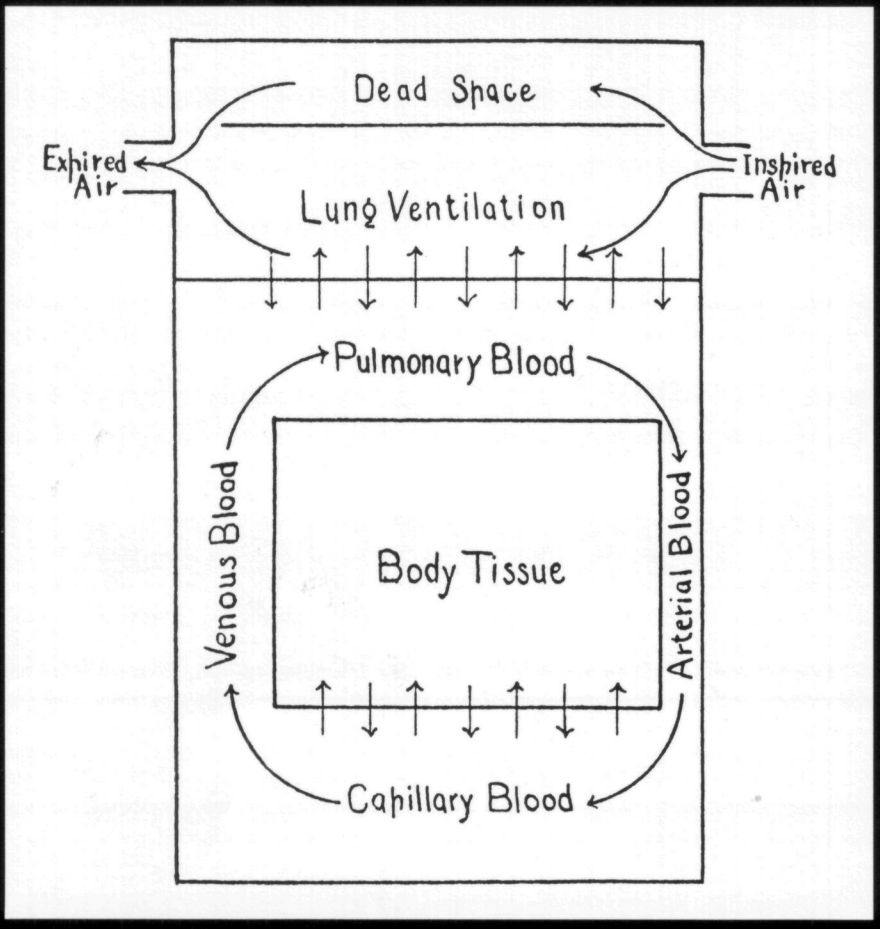
The History of Anesthesiology

Reprint Series: Part Fifteen



From JOURNAL OF BIOLOGICAL CHEMISTRY, 59:754, 1924. Reprinted by permission.

An illustration from Howard W. Haggard's classic articles on The Absorption, Distribution and Elimination of Ethyl Ether. In this diagram, Haggard depicts the relations among respiration (with lung dead space), alveolar diffusion, pulmonary blood flow, tissue blood flow, and solubility of ether in the body tissues. Mistakenly, however, he assumed a uniform blood supply to tissues as well as a uniform solubility in those tissues.

UPTAKE AND DISTRIBUTION OF INHALATION ANESTHETICS

Uptake and Distribution of Inhalation Anesthetics

CONTENTS

A Synopsis of the Uptake and Distribution of Inhalation Anesthetics

Those true pioneers of anesthesia, among them John Snow, knew solely on the basis of clinical observation that the nature of respiration and the circulation of blood through the lungs were elemental to the phenomenon of clinical anesthesia. Beset with three agents at the extremes of differing physical properties, nitrous oxide, chloroform, and diethylether, they could only surmise why there were marked variations in induction and emergence times during anesthesia. A beginning toward defining the process arose in 1870 when Adolf Fick advanced his proposal for measurement of the stroke volume of the left ventricle of the heart, a remarkable, less than two page communication supported by no physiological data whatsoever.

Around that time Paul Bert conducted his studies on barometric pressure with the result that a knowledge of partial pressures of gases and their solubilities in aqueous media (Henry's Law) could be applied to the administration of nitrous oxide in man, also allowing the determination of chloroform percentages in inhaled gas mixtures. Subsequently, Walter M. Boothby of Boston adapted the Waller chloroform balance to the assay of ether concentrations, permitting estimation of the rate of saturation and desaturation of body tissues. "The term, 'anesthetic tension' is employed to indicate the partial pressure of ether vapor, that, after equilibration is established, can, for an indefinite period, maintain the subject in the stage of ideal surgical anesthesia." Apparently, variation among individuals could be accounted for by: (a) changes in volume of respiration; (b) changes in rate of circulation; and (c) by a possible alteration in the rapidity with which the reversible reaction (in susceptible nerve cell molecules) takes place under slightly different chemical environments.

Howard W. Haggard's classic reports on the Absorption, Distribution, and Elimination of Diethyl Ether are too voluminous for complete reproduction here. The innovations comprised a quantitative method for ether analysis, the iodine pentoxide train, as well as measurement of solubilities in blood and tissues, thereby enabling him to express uptake and distribution in mathematical terms. The schema reproduced on the cover of this packet illustrates the process in general, but mistakenly assumes a uniform gas solubility as well as blood flow in all of the body tissues.

In Carl Schmidt's laboratory at Pennsylvania, long involved in studies on organ blood flow — heart and kidneys for example, Seymour Kety, utilizing the direct Fick principle and the relatively insoluble nitrous oxide gas, was able to assay cerebral blood flow in addition to the physiologic and pathophysiologic factors that modify it. The information gained from his epoch making experiments resulted in the all encompassing review on the Theory and Applications of the Exchange of Inert Gas at the Lungs and Tissues. Clinical measurements of anesthetic uptake and elimination followed as evidenced by Severinghaus' ingenious estimation, in an operating room setting, of the uptake of nitrous oxide. With better methods for quantitative analysis of other inhalation anesthetics and use of tagged molecules, these studies on pharmacokinetics were eventually extended to intravenous and local anesthetics as well. The accumulated body of knowledge on this subject has resulted in safer administration of anesthetics, synthesis of new agents with improved physical properties, and the valuable concept of minimal anesthetic concentration (MAC).

Leroy D. Vandam, M.D.

Gesammelte Schriften

von

Adolf Fick

weil. Professor der Physiologie in Würzburg.

III. BAND.

Physiologische Schriften (Schluss).

1904.
Stahel'sche Verlags-Anstalt in Würzburg
Königl. Hof- und Universitäts-Verlag.

Ueber die Messung des Blutquantums in den Herzventrikeln.

Sitzungsber. der Phys.-med. Gesellsch. zu Würzburg, 1870, S. XVI.
(Würzburg, Stahel, 1871.)

Herr Fick hält einen Vortrag über die Messung des Blutquantums, das in jeder Systole durch die Herzventrikel ausgeworfen wird, eine Grösse, deren Kenntniss ohne Zweifel von grösster Wichtigkeit ist. Gleichwohl sind darüber die abweichendsten Ansichten aufgestellt. Während Th. Young die in Rede stehende Grösse auf etwa 45 ccm anschlägt, kursiren in den neueren Lehrbüchern der Physiologie meist sehr viel höhere Angaben, welche, gestützt auf die Schätzungen von Volkmann und Vierordt, sich bis auf 180 ccm belaufen. Bei dieser Sachlage ist es seltsam, dass man noch nicht auf folgenden naheliegenden Weg gekommen ist, auf dem diese wichtige Grösse wenigstens an Thieren direkter Bestimmung zugänglich ist. Man bestimme, wie viel Sauerstoff ein Thier während einer gewissen Zeit aus der Luft aufnimmt und wie viel Kohlensäure es abgibt. Man nehme ferner dem Thiere während der Versuchszeit eine Probe arteriellen und eine Probe venösen Blutes. In beiden ist der Sauerstoffgehalt und der Kohlensäuregehalt zu ermitteln. Die Differenz des Sauerstoffgehaltes ergibt, wie viel Sauerstoff jedes Kubikcentimeter Blut beim Durchgang durch die Lungen aufnimmt, und da man weiss, wie viel Sauerstoff im Ganzen während einer bestimmten Zeit aufgenommen wurde, so kann man berechnen, wie viel Kubikcentimeter Blut während dieser Zeit die Lungen passirten, oder wenn man durch die Anzahl der Herzschläge in dieser Zeit dividirt, wie viel Kubikcentimeter Blut mit jeder Systole des Herzens ausgeworfen wurden. Die entsprechende Rechnung mit den Kohlensäuremengen gibt eine Bestimmung desselben Werthes, welche die erstere kontrollirt.

