Uptake and Excretion of Subanesthetic Concentrations of Nitrous Oxide in Man

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THEORETICAL analyses of the rates of uptake and excretion of an inert gas by the body have been based upon a schematic model of the physiologic forces which determine these rates.[1, 2] Although this model involves a number of assumptions, it has led to a prediction that uptake and excretion of the inert gases are identical or nearly so. An inert gas, furthermore, is determined substantially only by physical processes which are also freely reversible. The time rates of uptake and excretion, therefore, should be identical, provided the gas has no physiological effect. Jones[1] has presented experimental data indicating that the resaturation of tissues with atmospheric nitrogen occurs as the reverse process of nitrogen elimination.

The present study seeks to confirm or deny the equivalence of N_2O uptake and elimination by measuring the two processes in the same subject. Although both phases of N_2O exchange have already been reported, each has been investigated individually and with different methods. Severinghaus[3] measured the volume uptake per minute during spontaneous breathing in the anesthetized subject. Frumin, Salanitre, and Rackow[4] measured the changing N_2O end-tidal concentration during excretion in the paralyzed, anesthetized subject artificially respired.

The use of anesthetized subjects in both these studies may have introduced instability in those physiological systems which determine gas transfer. Such variations, if present, would make less meaningful a comparison of uptake with excretion. The use of subanesthetic concentrations of N_2O should make possible the comparison of uptake and excretion in the same subject during reasonably steady physiological states.

Methods

Five subjects, four men and one woman, were used in the study. None of the individuals had any evidence of systemic disease. Their weights ranged from 148 to 185 pounds. Each was studied in the supine position.

During a control period 100 per cent oxygen was inspired from a nonrebreathing system, followed by a constant mixture of approximately 10 per cent N_2O in oxygen during the uptake period and then by 100 per cent oxygen during the excretion phase. The subject breathed through a mouthpiece attached to a Rahn-Otis sampling system.[5] * The inspiratory gases were supplied from an anesthetic reservoir bag fitted with a pop-off valve which prevented overflow of inspiratory gas into the system during expiration and dilution with room air during inspiration. The pop-off valve was designed to open at a pressure lower than that necessary to open the inspiratory valve. Expiratory volumes were collected in a 120-liter Tissot spirometer and recorded on a direct-writing kymograph. All connecting tubing had an internal diameter of 2.2 cm.

The change of inspiratory gas from 100 per cent oxygen to 10 per cent N_2O in oxygen for uptake and then back to 100 per cent oxygen for excretion was accomplished abruptly, and the system flushed briefly with high gas flows. The change was complete in less than 30 seconds.

The establishment of a steady state during the control period was determined by the

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TABLE 1. Exponential Constants Derived from Uptake and Excretion Curves for Each of Five Subjects

Subject	Weight (kg.)	Height (cm.)	Surface Area (m.²)	Uptake					Excretion				
				R.M.V.	A_1	A_2	k_1	k_2	R.M.V.	A_1	A_2	k_1	k_2
1	75	183	1.95	8.1L.	0.092	0.13	0.051	0.95	8.5L.	0.075	0.19	0.029	0.30
2	80	170	1.90	6.6	0.048	0.11	0.019	0.09	6.1	0.076	0.19	0.023	0.30
3	83	183	2.02	5.5	0.058	0.31	0.011	0.25	5.2	0.10	0.28	0.023	0.31
4	64	168	1.78	6.2	0.026	0.17	0.005	0.15	6.1	0.059	0.13	0.007	0.15
5	72	172	1.88	5.8	0.092	0.34	0.017	0.31	5.7	0.087	0.18	0.013	0.19
Composite Awake					0.066	0.17	0.021	0.21		0.086	0.19	0.021	0.21
Composite Anesthetized*										0.13	0.22	0.022	0.24

R.M.V. = Average respiratory minute volume.
* Frumin, and others: J. Appl. Physiol. **16**: 720, 1961.

measurement of end-expiratory CO_2 tension (PA_{CO_2}) and by inspection of the slope of the ventilation record as seen on the kymograph. If the range of end-tidal CO_2 tension was 4 mm. of mercury or less and the slope appeared to be constant for ten minutes prior to the start of uptake, it was assumed that a steady state existed. The duration of N_2O uptake was approximately one hour in each subject. The excretion phase was followed for at least 30 minutes.

