rate of uptake is determined by the gradient in gas tension between alveolar gas and mixed venous blood. After partial saturation, small changes in alveolar N_2O tension, caused by changes in inspired tension, may produce very large percentage changes in the gradient between alveoli and mixed venous blood tension.

[3] Beckman Instruments, South Pasadena, Calif.

For example, if after one-half hour the tension gradient is 20 mm. Hg, a fall of alveolar N_2O tension of 20 mm. (3 per cent in concentration) would result in temporary equilibrium, and the uptake of N_2O would cease. These concentration changes result from the human inability to rapidly correct gas flow rates, a factor which is considerably reduced by experience.

In Figure 2 the measured rate of uptake of N_2O of one of the six subjects is presented on log-log coordinates; as suggested by Stevens, Ryder, Ferris, and Inatome (4) these coordinates most nearly result in a straight line relationship between rate of uptake and time. A line was selected visually to average out the oscillations in the rate of uptake of N_2O. In Figure 3 the N_2O uptake rates of the six subjects corrected by this graphical method are plotted on semi-logarithmic coordinates. This procedure introduces errors in the reporting of the actual gas uptake, but none are cumulative, so the result is an approximation of the uptake rate which would occur with a constant inspired concentration of N_2O.

The total volume of N_2O taken up in solution in the body of each of the six patients is listed in Table I. This volume is compared with the volume of the gas which would be required to saturate the body at a partial pressure of 570 mm. (inspired concentration 80 per cent), knowing the solubilities at this pressure to be 1,150 ml. per liter of adipose tissue and 360 ml. per liter of watery tissues. The body was assumed to be 20 per cent fat and 72.4 per cent watery tissue (1); these predicted values are therefore only approximations. They are presented to indicate that the large volume of gas absorbed by the patient is reasonably in accord with expectations.

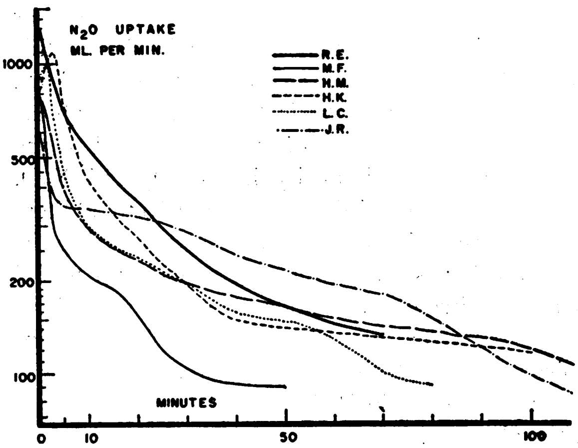

FIG. 3. THE RATE OF UPTAKE OF N_2O BY SIX SUBJECTS DURING ANESTHESIA WITH 80 PER CENT N_2O AND 20 PER CENT O_2.

These curves were obtained from the measured values by the graphical procedure shown in Figure 2.

Oxygen consumption in Table I was roughly measured with the rotameter in four subjects. The reasonable agreement with predicted metabolic rate serves to demonstrate the absence of significant gas leaks during the procedure.

DISCUSSION

There are several sources of error in the determination of the rate of uptake of N_2O. Cumulative errors arise from nitrogen in the inspired gas, and from loss of nitrous oxide through the skin, the wound and rubber tubing. These errors are in opposite directions. Nitrogen, by its presence, lowers the inspired concentration of nitrous oxide, thereby lowering the rate of nitrous oxide uptake; its sources are: 1) the N_2 dissolved in the tissues of the body, amounting to 700 to 1,200 ml., some of which diffuse outward during the experi-