Da zur Ausführung dieser Methode 2 Gaspumpen gehören, so ist der Vortragende leider nicht in der Lage, experimentelle Be-

stimmungen mitzutheilen. Er will daher nur noch nach dem Schema der angegebenen Methode eine Berechnung der Blutstromstärke des Menschen geben, gegründet auf mehr oder weniger willkürliche Data. Nach den von Scheffer in Ludwig's Laboratorium ausgeführten Versuchen enthält 1 ccm arterielles Hundeblut 0,146 ccm Sauerstoff (gemessen bei 0° Temperatur und 1 m Quecksilber Druck), 1 ccm venöses Hundeblut enthält 0,0905 ccm Sauerstoff. Jedes Kubikcentimeter Blut nimmt also beim Durchgang durch die Lungen 0,0555 ccm Sauerstoff auf. Nehme man an, das wäre beim Menschen gerade so. Nehme man ferner an, ein Mensch absorbirte in 24^h 833 gr Sauerstoff aus der Luft. Sie nehmen bei 0° und 1 m Druck 433200 ccm Raum ein. Demnach würden in den Lungen des Menschen jede Sekunde 5 ccm Sauerstoff absorbirt. Um diese Absorption zu bewerkstelligen, müssten aber der obigen Annahme gemäss $\frac{5}{0.0555}$ ccm Blut die Lungen durchströmen, d. h. 90 ccm. Angenommen endlich, dass 7 Systolen in 6 Sekunden erfolgten, würden mit jeder Systole des Ventrikels 77 ccm Blut ausgeworfen.

Herr Fick gave a lecture on the measurement of the quantity of blood ejected by the ventricle of the heart in each systole, a figure the determination of which is without doubt of the greatest importance. Nevertheless the most different opinions thereof have been given. While Th. Young placed the value in question at 45 cc., the newer textbooks of Physiology give much higher values, which, based on the estimations of Volkmann and Vierordt run as high as 180 cc. In such circumstances it is unusual that no one has yet hit upon the following obvious method by which this important value may be determined directly, at least in animals. One determines how much oxygen an animal takes out of the air in a given time and how much carbon dioxide it gives off. During the experiment one obtains a sample of arterial and a sample of venous blood. In both, the content of oxygen and the content of carbon dioxide are to be determined. The difference in oxygen contents tells how much oxygen each cubic centimeter of blood takes up in its course through the lungs, and since one knows the total quantity of oxygen absorbed in a given time, one can calculate how many cubic centimeters of blood passed through the lungs in this time, or, if one divides by the number of heartbeats in this time, how many cubic centimeters of blood are ejected with each beat of the heart. The corresponding calculation with the quantities of carbon dioxide gives a determination of the same value, which controls the first.

Since two gas pumps are required to carry out this method, the lecturer is unfortunately not able to report experimental findings. He will therefore give only a calculation of the extent of the circulation in man according to the schema of the method here described, based on more or less arbitrary data. According to experiments carried out by Scheffer in Ludwig's laboratory one cc. of arterial blood of the dog contains 0.146 cc. of oxygen (measured at 0° temperature and 1 meter Hg. pressure); 1 cc. venous dog's blood contains 0.0905 cc. of oxygen. Each cubic centimeter of blood takes up in its passage through the lungs 0.0555 cc. Assume that this were also true in man. Assume further that a man absorbs 833 g. of oxygen out of the air in 24 hours. At 0° and 1 m. pressure this would occupy a space of 433200 cc. Accordingly 5 cc's. of oxygen would be absorbed by the lungs every second. In order to make possible this absorption there must, however, according to the above assumption, 5/0.0555 cc. of blood flow through the lungs, or 90 cc. Assuming finally 7 systoles take place in 6 seconds, 77 cc. of blood would be ejected with each systole of the ventricle.

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LA

PRESSION BAROMÉTRIQUE

RECHERCHES

DE PHYSIOLOGIE EXPÉRIMENTALE

PAR

PAUL BERT

PROFESSEUR A LA FACULTÉ DES SCIENCES DE PARIS

LAURÉAT DE L'ACADÉMIE DES SCIENCES
(Prix de physiologie expérimentale, 1865)
LAURÉAT DE L'INSTITUT (Grand Prix biennal, 1875)

AVEC 89 FIGURES DANS LE TEXTE

PARIS

G. MASSON, ÉDITEUR

LIBRAIRE DE L'ACADÉMIE DE MÉDECINE

BOULEVARD SAINT-GERMAIN, EN FACE DE L'ÉCOLE DE MÉDECINE

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THE DETERMINATION OF THE ANAESTHETIC TENSION OF ETHER VAPOR IN MAN, WITH SOME THEORETICAL DEDUCTIONS THEREFROM, AS TO THE MODE OF ACTION OF THE COMMON VOLATILE ANAESTHETICS[1]

WALTER M. BOOTHBY

From the Surgical Service and Respiration Laboratory of the Peter Bent Brigham Hospital, Boston. Clinic of Professor Cushing

Received for publication, January 5, 1914

The perfection and accuracy[2] of the anaesthetometer devised by Dr. Karl Connell (1) of the Roosevelt Hospital, New York, has rendered available a new method applicable to both man and animals, for studying the strength of action of the volatile inhalation anaesthetics.

So far as the apparatus is concerned, the dosage of the anaesthetic can be expressed with equal ease in percentage by weight, percentage by volume, or in millimeters of mercury representing the vapor pressure equivalent (tension). Dr. Connell originally calibrated his apparatus in percentage by weight, and in a recent article on "Ether Percentage" (2), I also adopted this standard. This is now regretted, as it is contrary to the general practice, and leads to confusion. The two other methods of expressing the dosage, namely, by volume and by tension, have the advantage of being readily interchangeable, and of these

[1] Read by invitation to the Society for Pharmacology and Experimental Therapeutics, Philadelphia, December 29, 1913.

[2] The Connell anaesthetometer is accurate to within ±3 mm. of the true tension. This error can be determined and allowed for if the accuracy of the other factors render it desirable. For a complete discussion of this point, reference may be made to an article by Boothby and Sandiford (3). The apparatus would be improved by making the steps between the possible tensions of less value. This could be done by having three times as many teeth on the ratchet wheel, and near the critical tension small steps between the available tensions.

two, though the former is frequently used, the latter is preferable because thereby allowance is made for barometric changes as well as for variations in the partial pressure of ether. This is an essential point in accurate work, because the mass of gas absorbed varies with extreme precision directly as the pressure.

The studies described in this paper were performed for the purpose of determining the lowest partial pressure of ether vapor which, when continuously respired, will maintain an ideal surgical narcosis after it has been once established. The term "anaesthetic tension" has been adopted to express this value.

In order to determine the tension of ether vapor proper to maintain an ideal surgical narcosis, it is necessary to obtain a condition of equilibrium between the tension of ether in the inspired air, alveolar air, blood and tissues. The anaesthetic tension is then equal to the tension of ether as delivered by the apparatus. The details of the precautions taken in the administration of the anaesthetic, to prevent leakage and consequent alteration in the composition of the mixture delivered by the Connell apparatus, need not be considered here.

It is the custom in the Brigham Hospital Surgical Clinic to plot an anaesthesia chart, on which are recorded the vapor tension of ether administered, the pulse and respiration rate, the systolic and diastolic blood pressure determined by the auscultatory method (sometimes with the intermediate phases), and the pulse pressure.

Figure I is a typical chart and represents an ideal ether anaesthesia. In order to produce narcosis, the vapor tension of ether is rapidly, yet gradually, increased to about 100 mm. This can be done without struggling, choking, or any feeling of suffocation on the part of the patient in four to seven minutes; the tension is maintained at this point for two to four minutes, and then gradually lowered, during the following half hour, to a pressure of about 54 mm. By this method, the patient is sufficiently anaesthetized at the end of about ten minutes to allow cleaning the skin and further preparation of the operative field. Complete anaesthesia occurs in about fifteen minutes, at which time the incision can be made without any reflex movements. The dura-