End-tidal N_2O and CO_2 concentrations were determined with Beckman LB-1 nondispersive infrared analyzers in parallel, used in conjunction with transistorized detector-amplifiers.†

A hand-triggered pneumatically activated pump took an 8 ml. end-tidal sample from the Rahn-Otis collection chamber and injected it into the analyzers. The outputs of the analyzers were recorded on a Grass polygraph and concentrations were read when the record indicated that flow through the cuvette had ceased. Essentially every breath was sampled except during calibration of the instruments. Calibration was done by methods previously described.[2] The sampling system had a lag which resulted in a five sample delay which was corrected in calculating elapsed time. Analysis of CO_2 concentration was used as a check on the end-tidal character of the sample. When an abrupt reduction in CO_2 concentration suggested contamination of the sample with dead space air, the corresponding N_2O value was discarded, as were those for the succeeding sampling delay period.

Two correction factors were applied to the measured FA_{N_2O}: (1) for the diluting effect of alveolar water vapor upon the dry inspiratory gas, and (2) for the concentrating effect upon the inspiratory mixture of the assumed respiratory quotient of 0.8. The net correction factor for both these effects was calculated to be close to 1.02 in all subjects. The corrected values were then converted to relative values to permit direct comparison between uptake and excretion curves, as follows:

$$\text{Relative Uptake } N_2O = (Y_u)$$

$$= 1 - \frac{FA_{N_2O}}{FI_{N_2O}} \quad (1)$$

$$\text{Relative Excretion } N_2O = (Y_e)$$

$$= \frac{FA_{N_2O}}{\text{Last } FA_{N_2O} \text{ of uptake}} \quad (2)$$

The relative N_2O values were plotted on semilogarithmic coordinates and the appropriate curve visually fitted. The composite uptake and excretion curves were obtained by averaging corresponding points on the individual curves at 2.5 minute intervals. The individual and composite curves were analyzed as in a previous report[4] and the curve constants A_1, A_2, k_1, k_2 were determined. The manner of this analysis will be discussed.

Results

Table 1 summarizes the physical characteristics of each subject and indicates the values

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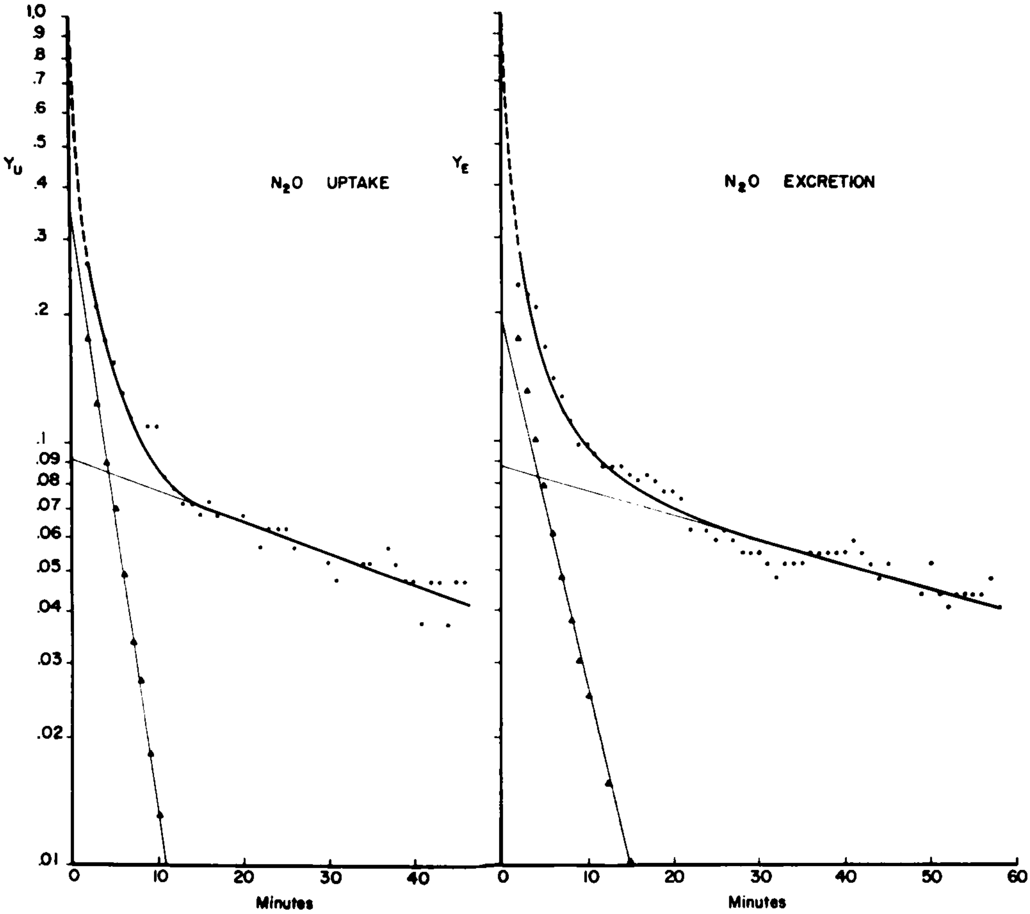
† Invengineering, Inc., Belmar, New Jersey.