TABLE I

The rate of uptake of nitrous oxide and oxygen

Patient	Age	Sex	Height	Weight	Duration of experiment *minutes*	Predicted total N_2O uptake in liters when saturated	Measured N_2O uptake at end *liters*	O_2 consumption *ml./minute* Predicted	Measured
R. E.	16	M	58	156	67	36.4	21.69	254	
H. K.	48	M	65	100	109	23.3	22.13	190	
L. C.	21	F	64	129	80	30.0	16.5	200	193
M. F.	34	F	65 est	120	50	28.0	7.58	190	190
H. M.	48	M	66	156	108	36.4	19.0	224	165
J. R.	49	M	74	162	155	37.8	29.95	260	203

ment; 2) gaseous N_2 remaining in the lungs after the 10 minute washout. In normal subjects this should be less than 2 per cent of lung gas, or 60 ml; 3) diffusion of atmospheric N_2 inward through the skin and open wounds (1); 4) N_2 added to the spirometer as an impurity in the O_2 and N_2O. Since about 15 to 25 liters of O_2 and 16 to 30 liters of N_2O are added to the closed system during the first 1½ hours, and both may contain up to 0.5 per cent nitrogen, this adds about 250 ml. of N_2 gas. The actual concentration of N_2O in the inspired air could have been determined in each subject as was done in R. E. by measuring the N_2 at intervals.

Loss of N_2O gave falsely high values for uptake rate. The only important source of loss of N_2O is diffusion outward through the skin and the open wound. Orcutt and Waters (6) estimated the loss through the skin of the entire body to be about 7 ml. per min. Wounds probably give rise to a considerable additional loss.

Some error is introduced by the variations of volume and concentration previously mentioned, but these are not cumulative, and tend to average out with time. The graphical method of cancelling out these oscillations is of course an approximation.

The wet-test gas meter is accurate to within 0.5 per cent at any volume. The oxygen analyzer is accurate in the presence of N_2O and at 20 per cent O_2 concentration is readable to 0.5 per cent, accurate to 1.0 per cent.

The prediction of N_2O uptake rate

The process of saturation of the body with a gas is believed to be exactly the reverse of the process of desaturation with the same gas (2). For example, if 5 hours of O_2 breathing are required to remove 90 per cent of the body N_2, then 5 hours of air breathing will be required to replace 90 per cent of the N_2. Furthermore, two gases with identical solubility coefficients will have identical uptake rates. Both Jones and Behnke have suggested that the uptake of any gas might be predicted from the nitrogen elimination rate according to the relative solubilities of the two gases.

Increased solubility of the gas in blood will delay the rise of arterial and alveolar tension, since a larger share of the gas will be removed from the alveoli and carried away by the blood. Fortunately, the time required for arterial saturation with N_2O at the inspired tension has been frequently measured by others (2). In general, 90 per cent saturation will occur in about 20 minutes with normal cardiac output and alveolar minute ventilation.

It is possible to predict from N_2 elimination data the volume of N_2O needed to saturate the entire body, as follows. N_2O is 32 times more soluble than N_2 in blood; it is 20 times more soluble than N_2 in fat. With 20 per cent of the body being fat, the average solubility of N_2O will be 30 times that of N_2. Since in these studies the inspired concentration of N_2O was 80 per cent, this gas saturated the body at the same tension that N_2 had exerted. Therefore, by volume, 30 times more N_2O than N_2 will dissolve in the body at the same concentration.

The prediction of the *rate* of uptake now involves several additional considerations. Tissue perfusion rate (not gas solubility) limits the saturation of the individual non-fat tissues of the body with an inert gas (3). Therefore, when arterial saturation is complete, each tissue (whether fat or non-fat) will reach saturation with N_2O at about the same rate that it becomes desaturated with N_2. This is true of fat only because of the similar fat to plasma partition coefficients for these two gases (5.2 to 1 for N_2 and 3.2 to 1 for N_2O). Gases with a high fat to plasma partition coefficient such as cyclopropane (35 to 1) require a longer time to fully saturate the fat. Therefore, in translating from N_2 data to N_2O predictions, the assumption was made that fat had a similar influence on the two gas exchange rates. Thus, for equal arterial tensions, the rate of uptake of N_2O will also be 30 times the rate of elimination of N_2.