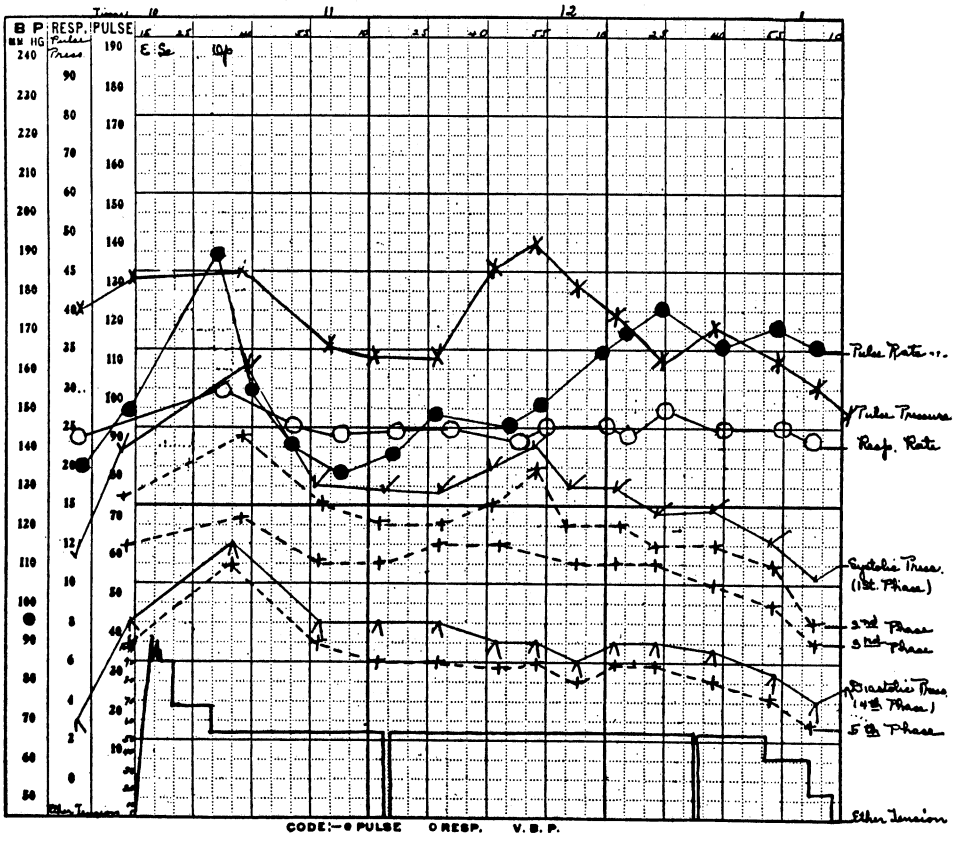

FIG. I

Name, C. B.; age, 50; date of operation, September 6, 1913; lungs, negative; heart, apparently normal; urine, negative; arteriosclerosis, none; operator, Dr. Cushing; first assistant, Dr. Bagley; anaesthetic, Squibb's ether, Connell apparatus, Gwathmey mask and towel, cerebellar position; operation, extirpation cerebellar tumor; preliminary drugs, atropin sulphate, 0.5 mgm. S. C. at 9.40; blood pressure, Sys.=110, Dias.=70, (Tycos); stimulants, none; practically no bleeding. Tycos correction = — 5 mm. (average).

Remarks: Induction accompanied by slight laryngeal spasm with coughing. It is especially noteworthy that "little ether" was needed for induction; as seen by the ether tension curve the higher tensions were given for only a short time. That is the patient came up to the anaesthetic tension quickly; it was necessary to maintain the ether tension at 54 mm. throughout the operation. Perfect anaesthesia. Anaesthetist, Dr. Boothby.

tion of the period in which the tension of ether administered is above the final tension, varies from twenty to forty minutes in different subjects; as a rule, at the end of thirty minutes, the apparatus can be set at 47 or 54 mm., and thereafter continued at this pressure without change.

Figures II, III, and IV, clearly illustrate how well a surgical anaesthesia can be maintained by the administration and inhalation of a constant mixture of air and ether in which the ether tension is between 47 and 54 mm. At the point marked *a*, spasmodic apnoea occurred as a result of a too high ether tension in an attempt to hurry the preliminary period. This is what frequently happens when using the cone method of administration, and indicates that the respiratory center is suddenly overwhelmed by a tension temporarily in excess of 60 mm.

Figure V is of especial interest. A cystic glioma was extirpated by Dr. Cushing from the cerebellum of a girl eight years old, and, at the point *H*, indicated in the chart, a brisk hemorrhage occurred with resultant drop in blood pressures.

At the point *F*,[3] the ether was interrupted for two or three minutes and, subsequently, an increased tension was necessary to bring about suitable anaesthesia. During the second hour, the pulse pressure dropped alarmingly, but the ether tension could only be lowered from 54 to 49 mm. On account of the continual fall in pulse pressure at point *a*, the administrative tension was reduced to 38 mm., but after an interval of eight minutes, it was necessary to return to 49 mm. At point *b*, the patient was nearly pulseless, yet an attempt to discontinue the anaesthetic during the closure of the wound, resulted in reflex movements, and ether had to be again administered for a brief period. At the conclusion of the operation, the patient was pulseless and the apex beat counted with a stethoscope was 220 to the minute; she was in a comatose condition due to oxygen want from circulatory failure. One hour and twenty minutes after the operation was concluded, a transfusion from the patient's father

[3] *F* in this and the other curves indicate when ether administration had to be interrupted to refill the apparatus.

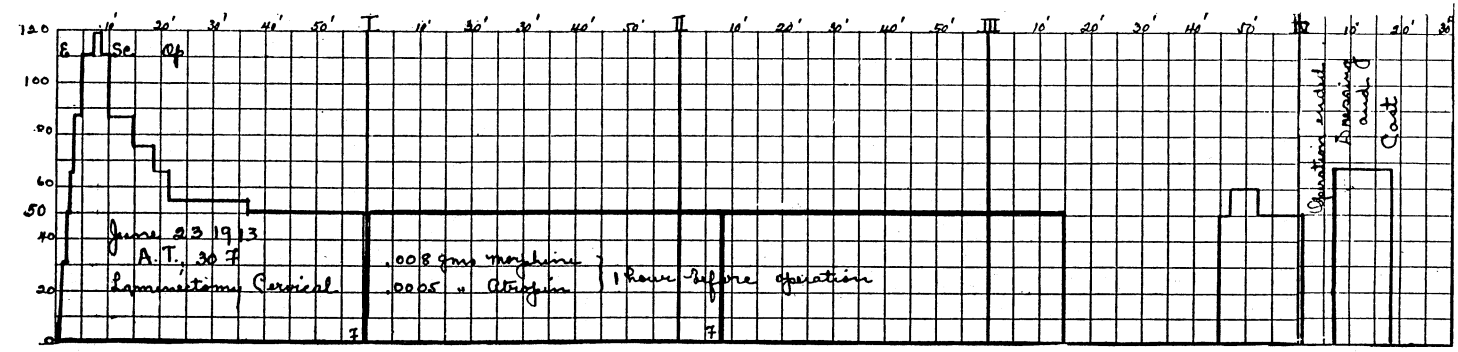

FIG. II

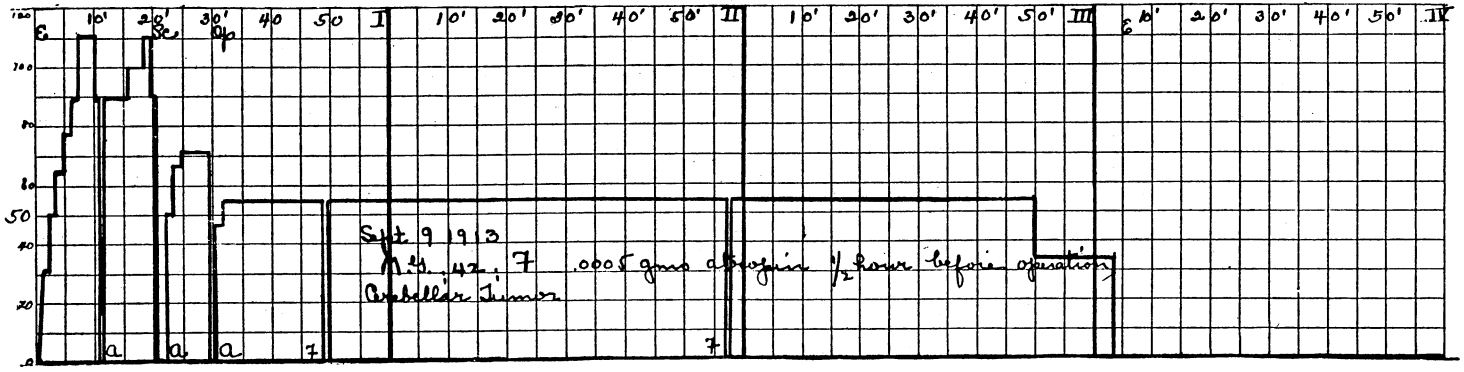

FIG. III

was started, and within forty minutes, the blood pressure had markedly improved as indicated on the chart.

Several similar cases of lowered blood pressure from loss of blood have occurred, but in none was a tension of ether lower than 47 mm. found to produce surgical anaesthesia. However, if the loss of blood exceeds a certain maximum, the patient is rendered comatose and unconscious probably from deprivation of oxygen. In such an extreme condition, no anaesthetic is needed as in the case cited from the time the cerebellar operation was completed till revived by the transfusion. Up to the time at which the loss of blood would have sufficed in itself to produce unconsciousness, it is necessary for surgical anaesthesia to maintain the same anaesthetic tension of ether despite the lowered blood pressure.