FIGS. 1 and 2. Uptake and excretion curve of subject 5 showing the relative measured values of end-tidal N₂O.

for the various constants (A_1, A_2, k_1, k_2) obtained by the mathematical analysis of the individual experimental curves.

Figures 1 and 2 show the uptake and excretion curves for subject 5. Their analyses yielded the equations:

$$Y_u = 0.092e^{-0.017t} + 0.34e^{-0.31t}, \quad t > 2‡ \quad (3)$$

$$Y_{ex} = 0.087e^{-0.013t} + 0.18e^{-0.19t}, \quad t > 2 \quad (4)$$

Figures 3 and 4 show the composite uptake and excretion curves for all five subjects. The analyses of these curves gave the equations:

$$Y_u = 0.066e^{-0.021t} + 0.17e^{-0.21t}, \quad t > 2 \quad (5)$$

$$Y_{ex} = 0.086e^{-0.021t} + 0.19e^{-0.21t}, \quad t > 2 \quad (6)$$

Figure 5 compares the composite *excretion* curve of the awake subjects of the present study with the corresponding curve of a group of three subjects reported by Frumin and co-workers,[4] who were artificially respired with a CO_2 servo-controlled respirator. The data of the latter group were converted from the originally reported absolute values to relative values to conform with the methods of this study. Analysis of the composite curve for the anesthetized group gave the equation:

$$Y_{ex} = 0.13e^{-0.022t} + 0.22e^{-0.24t}, \quad t > 2 \quad (7)$$

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‡ For values of Y when t is less than two minutes, a third exponential would be required. Calculation of this portion of the curve was omitted because the data were considered insufficiently precise, due to lag both in changing of inspired mixture and in sampling.

Discussion

The kinetics of pulmonary gas exchange and its mathematical treatment have been reviewed in detail,[1, 2, 6-9] therefore, only a brief discussion will be included here. The saturation of the body by an inert gas inspired at a constant tension, and the subsequent desaturation, are controlled by the physical characteristics of the gas and by the physiological factors which govern its rates of turnover in the various body tissues.

Solubility in the different compartments (blood, muscle, viscera, fat, etc.) determines the final distribution of the gas throughout the body. The difference in solubilities in the various tissues gives rise to partition coefficients which, at equilbrium, express the ratio of concentrations between any adjacent pair of compartments and help determine the proportionate volume of gas in each compartment.