The N_2 elimination rates of volunteers have been published by Jones (3), Stevens, Ryder, Ferris, and Inatome (4) and Behnke and Willmon (1, 7). These data were utilized by multiplying the rate of N_2 elimination by the factor

$$30 \times \frac{\text{arterial nitrous oxide tension}}{\text{inspired nitrous oxide tension}}$$

assuming 70 per cent of inspired tension after 3 minutes and 90 per cent after 20 minutes. These several curves predicting the rate of uptake of N_2O are compared graphically in Figure 4 with the average N_2O uptake as measured in the six subjects reported herein. The correlation is reasonably good in spite of variations in body size, amount of adipose tissue, cardiac output, pulmonary ventilation, other effects of anesthesia, and the many assumptions made both in the predicted and the measured uptake rates. Ventilation in the anesthetized subjects was undoubtedly less than that in the conscious volunteers studied for N_2 elimination.

The average N_2O uptake of the six subjects when plotted on log-log coordinates (Figure 4) is nearly a straight line. An approximate formula fitting this straight line is N_2O uptake rate = 1,000 $t^{-0.5}$. Stevens provides formulae for several subjects, which, converted by the factor 30 for comparison with N_2O, for a 60 Kg. body weight would give, with wide variations, N_2O uptake rate = 1,800 $t^{-0.6}$.

Behnke's data were graphically differentiated to obtain rate from his published curves of total N_2 elimination. Jones' curves were obtained by differentiation of a 5 term exponential equation.

Also plotted in Figure 4 is a curve of N_2O uptake as predicted by use of Kety's theoretical equations for arterial and mixed venous concentration *vs.* time. The similarity of slope during the first 30 minutes is in accord with the derivation of this equation intended to predict the course of arterial saturation.[4]

The rough agreement between the experimentally determined N_2O uptake rate and the predicted N_2O uptake rate supports the thesis that, as an approximation, the N_2O uptake rate is 30 times the N_2 elimination rate in ml. per min. throughout the process of body saturation.

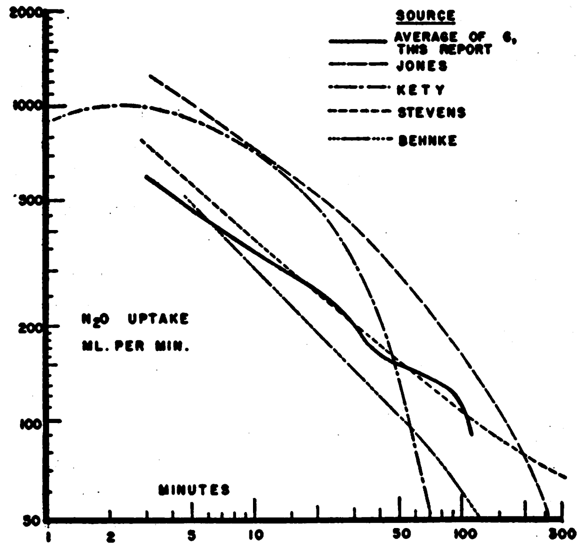

FIG. 4. COMPARISON OF THE AVERAGE OF THE CURVES OF N_2O UPTAKE OF SIX PATIENTS, DISREGARDING BODY SIZE, WITH THE RATE OF UPTAKE OF N_2O AS PREDICTED BY VARIOUS METHODS

The curve from Kety's theoretical equation was predicted by assuming the following physiological parameters: cardiac output 6 L. per m, alveolar minute ventilation 3 L. per m, functional residual capacity 3 L., wt. 70 Kg. The curves from Jones, Behnke and Stevens were obtained by multiplying the N_2 elimination rate curves by the factor $\left(30 \times \frac{\text{arterial } N_2O \text{ tension}}{\text{inspired } N_2O \text{ tension}}\right)$.

The significance of these observations in anesthesia

Nitrous oxide is commonly used in a semi-closed or partial rebreathing system to provide a pleasant induction to ether anesthesia. After induction has been completed, the flow of N_2O is stopped and ether is administered in a closed system with CO_2 absorption. It is generally recognized that, during induction, the inspired concentration of O_2 is lower than the concentration of O_2 in the administered mixture because of the absorption of O_2 by the pulmonary blood. However, the high rate of uptake of N_2O tends partially to cancel out the effect of oxygen absorption on the inspired concentration. If the two gases were taken up in proportional amounts, which they are during the first 1 to 3 minutes, no reduction in oxygen concentration would occur. It is therefore reasonable to use a slightly lower O_2 proportion in the administered mixture during induction than during maintenance of anesthesia with N_2O.