Figures VI, VII, and VIII, emphasize the similarity in the ether curve of different patients and further illustrate the conception that for surgical narcosis, the nerve cells [not under the influence of other drugs] must be exposed to an ether tension between 47 and 54 mm., probably about 51 mm. Age, sex, or chronic alcoholism, so far as my experience goes, does not alter the anaesthetic tension of ether. The opportunity has presented itself to test the influence of age on two babies—one nine months, the other eighteen hours old. The fact that new born babies require the same ether tension as adults is not surprising because had an operation taken place on the mother before delivery the foetus would have been saturated—and with safety—by the same anaesthetic tension as the mother. It is very probable that the same tension likewise holds for animals.

Dr. Waller (6) gives "as a preliminary result that full anaesthesia can be produced and maintained by ether and air at approximately 10 per 100." The balance used by him was one in which the chloroform scale 1, 2, and 3, per 100 (by volume) was taken to be practically equivalent to an ether scale, 5, 10, 15, per 100, which makes the ether determination roughly a percentage by weight (3). Ten per cent by weight equals 4.11 per cent by volume, which represents a tension of 31 mm.—evidently too low, but in fairly close agreement with Spenzer's so-called corrected (?) figures.

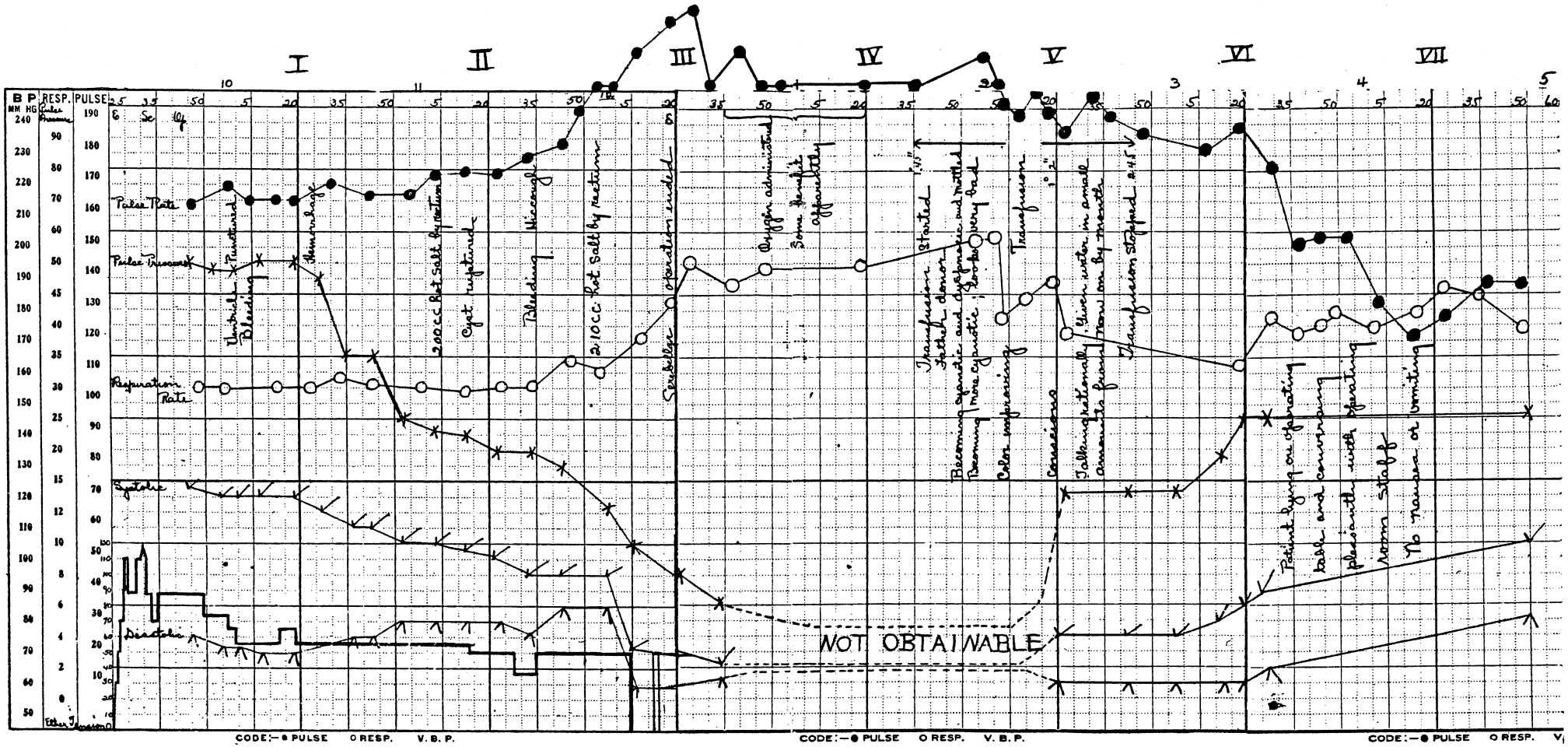

FIG. V

Name, M. E. S.; age, 8; date of operation, June 5, 1913; lungs, normal; heart, normal; urine, negative; arteriosclerosis, none; operator, Dr. Cushing; first assistant, Dr. Bagley; anaesthetic, Squibbs ether, Connell apparatus; operation, extirpation cystic tumor cerebellum; preliminary drugs, atropin sulphate, 0.3 mgm. at 8.30; stimulants, 11.10—200 cc. hot salt by rectum, 12—210 cc. hot salt by rectum, oxygen administered pure from 12.40 till 1.20 with some apparent benefit, patient looked better. Tycos correction = — 2 mm. (average).

Remarks: After 12 noon blood pressure was so low that hand on Tycos barely moved; no sounds audible therefore pressure had to be estimated. Very faint thready pulse palpable in temporal region till 12.15; after that no perceptible pulse till transfusion. Transfusion started with father as donor, at 1.43. Elsberg canular; stream very slow. After ten minutes patient became worse; gradually cyanosis increased in face and body—the latter becoming mottled. At 2 o'clock appeared as though patient would die any moment; then turning point came and in five minutes color was good, respiration less dyspnoeic. By 2.20 patient was conscious and asking rationally for water which was allowed. From 2.40 on till wounds closed in arm conversed with her father. Slight hemolysis apparently occurred at beginning of transfusion. Anaesthetist, Dr. W. Boothby.

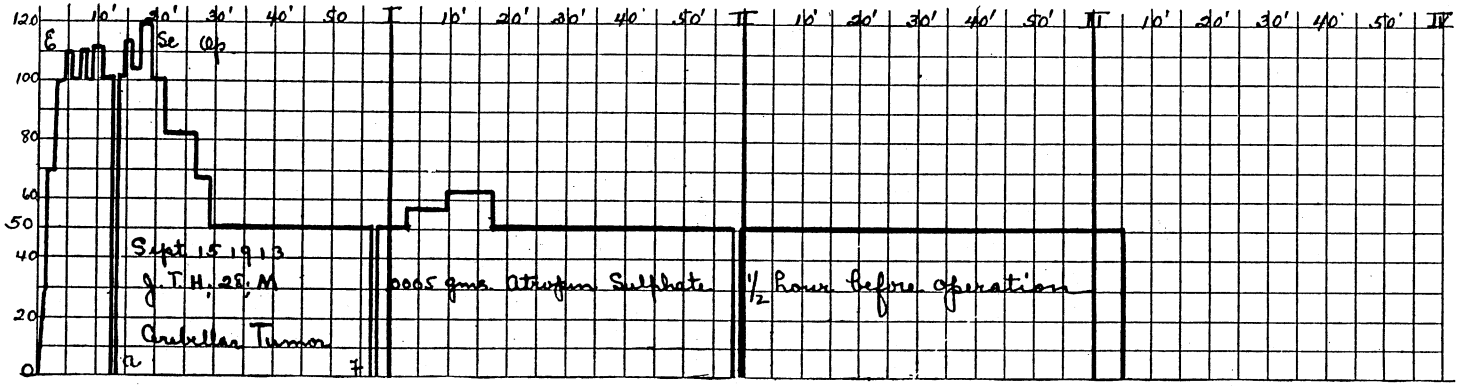
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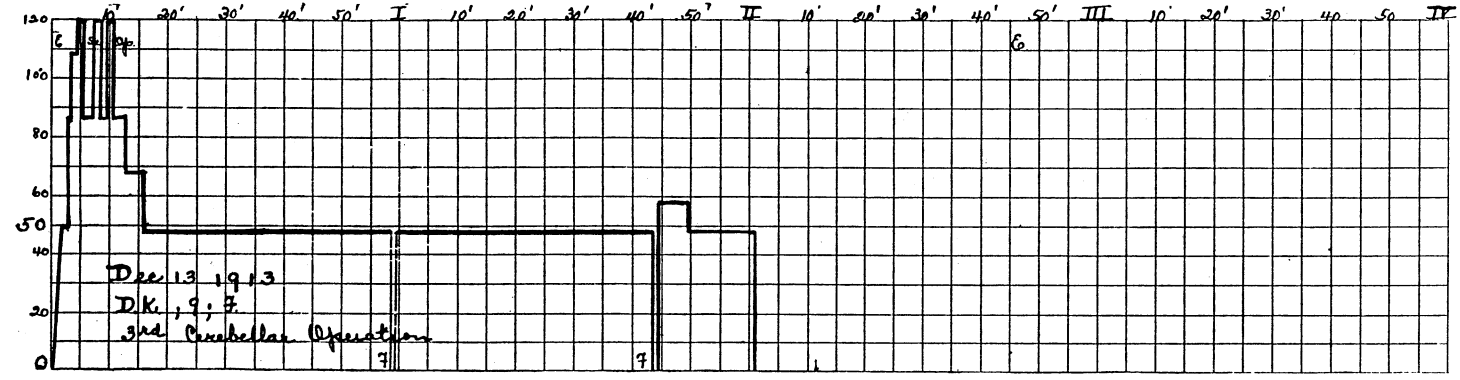
FIG. IV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3rd Cerebellar Operation
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FIG. VI