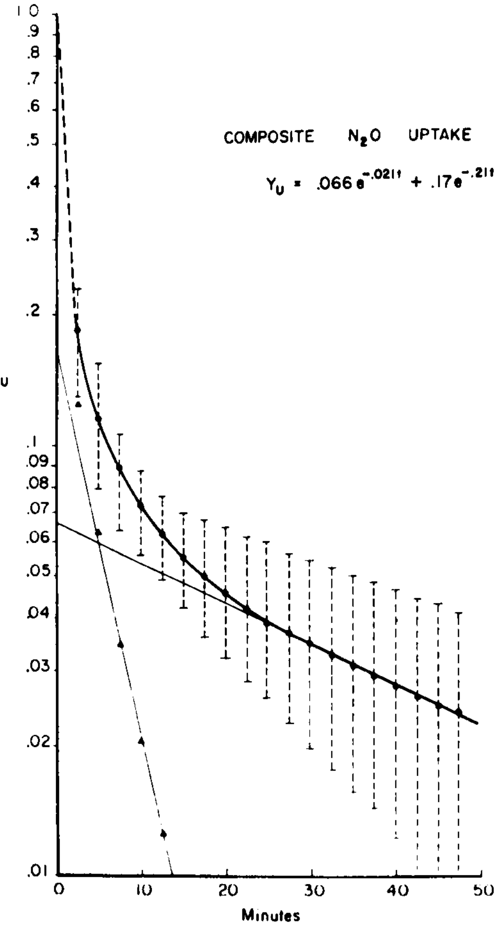

FIG. 3. Composite N_2O uptake curve for five subjects. The bars indicate the range of values.

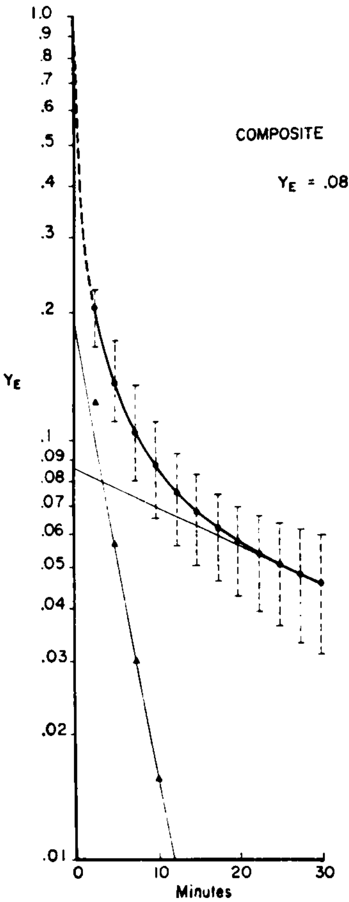

FIG. 4. Composite N_2O excretion curve for five subjects. The bars indicate the range of values.

The physiological factors which influence rate of transport of the gas to tissues include: pulmonary ventilation, pulmonary blood flow, distribution of cardiac output to the tissues and the tissue volumes. Other factors which will not be discussed include blood shunts and possible diffusion barriers.

Although inert gas exchange follows simple physical laws, the dynamics of the processes are complicated because the body consists of a system of compartments, connected both in series and in parallel with respect to the gas pathway, each with its own rate of gas exchange. The lung represents the open end

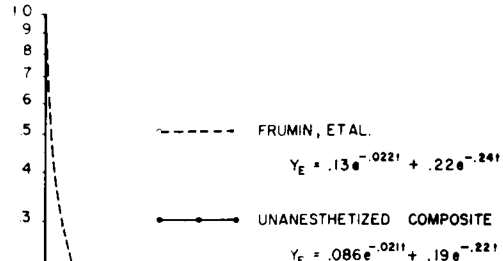

FIG. 5. Comparison between the composite N_2O excretion curve of a group of anesthetized subjects reported by Frumin and associates,[4] and the composite N_2O excretion curve for the five awake subjects of this study.

compartment of the system. Measurements of uptake and excretion taken from this compartment must reflect changes in every compartment of the body, but these changes are buffered, and to a large extent concealed, by the interposition of mixed venous blood between the body tissues and the lung. Sampling of alveolar air, therefore, yields limited data on gas transfer in these tissues. Some information, however, may be obtained by appropriate mathematical analysis of the experimental curve constructed from the measured changing values in end-expiratory air.