A common clinical observation is the tendency for the depth of anesthesia to lessen if the flow of N_2O is stopped, as when used for induction of ether anesthesia. The explanation for this occurrence is as follows: After the flow of N_2O has ceased, the gas continues to be taken up in solution

[4] Using Kety's symbols, the equation for the rate of uptake of an inert gas, derived from his equation 55, is as follows:

$$\text{Rate of uptake} = \frac{dC_v}{dt} \cdot V_t$$
$$= C_I \cdot [A_1 M_A - V_A k_1] \cdot [e^{-k_1 t} - e^{-k_2 t}].$$

by the patient at a rate of about 200 to 500 ml. per min. This depletes the supply of gaseous N_2O in the lung and reservoir bag, and lowers its concentration. Also, O_2 is usually added more rapidly than it is metabolized, and is used to refill the bag as N_2O is absorbed. As the concentration of N_2O in the lung falls, the arterial concentration also falls, diminishing the depth of anesthesia. Since the amount of ether absorbed during the N_2O induction is relatively small, the patient may then show signs of lighter anesthesia.

This information has a bearing on the use of closed systems with N_2O. The gas continues to be taken up in solution in the body for many hours, so the concentration of N_2O in the breathing reservoir and lung will fall when the flow of N_2O is stopped even after several hours, provided the oxygen flow is at least sufficient to meet metabolic needs. This precludes the maintenance of an even depth of anesthesia with N_2O in a closed system unless the O_2 concentration is periodically measured. Several reports describe the use in semi-closed systems of low flow rates of both O_2 and N_2O which have been shown to result in desirable O_2 concentrations (5, 8). The resulting gas concentrations will depend somewhat on the uptake of N_2O and will vary, accordingly, with the duration of anesthesia.

The time required for elimination of N_2O from the body during the recovery period is similar to that required for saturation with the gas; it follows that the body tissues as a whole require about 5 hours to lose 90 per cent of their N_2O. Arterial blood likewise loses 70 per cent of its N_2O in 3 minutes, 90 per cent in 20 minutes.

Fink, Carpenter, and Holaday (9) have demonstrated that this large volume of N_2O being eliminated during the first few minutes of air breathing results in a lowered alveolar oxygen tension, which may be enough to produce arterial unsaturation with usually adequate ventilation.

The metabolic rate during anesthesia, as reflected in O_2 consumption, can be measured by the method used herein for N_2O uptake, if O_2 is added through a wet-test gas meter. At least 20 minutes should be allowed to average out the previously mentioned oscillations in concentration and reservoir volume. Although this was not done in the present study, the setting of the O_2 flowmeter was recorded in four of the six patients. Table I lists the average O_2 consumption during the entire procedure calculated from this data, along with the O_2 consumption predicted for each subject under basal conditions according to the DuBois tables.

SUMMARY

The volume rate of uptake of N_2O by the body was measured during surgical anesthesia. After 90 minutes of inhalation of an 80 per cent N_2O – 20 per cent O_2 mixture, the body is still absorbing about 100 ml. of N_2O per minute from the gaseous phase in the lungs. Seven and one-half to 30 liters of N_2O are taken up in solution in the body during 1 to 2½ hours of anesthesia.

The rate of uptake of N_2O during at least the first 2 hours of anesthesia is about 30 times the volume rate of elimination of nitrogen as reported by others (30 is the ratio of solubility of the two gases). This evidence supports the suggestion that the approximate uptake rate of other inert gases can be predicted from data on nitrogen elimination.

The average rate of uptake of N_2O in six subjects was described approximately by the equation: Rate $= 1{,}000\ t^{-0.5}$ ml. per min.

The experimental findings were discussed in relation to several clinical problems in anesthesia.

The method can be used to determine the oxygen consumption as an index of the metabolic rate during anesthesia with gases or vapors.

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