Spenzer (7), in 1893, published some very interesting experiments by which he determined the volume per cent of ether that would induce and maintain narcosis in dogs and cats. A mixture of ether and air was carefully made in a spirometer and then analyzed by a combustion method. Spenzer found that an ether and air mixture containing, according to calculation 6.7 per cent by volume, and according to analysis 3.4 per cent by volume, produced complete anaesthesia in twenty-five minutes, and that this mixture could be inspired indefinitely without untoward symptoms. Spenzer's uncorrected figure, 6.7 per cent gives a tension of 49 mm., which is in agreement with our figures. Undoubtedly, Spenzer's method of analysis was at fault. He was probably led to accept the per cent by analysis, because this agreed with the data obtained by Dreser (8) of the volume per cent of ether contained in samples of air taken from within a Julliard mask during narcosis. It is very likely that the same analytical error was made in both Dreser's and Spenzer's experiments.

Boycott, Damant, and Haldane (4) have studied the rapidity of saturation and desaturation of nitrogen up to a pressure of six atmospheres. According to their calculation, the body of a man would be half-saturated with the excess of nitrogen in twenty-three minutes, three-fourths saturated in forty-six minutes, etc., the pressure remaining constant. They also point out that the rate of saturation and desaturation would vary in different individuals according to the relative mass of blood and the rate of circulation. In the same individual, different organs would be more or less quickly saturated and desaturated, according to the proportional volume of their blood-supply. If ether were substituted for nitrogen, it is probable that the rate of saturation would be nearly the same.[4]

Therefore, the time requisite to saturate the body of an average patient up to the anaesthetic tension of 51 mm. is theoretically between one-half and three-quarters of an hour, because

[4] Although the rate of diffusion of gases is inversely according to their densities, it seems probable that the anatomical perfection of the capillary system allows complete equilibrium to occur during the passage of the blood through the capillaries in either case.

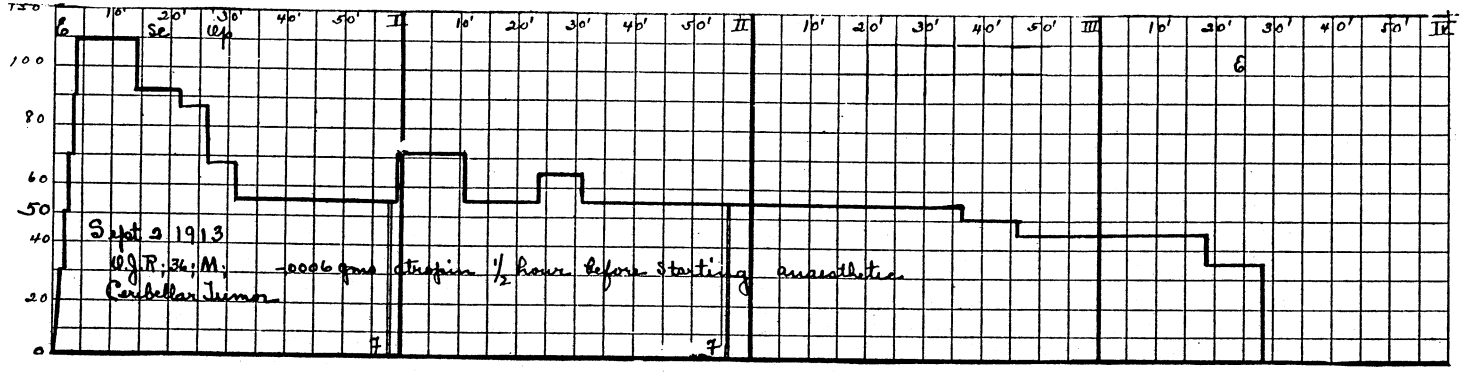

FIG. VII

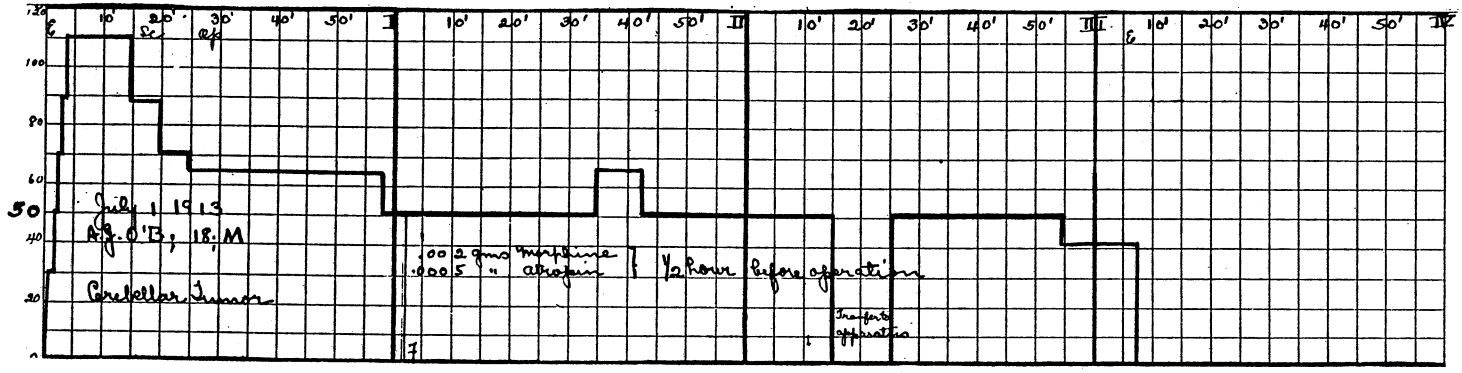

FIG. VIII

during a part of this time, a tension of 100 mm. can be administered, and during the remainder, a tension between 80 and 60 mm. As the point of saturation is approached, the tension of administration must be reduced to 55 mm., so as not to suddenly and dangerously over-shoot the desired tension of 51 mm. My experience indicates that a general body tension of 60 mm. would be dangerous.[5]

The rate of solution saturation and desaturation of ether and nitrogen for the body fluids, in general, is, as stated above, probably very similar. Ether has, however, been shown by Meyer, Overton, and others, to form a "loose (reversible) physico-chemical combination with the lipoids of the cell" (5), thereby producing an inhibition of the cell mechanism resulting in narcosis. The rapidity of action and reaction, and the degree of completeness or percentage saturation of the nerve cell with ether in contrast to the solution saturation of the body fluids, is, therefore, dependent on the chemical inter-relationship and peculiarity of the dissociation curve of the lipoids of the cells and not on the laws of simple solution.

The experimental data given above show that surgical narcosis is produced by a tension of 51 mm.—a higher tension produces a dangerously deep narcosis and a lower tension, an inconveniently light anaesthesia. The percentage saturation of the nerve cell caused by any given tension of ether is not known. However, it can be assumed that the same degree of saturation is always produced by the same tension, and that eventually a correct dissociation curve can be determined as in the thoroughly studied reversible reaction

$$Hb + O_2 \rightleftarrows HbO_2$$

in which the percentage saturation of the haemoglobin with O_2

[5] I feel that a warning should be here given against the danger of an unduly prolonged administration of an ether tension above 55 mm. Dr. Connell's idea of the *safety* of an automatic machine anaesthesia is correct *after* the tension of administration has been *reduced to* 55 mm. An interne forgetting to step down the percentage of administration at the appropriate time, would quickly run his patient into serious danger. True ether poisoning is a rare occurrence with the usual cone method; it may be a frequent occurrence if the use of the Connell apparatus becomes general.

is dependent on the oxygen tension to which the haemoglobin is exposed.