The rates of uptake and elimination of an inert gas in a *one compartment* system § will depend upon the concentration gradient. The rate of change in concentration may be represented by the equation $dy/dt = -ky$, where y is the concentration at any time, t, and k is the rate constant for the process. Integrating this equation we obtain for the desaturation process: $y_{ex} = A_n e^{-kt}$, where A_n is the concentration in the compartment at time zero. The plot of log y against t is a straight line. Conversely, if the logarithm of the gas concentration is plotted against time and gives rise to a straight line, the equation of the line will be of the exponential form seen above. Since theory predicts that the saturation process is equivalent to desaturation, its equation may theoretically be represented by: $y_u = A_n (1 - e^{-kt})$. The use of relative values restores this to the form $y_u = A_n e^{-kt}$, to permit direct comparison of uptake and excretion.

In the *multi*-compartment system represented by the body the interrelationships of gas transfer are considerably more complicated and the interpretation of the equations more difficult. The form of the expression describing total body gas transfer will be that of the sum of a series of exponential equations:

$$Y = A_1 e^{-k_1 t} + A_2 e^{-k_2 t} + \cdots A_n e^{-k_n t} \quad (8)$$

In general, however, none of the *A*'s or *k*'s of this expression is a simple measure of the characteristics of any single compartment, but are rather determined by contributions from all of them. Biological systems do not usually yield data of such precision that meaningful analysis into more than three such terms is possible. Often only two terms can be determined. This limitation is, in part, responsible for the apparent simplicity of many biological systems.[9] It is generally true, however, that the slowest exchanging compartments will contribute most heavily to the terms of equation 8 which have the smaller k values, while the rapidly exchanging compartments will principally influence the terms with the larger k values.

The analysis of the experimental curve may then proceed in the following manner. The measurement at the lung is continued long enough to expose the compartment having the slowest rate of turnover. The resulting curve, plotted on semilogarithmic coordinates, will have a terminal segment to which a straight

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§ A *one* compartment system is defined as a single finite compartment emptying into or filling from a compartment that has a constant concentration.

line can be fitted. The breakdown of the curve can then be done graphically by extending the straight line segment back to time zero and plotting the absolute value of the difference between the ordinates of the straight line and the original curve. Repetition of this procedure results in the construction of a number of straight line sections, as represented by equation 8. The k constants may be calculated[1] from the half-time ($t_{\frac{1}{2}}$) of the straight line curves (*i.e.*, the time required for the concentration to be halved) using the expression $k = \log_e 2 / t_{\frac{1}{2}}$. The constants A_1, $A_2 \cdot \cdot \cdot A_n$ represent the intercepts of the straight lines on the ordinate at time zero.

The composite uptake and excretion curves of our subjects show close agreement and their empirical equations are remarkably similar. This close correspondence is not necessarily conclusive evidence for the expected equivalence of uptake and excretion, but appears to lend experimental support to this contention. The relatively wide range of values from which each composite curve was derived is in part due to the variation in anatomic and functional characteristics of each subject. The constants seen in table 1, however, indicate that the uptake and excretion curves in the same individual did not show a striking similarity. This would suggest that other factors, which are averaged out in the composite curve, may have played a role. The corresponding k_1 and k_2 values for subjects 2, 4 and 5 are sufficiently close to fall within the range of experimental and/or physiological variability, but this cannot be said of subjects 1 and 3. If the agreement between the composite curves is not merely a fortuitous averaging of unrelated values, the observed differences require satisfactory explanation. Since for any one subject the physical characteristics of the system were constant, the explanation must be found either in the experimental methods and/or in changes of the physiological environment.

The relative insensitivity of the analyzer, together with the method of curve analysis used, may have been a source of experimental error. The N_2O analyzer could detect differences in concentration of about 0.025 per cent, at its maximal sensitivity. This degree of sensitivity, associated with the fact that at the terminal segments of the individual curves the change in absolute end-tidal N_2O concentration was in the range of 0.05 per cent per minute or less, resulted in a wider scatter of points than anticipated. This made the selection of the slope of the straight line fit through the tail of each curve arbitrary, within certain limits. Statistical fitting of the terminal segment separately, as by the method of least squares, is not appropriate in this situation.[7] The values of the intercept constants reflect the selection of the slope of the straight line, and deviation from the true value of the slope would cause differences in the calculated values of the constant.