If such be the case, our conception of the theory of production, maintenance, and recovery from anaesthesia can be rendered more concrete by the following hypothetical formula. Let Mn represent the molecules in the nerve cell affected by the anaesthetic, and let An represent the group of inhalation anaesthetics. Then, substituting in the above haemoglobin-oxygen equation, the reversible reaction

$$Mn + An \rightleftarrows MnAn$$

is seen to take place. In this reaction, the percentage saturation of the Mn molecules in the nerve cells, and, therefore, the depth of anaesthesia, is dependent on the tension of the anaesthetic vapor to which these susceptible molecules are exposed. The percentage saturation caused by ether at a pressure of 51 mm., produces that degree of cell inhibition that is necessary for ideal surgical anaesthesia.

The evidence here cited shows that there is little or no variation in the anaesthetic tension of ether in different individuals. Clinical experience has proven that some patients require by the ordinary methods of anaesthesia more ether poured upon the cone than do others. The apparent discrepancy between these two facts can be accounted for by the following three factors.

In the first place, as I explained in an earlier paper (2), there is a wide variation in the amount of air breathed by different patients: therefore, varying amounts of ether must be poured upon the cone to bring the fluctuating amounts of air up to the same tension. When attempting to obtain the higher tensions in the larger amounts of air, the waste of liquid ether is tremendous—just as the amount of fuel necessary to increase the speed of an engine above a certain point is proportionately very great to the result obtained.

Secondly, the volume of blood flowing through the lungs per minute varies greatly, not only in different individuals, but at different times in the same individual; further, the relative amount passing through the various organs will fluctuate from

time to time. Accordingly, it is evident that the rate at which the brain, for example, becomes saturated or desaturated—that is, the rate at which the patient becomes anaesthetized or recovers therefrom—depends on the amount of blood flowing between the lungs and the brain (assuming the alveolar ether tension to remain constant). At present, we have no means of estimating changes in the circulation rate, and therefore, cannot calculate the exact value of this factor. That it is of considerable moment, however, can be judged from the experiments previously reported by me, which showed that the rate of elimination of CO_2 was dependent not only on the volume of respiration, but also on the rate of the blood-flow (9).

The third factor is the possibility of a variation in the rate of the chemical reaction due to slight changes in the chemical environment. On account of the well-known influence that environment exerts on the rapidity of chemical reactions, it seems quite possible that even small changes in acidity, viscosity, permeability, or temperature might affect both the rate at which union between the ether and lipoid takes place during the period of saturation and also the rate at which dissociation occurs during desaturation on the reduction of the ether tension.

Dr. A. D. Waller has shown that for chloroform "the maximum value is between 2 and 3 per cent (by volume). The subsequent steady minimal value is about 1.5 per cent" (6). The relationship between the anaesthetic tension of ether and chloroform and their molecular weights is of interest and is shown by the following equations.

$$\frac{\text{Molecular weight } C_4H_{10}O}{\text{Molecular weight } CHCl_3} = \frac{74.1}{119.4} = \frac{1}{1.61}$$

$$\frac{\text{Anaesthetic tension } C_4H_{10}O}{\text{Anaesthetic tension } CHCl_3} = \frac{53}{11} = \frac{1.61 \times 3}{1}$$

SUMMARY

1. The term "anaesthetic tension," is employed to indicate the partial pressure of ether vapor that, after equilibrium is

established, can, for an indefinite period, maintain the subject in the stage of ideal surgical anaesthesia.

2. Curves are given showing that the anaesthetic tension of ether vapor for man is between 47 and 54 mm.—probably 51 mm.

3. A working hypothesis based on the theory of Meyer and Overton is suggested to explain the mode of action of the volatile inhalation anaesthetics which can be summarized in the quantitative reversible equation

$$Mn + An \rightleftarrows MnAn$$

in which the percentage saturation of the susceptible molecules in the nerve cells (Mn), and, therefore, the inhibition of the cell function (the depth of anaesthesia), is dependent on the tension of the anaesthetic vapor (An) to which these susceptible molecules are exposed.

4. To harmonize the fact that large variations occur in the amount of ether required by the usual methods of anaesthesia with the fact that the same ether tension produces the same degree of anaesthesia in all patients, it is pointed out that the apparent variation can be accounted for by (a) changes in volume of respiration; (b) changes in rate of circulation; and (c) by a possible alteration in the rapidity with which the above reversible reaction takes place under a slightly different chemical environment.

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THE ABSORPTION, DISTRIBUTION, AND ELIMINATION OF ETHYL ETHER.

I. THE AMOUNT OF ETHER ABSORBED IN RELATION TO THE CONCENTRATION INHALED AND ITS FATE IN THE BODY.

By HOWARD W. HAGGARD.

(From the Laboratory of Applied Physiology, Yale University, New Haven.)

(Received for publication, March 1, 1924.)

This series of papers deals with the quantitative aspects of the absorption, elimination, and distribution of ethyl ether in the body, and its general physiological effects. The mechanism of absorption, distribution, and elimination presented is applicable not alone to ether but to any gas or vapor which is not altered or destroyed in the body.

This investigation has been made possible through the development by the writer of a method for the analysis of ethyl ether in air and blood, by means of a train containing iodine pentoxide. The ether vapor, drawn through such a train, is oxidized and thus liberates iodine which is collected and determined by titration with thiosulfate, using starch as an indicator. In rapidity, accuracy, and ease of technique, when familiarity has been acquired, this method has great advantages over the methods which former investigators have had at their service. The method of analysis is detailed in a previous paper (1).

This paper deals with the general experimental procedures, the fundamental principles governing the physical behavior of ether vapor, and its distribution between blood and air. In addition, the total amount of ether absorbed in relation to the concentration inhaled and the fate of the ether in the body, have been determined experimentally. These data form the basis for the theoretical discussion of the mechanism of absorption and elimination presented in subsequent papers.

THE ABSORPTION, DISTRIBUTION, AND ELIMINATION OF ETHYL ETHER.

II. ANALYSIS OF THE MECHANISM OF ABSORPTION AND ELIMINATION OF SUCH A GAS OR VAPOR AS ETHYL ETHER.

By HOWARD W. HAGGARD.

(From the Laboratory of Applied Physiology, Yale University, New Haven.)

(Received for publication, March 1, 1924.)

The present paper presents a mathematical analysis of the mechanism of ether absorption and elimination. This analysis is fundamental to any conception of the physiology of ether anesthesia. Furthermore, the principles here defined apply in general to any gas or vapor which, like ether, is absorbed and eliminated unchanged; the solubility or coefficient of distribution of each substance determining, according to these principles, the amount and rate of absorption and the relative importance of respiration and the circulation in determining absorption.

Fig. 1 represents diagrammatically the relations of circulation, respiration, and body tissue, which are the factors concerned in the mechanism under study. In this diagram the upper chamber represents the lungs. For convenience the ventilation is considered as a continuous flow of air with the inspired entering at the right and the expired passing out at the left. The partition across the chamber divides the air stream so that a portion does not come in contact with the blood. The area above the partition is the virtual dead space through which the air passes from inspiration into expiration without loss of ether. The remainder of the air, the effective pulmonary ventilation, comes into free diffusion with the pulmonary blood and reaches equilibrium with it.

At the commencement of inhalation the ether taken up by the blood is carried in the arterial stream to the capillaries, where it diffuses into the tissues. The venous blood leaves the tissues with a concentration of ether identical with that of the tissues

THE ABSORPTION, DISTRIBUTION, AND ELIMINATION OF ETHYL ETHER.

III. THE RELATION OF THE CONCENTRATION OF ETHER, OR ANY SIMILAR VOLATILE SUBSTANCE, IN THE CENTRAL NERVOUS SYSTEM TO THE CONCENTRATION IN THE ARTERIAL BLOOD, AND THE BUFFER ACTION OF THE BODY.

By HOWARD W. HAGGARD.

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In the two previous papers of this series (1, 2) a general demonstration has been made of the fact that ether is distributed throughout the body as a whole in approximately the same concentration that it exists in the blood. At the same time it was indicated that this cannot apply to any one tissue or organ but is an expression of the integration of all the tissues; some of which take up more and some less ether than others.

The present paper deals with the absorption of ether by the central nervous system and the part which the peculiarities of this absorption play in the development of anesthesia.

Anesthesia as a Result of the Action of Ether upon the Brain.

In respect to the anesthetic action of ether, the body may be divided into two classes of tissues; those upon which ether has an action resulting in the phenomena of anesthesia; and those upon which ether has no physiological reaction of this sort. This division at once places the nervous system in the first class and the remainder of the body in the second.

The general phenomena of anesthesia, loss of consciousness, and reduction or abolition of the reactions to pain, are due solely to the action of ether upon the brain. As evidence that such is the case, the following experiment is significant. A 5 per cent solution of ether in saline solution was injected under pressure

THE ABSORPTION, DISTRIBUTION, AND ELIMINATION OF ETHYL ETHER.

IV. THE ANESTHETIC TENSION OF ETHER AND THE PHYSIOLOGICAL RESPONSE TO VARIOUS CONCENTRATIONS.

By HOWARD W. HAGGARD.

(From the Laboratory of Applied Physiology, Yale University, New Haven.)

(Received for publication, March 1, 1924.)

In a recent paper by Ronzoni (1), which appeared in print after the present work had been completed, there is presented a summary of the anesthetic tensions of ether found by previous investigators. The very extensive work of Gramen (2) is not included in this review nor are the recent findings of White (3). Although the preponderance of evidence points to a concentration of 3 to 3.5 per cent by volume of ether vapor as the anesthetic tension, there exists an apparent incongruity which is set forth here briefly and which makes the present author, for reasons which will be apparent, hesitate to dogmatize.

The blood of anesthetized subjects, man or animal, has been found by most investigators (1, 2, 3, 4) to contain from 1.0 to 1.5 or 1.7 gm. of ether per liter. The extremes express light and deep anesthesia. Upon these values there is complete experimental agreement and further confirmation in the present work. In a previous paper the writer has determined the ratio of distribution of ether between air and blood as 1 to 15; and Shaffer and Ronzoni (5), employing an entirely different technique, have confirmed this ratio. When this coefficient is applied to the accepted concentration of ether in the blood at anesthesia, the corresponding tension of ether vapor in the respired air becomes 2.6 to 4.0 per cent by volume.

Spenzer (6) and Ronzoni (1) have kept animals anesthetized for long periods through the inhalation of air containing from 3 to 4 per cent of ether vapor. In the present work a similar result will be reported. In all these investigations the concen-

THE ABSORPTION, DISTRIBUTION, AND ELIMINATION OF ETHYL ETHER.

V. THE IMPORTANCE OF THE VOLUME OF BREATHING DURING THE INDUCTION AND TERMINATION OF ETHER ANESTHESIA.

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(From the Laboratory of Applied Physiology, Yale University, New Haven.)

(Received for publication, March 1, 1924.)

Rapid induction of ether anesthesia is desirable for the reason that the prolongation of the subanesthetic stages is detrimental to the subject. In order to induce rapid anesthesia it is the practice to administer a concentration of ether vapor much higher than that necessary to maintain fully developed anesthesia. This procedure requires skill upon the part of the anesthesist; it also results in a great increase in the irritant action upon the lungs.

The following discussion deals with the action of ether as a pulmonary irritant and presents a method whereby induction can be made rapid without the employment of high concentrations of ether vapor.

Action of Ether as a Pulmonary Irritant.

Ether vapor is unquestionably an irritant. Its action elicits from the respiratory tract the response common to all respired irritants; it causes reflex coughing by laryngeal irritation and under suitable conditions inhibition of respiration; it produces increased mucous flow through the stimulation of the glands of the respiratory mucosa. Its irritant action upon the cornea and conjunctiva is known so well as to require no comment.

As an irritant ether presents certain peculiarities which differentiate it from the common lung irritants, nevertheless, a brief summary of the general characteristics of pulmonary irritants

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THE PHYSIOLOGICAL AND PHYSICAL FACTORS GOVERNING THE UPTAKE OF ANESTHETIC GASES BY THE BODY *

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Received for publication December 13, 1949

THE various theories of narcosis, despite their differences as to the exact mechanism whereby the narcotic substance produces its effects upon the neuron, are in general agreement that depth of anesthesia depends primarily upon the concentration or the partial pressure of a particular anesthetic in the brain, and further that the rate of recovery or induction of anesthesia is governed by the rate of change of this brain tension. Anesthetic gases in general are physiologically inert. They undergo no significant oxidation or utilization by the body, are released from the body eventually in exactly the same amount as was originally taken up, and they obey the simple physical laws of diffusion and solubility. Considerable thought and some experimental investigation have been brought to bear on the problem of inert gas exchange in the body. The names of Haggard, Behnke, Morales and Smith stand out among those who have made significant contributions to this problem. Much of what I shall say is based upon lines of thinking initiated by them.

The tension of an inert gas in the brain depends upon two primary factors; one, the tension of the gas in arterial blood, and two, the supply of that arterial blood to the brain, that is, the cerebral blood flow. Let us consider these two items separately, and turn first to the factors which regulate the tension of an anesthetic gas in arterial blood. This in turn depends upon two other factors: the tension of the gas in the alveoli, and the nature of the pulmonary diffusion surface. This latter factor depends upon the size of functioning lung, on the thickness

* An address delivered before the New England Society of Anesthesiologists, Boston, October 11, 1949.

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of the diffusion membrane, the presence or absence of edema, and the adequacy of pulmonary blood flow. With normal lungs diffusion is rarely a limiting factor in uptake of inert gas, and therefore arterial tension may be said, in general, to equal alveolar tension.

We may turn then to a discussion of the factors which regulate alveolar tension. The first of these is the effective respiratory minute volume, that is, the liters per minute of inspired gas which reach functioning diffusion surface. This is obviously a very important factor since all the gas taken up by the body has to be breathed into the lungs. This function is equal to the tidal volume minus the dead space, multiplied by the rate of respiration. It is apparent that six breaths of one liter each are more effective than twenty breaths of 300 cc. each, even though both give one a total minute volume of 6 liters.

The second factor governing alveolar tension is the lung volume, that is, the volume which dilutes each inspired breath of gas. It is obvious that a small room is more quickly filled with cigarette smoke than a large. Similarly, a small lung is more readily and rapidly filled with gas at a certain tension than is a large lung. A third factor is pulmonary blood flow. Except in congenital heart disease and in those rare cases of pulmonary hemangioma, pulmonary blood flow is equivalent to cardiac output.

Why is pulmonary blood flow so important in regulating the alveolar partial pressure of a foreign gas? It is the pulmonary blood flow which carries anesthetic gas away from the alveoli, especially in the early stages, and therefore tends to lower its partial pressure in the alveoli. Along with pulmonary blood flow belongs another equally important factor which is the solubility of the gas in blood. This may be expressed as the partition coefficient (λ) which equals the ratio of the concentration of gas in blood to the concentration of that gas in air at equilibrium. Thus, ether which has a λ of 15 and represents the most soluble of the usual anesthetic gases will exist in the blood at a concentration of 15 mg. per 100 cc. when the blood is in equilibrium with air containing only 1 mg. per 100 cc. Thus the blood concentration is fifteen times as great as the concentration in the air. The solubility in blood and the pulmonary blood flow are the factors responsible for the loss of gas from the alveoli. A more soluble gas is more easily carried away by the blood and therefore the alveolar tension of such a gas will build up more slowly.

Thus we come to the last of the factors regulating alveolar tension, the partial pressure of the gas in the mixed venous blood coming back to the lungs. Since this brings gas back to the alveoli it helps to raise the alveolar tension. If the tension in venous blood is rising rapidly, this will permit alveolar tension to rise rapidly, but if venous tension stays low it will keep alveolar tension low for a longer period of time. Mixed venous tension of an inert gas depends upon three other factors:

(a) the cardiac output in general, but in particular on the blood flow to muscles and fat, which constitute the bulk of the gas-absorbing regions of the body simply by virtue of the fact that they represent the greatest tissue bulk in the body; (b) the mass of muscles and fat and (c) the partition coefficient of the gas between fat and blood. The solubility of gases in general is the same for muscles as for blood, but all inert gases are much more soluble in fat. A large amount of fat or a high fat solubility will cause the removal of large quantities of that gas from the blood, and will therefore tend to keep venous blood tension low, keeping alveolar tension down and slowing the rate of induction.

The second factor regulating the tension of anesthetic gas in the brain is the rate of cerebral blood flow. It is apparent that the more rapid the cerebral blood flow, the more anesthetic will be brought to the brain per minute which, therefore, will permit a more rapid accumulation of tension in the brain and hasten the induction of anesthesia. Cerebral blood flow in turn depends upon two other factors: the first, mean arterial blood pressure, which is the force responsible for pushing blood through the brain, and second, cerebrovascular resistance which represents the total of all the factors that tend to impede the flow of blood through the brain. There persists an old concept that cerebral blood flow passively follows the blood pressure. This idea is based upon studies in animals in which, as a result of anesthesia and fairly drastic surgical procedures, whatever intrinsic reflexes exist were destroyed or obtunded with the result that the brain lost much of its intrinsic control. Then, indeed, the cerebral blood flow did passively follow the blood pressure. We know today that in normal human beings there is a great deal of intrinsic control of the cerebral circulation, in fact that mean blood pressure has very little to do with regulating the blood flow through the brain except in so far as the pressure must be sufficiently high to permit a normal blood flow. Only when the blood pressure falls sharply is cerebral blood flow influenced by the pressure; at normal levels most of the influence is obtained by intrinsic mechanisms within the brain.