Another source of experimental error could be failure to continue the study long enough to expose the slowest exchanging compartments. The method of curve analysis used requires that the tail of the curve represent a constant rate of gas turnover, thus indicating primary contribution of a final group of compartments. The degree to which this requirement is fulfilled will be a measure of the proximity of the calculated values to their true values. The high ($k_1 = .051$) value for the slope of the terminal segment on uptake in subject 1 suggests that the more rapidly exchanging compartments were still making significant contribution to the measured N_2O value. Under these circumstances, the empirical equation of this uptake curve is relatively less representative of the uptake process.

Changes in physiological function could not be completely eliminated from the study. Although table 1 shows that in all five subjects the average respiratory minute volumes were not greatly different during each phase of the experiment, all subjects showed frequent and considerable fluctuations in tidal volume in both phases. These variations in ventilation may have been related to, among other things: apprehension during the initial parts of the study, followed by a return to a more tranquil state, salivation, swallowing, tedium during the later parts of the experiment, and N_2O effect.

The inhalation of 10 per cent N_2O in oxygen was not entirely devoid of systemic effect. Other investigators have reported the effects of low concentrations of N_2O.[10, 11] Although periods of drowsiness occurred during both

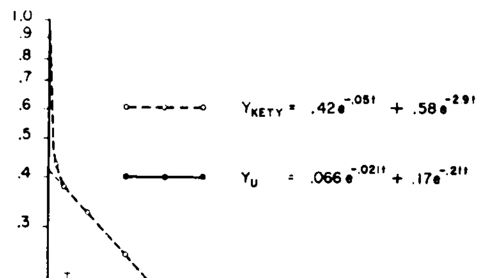

FIG. 6. Comparison between the composite N_2O uptake curve of this study and a predicted curve derived from the desaturation form of the uptake equation 55 of Kety.[2]

uptake and excretion, in the excretion phase they were infrequent and characterized by quick arousal to a vocal stimulus. During uptake, however, these periods were frequent, deeper, and required continuous observation of the subject to prevent dozing. Varying degrees of amnesia resulted. The sedative effect of this low concentration of N_2O, associated with the psychic arousal to the spoken stimulus, caused fluctuations in ventilation which were reflected in the measured N_2O concentration. This tendency to a greater scatter during uptake may explain the larger range of values for the individual uptake curves as compared to the excretion curves (figs. 3 and 4). A comparable effect upon circulation could be hypothesized, but no data were obtained. These considerations make it improbable that the uptake and excretion processes could be demonstrated to be equivalent in all subjects.

The composite excretion curve for the awake subjects of the present study was compared with the composite excretion curve of anesthetized subjects artificially respired with a CO_2 servo-controlled respirator reported in the study of Frumin and associates.[4] The results (fig. 5) showed a close agreement between the corresponding k_1 and k_2 values. This indicated comparable rates of excretion from the slower compartments and suggested that the desaturation process was substantially the same for the two groups. The upward displacement of the curve (large A's) under anesthesia may have been related to one or more of the following:

(1) Possible differences in anatomic and physiological characteristics of the two groups.

(2) Reduced alveolar ventilation in the anesthetized subjects. Changes in ventilation particularly may have arisen because of the effects of the preanesthetic medication, the barbiturates and narcotics used in the management of the anesthesia. The fact that both groups of subjects had CO_2 tensions within the physiological range did not necessarily imply similar ventilation. The use by Frumin and co-workers of thiopental, pentobarbital, and heavy doses of meperidine for anesthesia may have produced a lowered CO_2 production,[12] which, in turn, would have resulted in a reduced alveolar ventilation by the CO_2 servo-controlled ventilator.

(3) The presence of a relatively larger reservoir of N_2O at the beginning of excretion in the anesthetized subjects. The longer duration of uptake in these subjects (one to four hours) made it likely that they were closer to equilibrium with the inspired N_2O tension than the awake subjects. This factor could help explain the separation between the two excretion curves. The identical slope but lower zero time intercept of excretion curves from systems farther from equilibrium has been confirmed on an electrical lung-body analog simulator.[13]

The composite uptake curve of the awake subjects was compared to a predicted curve derived from the desaturation form of the uptake equation 55 of Kety.[2] For this purpose averages were calculated from our measured physiologic variables for respiratory frequency, minute volume, body weight, and surface area, and assumptions were made of nonmeasured values as follows: mean functional residual capacity 2.1 liters to which was added one-half the mean tidal volume to yield a mid-cycle lung volume of 2.35; cardiac index 3.1 liters yielding a mean cardiac output of 5.9 liters, dead space 175 ml. including instrumental dead space. The body volume was calculated from the relation 1 kg. = 1 liter. The blood-air ratio of N_2O was taken to be 0.47. The alveolar ventilation calculated from these assumptions was 4.0 liters/minute.

The uptake equation resulting is:

$$Y_{calc} = 0.42e^{-0.05t} + 0.58e^{-2.9t} \tag{9}$$

and is plotted together with our composite relative uptake curve in figure 6. It may be seen that the measured curve approaches the equilibrium value in alveolar air (and hence arterial blood) considerably more rapidly than the calculated curve. Sechzer, Dripps, and Price[14] have clearly pointed out that a similar deviation for cyclopropane arises from Kety's assumption of a single body compartment. They have used their observed data to calculate an "apparent distribution volume" for inert gas. Another, somewhat more straightforward explanation arises directly from the fact that the bulk of the cardiac output (70 per cent) flows to a small mass of vital organs constituting 7 per cent of the body mass.[15] This small mass quickly becomes equilibrated so that the large proportion of venous blood leaving this tissue contains a high residual concentration of nitrous oxide and absorbs little gas in the lungs. The alveoli, therefore, approach the inspiratory concentration more rapidly than in a uniformly perfused body.

Although there is a discrepancy between the measured alveolar concentration and that predicted by Kety's equation, the implication in his development that the blood-gas partition coefficient is the principal property of the gas determining the time course of absorption can be tested. The value of this coefficient for nitrous oxide is 0.47 and for cyclopropane is 0.42. The data of Sechzer, Dripps, and Price were recalculated, for those studies lasting at least 30 minutes, to conform with the method of equation 1. A comparison of our composite uptake curve for N_2O with that of Sechzer for cyclopropane is shown in figure 7. There is good agreement in general between the two curves. Since the greater solubility of cyclopropane in fat would be expected to make the approach to eventual equilibrium slower than for nitrous oxide, some of this apparent agreement must be ascribed to the relatively short period of observation. This relationship is being tested further in subjects given both gases simultaneously over somewhat longer periods of time.

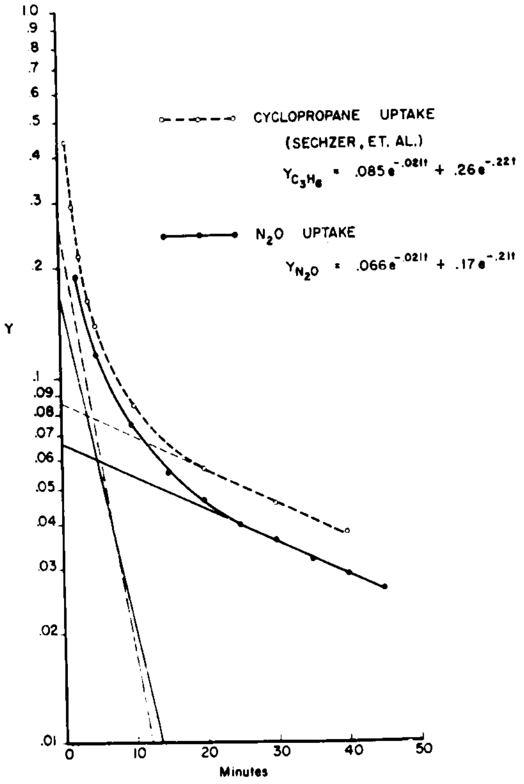

FIG. 7. Comparison between composite N_2O uptake curve of this study and a composite C_3H_6 uptake curve derived from Sechzer's data.[14]

Conclusions

The uptake and excretion of 10 per cent N_2O in oxygen was measured in five awake, supine subjects. Good correlation was found in the composite uptake and excretion curves.

This agreement did not extend to all the individual sets of curves. The reasons for the lack of complete agreement between individual uptake and excretion curves were ascribed to instrument sensitivity, limitations in the method of curve analysis, and difficulty in maintaining the same physiological conditions during both phases of study.

The composite excretion curve of this group of awake subjects was compared to a corresponding curve of a group of anesthetized subjects. The two curves differed only in the upward displacement of the curve seen under anesthesia. This displacement could have arisen in anatomic and physiological differences in the two groups, but may have been in part due to a greater degree of N_2O saturation in the anesthetized subjects at the beginning of excretion.

The composite uptake equation was compared with Kety's general equation for inert gas exchange and with an equation calculated from the data of Sechzer and associates, in their study of cyclopropane uptake. The devation from the general equation may be explained by Kety's assumed homogeneity of body mass and by his implication that blood-gas partition coefficient was the only gas property involved in the gas exchange process. It appeared that the latter implication could be tested by comparing uptake processes of two gases with similar blood-gas partition coefficients and different fat solubilities. The comparison of N_2O and C_3H_6 uptake equations, obtained by alveolar gas measurements, revealed no significant differences in the first 40 minutes of absorption.

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References

1. Jones, H. B.: Medical Physics. Otto Glasser, Editor. Chicago, Year Book Publishers, Inc., 1950, vol. 2, pp. 855–951.
2. Kety, S. S.: Theory and application of the exchange of inert gases at the lungs and tissues, Pharmacol. Rev. **3**: 1, 1951.
3. Severinghaus, J. W.: The rate of uptake of N_2O in man, J. Clin. Invest. **33**: 1183, 1954.
4. Frumin, M. J., Salanitre, E., and Rackow, H.: Excretion of N_2O in anesthetized man, J. Appl. Physiol. **16**: 720, 1961.
5. Comroe, J., Editor: Methods in Medical Research. Chicago, Year Book Publishers, Inc., 1950, vol. 2, p. 124.
6. Defares, J. G., and Sneddon, I. N.: The Mathematics of Medicine and Biology. Chicago, Year Book Publishers, 1961.
7. Robertson, J. S.: Theory and use of tracers in determining transfer rates in biological systems, Physiol. Rev. **37**: 133, 1957.
8. Perl, W., Lesser, G. T., and Steele, J. M.: Kinetics of distribution of fat-soluble inert gas cyclopropane in the body, Biophys. J. **1**: 111, 1960.
9. Solomon, A. K.: The Kinetics of Biological Processes. Advances in Biological and Medical Physics. New York, Academic Press, Inc., 1953, vol. 3.
10. Robson, J. G., Burns, B. D., and Welt, P. J. L.: Effect of inhaling dilute N_2O upon recent memory and time estimation, Canad. Anaesth. Soc. J. **7**: 399, 1960.
11. Burns, B. D., Robson, J. G., and Welt, P. J. L.: Effect of N_2O upon sensory thresholds, Canad. Anaesth. Soc. J. **7**: 411, 1960.
12. Elam, J. O., and Brown, E. S.: Carbon dioxide homeostasis during anesthesia; ventilation and carbon dioxide elimination, ANESTHESIOLOGY **17**: 116, 1956.
13. Epstein, R. M.: Unpublished data.
14. Sechzer, P. H., Dripps, R. D., and Price, H. L.: Uptake of cyclopropane by the human body, J. Appl. Physiol. **14**: 887, 1959.
15. Bard, P.: Medical Physiology, ed. 11. St. Louis, C. V. Mosby Co., 1961, ch. 14, p. 240.