This takes us to the intrinsic regulation which we have called the cerebrovascular resistance. It depends, among other factors, upon viscosity. Patients with polycythemia show a much greater resistance to the flow of blood than do normal or anemic patients. Intracranial pressure also affects resistance since patients with high cerebrospinal fluid pressure show a restriction of cerebral blood flow. It depends upon the patency of the small vessels in the brain so that in cerebral arteriosclerosis one finds an increase in resistance and a decrease in cerebral blood flow. Finally it is governed by the physiologic or functional tone of cerebral vessels. This regulation may be chemical or neurogenic.

Under the chemical influences carbon dioxide has a powerful effect. The inhalation of 5 to 7 per cent carbon dioxide will increase the cerebral blood flow markedly to about 75 per cent above its former value, conversely a low carbon dioxide tension in the blood wil significantly depress the blood flow by constriction of cerebral vessels. With moderate hyperventilation cerebral blood flow will fall an average of 35 per cent. Acidosis itself is apparently capable of dilating cerebral vessels, for in diabetic acidosis which is not associated with a high carbon dioxide tension (in fact, the carbon dioxide tension is quite low), there is seen a decrease in cerebrovascular resistance and a tendency for the cerebral blood flow to increase. Oxygen tension also exerts an effect. When tensions of oxygen are breathed which are close to 100 per cent there is moderate constriction of cerebral blood vessels and a decrease of 12 per cent in cerebral blood flow. On the other hand, anoxemia obtained by the inhalation of 10 per cent

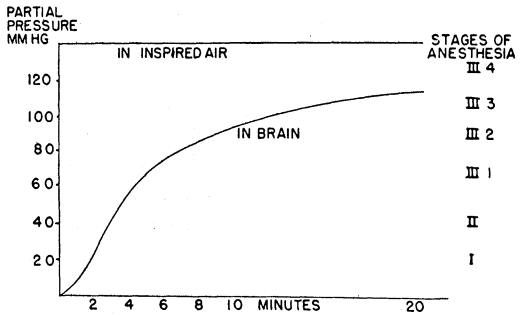

FIG. 1. The rate of rise of brain tension and simultaneous depth of anesthesia following inhalation of a constant partial pressure of an anesthetic gas. The actual values are rough approximations to those expected with cyclopropane.

oxygen has resulted in vasodilation in the brain comparable to that seen with 5 or 7 per cent carbon dioxide. Thus it can be seen that anoxemia is just as potent a vasodilator as are these concentrations of carbon dioxide.

The neurogenic regulation of cerebrovascular tone is not clearly defined. Apparently there is little tonic constrictor innervation entering the brain by way of the cervical sympathetic chain, at least Harmel in our laboratory was not able to show significant increase in cerebral blood flow or decrease in the vascular resistance of the brain following bilateral stellate ganglion block. It is possible that in acute conditions there may be a reflex spasm of cerebral vessels mediated through the sympathetic cervical chain, but there was no evidence in his work for a normal constrictor tone.

A third factor modifying cerebral vascular functional tone I have had to call an ill-defined factor. Prominent in this group is the disease

of essential hypertension. In this condition, despite a mean blood pressure which may be twice normal, the cerebral blood flow is kept within normal range by virtue of a high degree of cerebral vascular tone, the exact nature of which is still obscure.

Now that the individual factors have been discussed, let us turn to a consideration of the relationship among these factors and how they affect the arterial and brain uptake curves. For simplicity now and for the remainder of the discussion, let us assume that a constant tension of each gas is inspired by means of an open system, and that such tension is just great enough to produce deep surgical anesthesia if continued indefinitely. For example, in figure 1 a constant partial pressure of cyclopropane of 140 mm. of mercury is administered. I make no claim that this is exactly the tension which will eventually

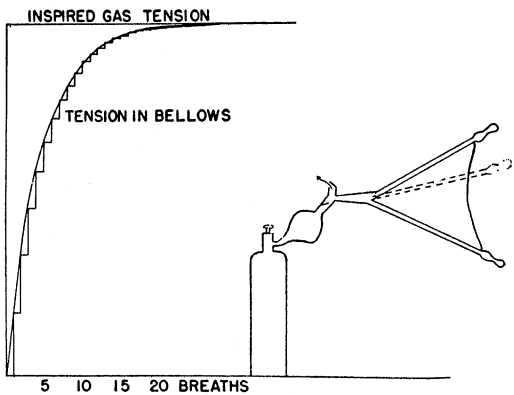

FIG. 2. The curve of tension of an anesthetic gas developing within a bellows (the lungs) where each stroke represents one-fifth of the total gas volume in the bellows. The anesthetic gas is administered at a constant tension by means of an open system.

produce deep surgical anesthesia. Quantitatively this figure may be in error, but qualitatively the principle remains the same. It is apparent from figure 1 that deep surgical anesthesia does not immediately ensue, but rather that anesthesia develops gradually along a curve which approximates the curve of increasing brain tension. Why does this increase in brain tension occur so leisurely? Why does not the brain tension immediately become equal to the inspired tension? The answer to that is the number of processes which are involved in going from the tension in the tank or in the mask to the tension in the brain.

The first of these processes is the accumulation of alevolar tension, and since arterial tension is practically equivalent to alveolar tension this factor would also mean the rise of arterial tension. The first phenomenon in this consideration is the phase of lung washout which I can best illustrate by a bellows (fig. 2). This bellows, let us assume,

has a 2500 cc. capacity and each stroke of the bellows instead of emptying it expels or inhales only 500 cc. Therefore, the gas which is inhaled is diluted fivefold with the gas in the bellows. If this bellows is connected by means of an open system to a tank supplying a constant tension of anesthetic gas and the concentration in the bellows is followed, what will be observed? The concentration of that gas in the bellows starts at zero. In the first breath it goes one-fifth of the way toward the inspired concentration since the tank gas is diluted by 5 volumes of air still in the bellows. On the second breath it moves another fifth of the distance toward the concentration in the inspired air, and so on in stepwise progression toward the inspired concentration, each breath bringing the concentration in the bellows one-fifth of the way toward completeness, finally reaching complete equilibrium only after numerous breaths. These steps may be smoothed out so that an expo-

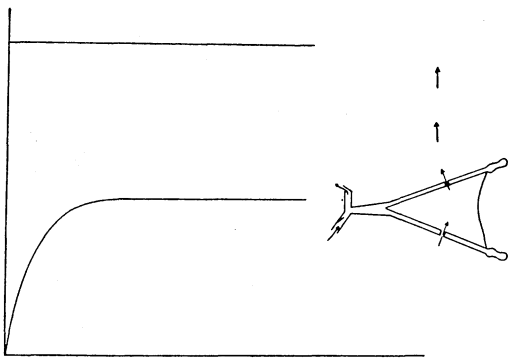

FIG. 3. The effect of a constant leak in the bellows (pulmonary blood flow) on the bellows (alveolar) tension of anesthetic gas.

nential curve is obtained, that is, one which constantly approaches a limiting plateau. It is obvious that if ventilation were increased or if the volume of the bellows were decreased this rate of washout would be faster. In fact, it may be said that the rate of washout depends upon the ratio of effective minute volume of respiration to lung volume.

The picture so far is quite over-simplified and different from the conditions which obtain in the body. We know that in the body the lungs are not merely a bellows, but that they have passing through them a considerable flow of blood. Let us then complicate this picture somewhat by including pulmonary blood flow. This may be done as in figure 3 by creating a leak in the bellows through which fresh air enters and bellows air leaves in addition to the process of respiration which is occurring through the neck of the bellows. It is now obvious that the concentration in the bellows will never reach the concentration in the tank, because after several hours or even days each breath from the

tank will be diluted by fresh air through the leak. Therefore, the bellows concentration approaches a new level which is determined by the ratio of the respiratory minute volume to the size of the leak. If the leak is small, the final level will be close to the inspired concentration; if the leak is large, the final value will be very low. This leak is analogous to pulmonary blood flow which carries gas away from the alveoli and prevents it from reaching inspired tension. The size of the leak depends upon pulmonary blood flow and the solubility of gas in blood.

Even this picture is not the complete story, however, for the blood which flows through the lungs eventually comes back to the lungs again carrying somewhat smaller amounts of the gas, but does not carry the gas away forever. Therefore, let us introduce a final complication

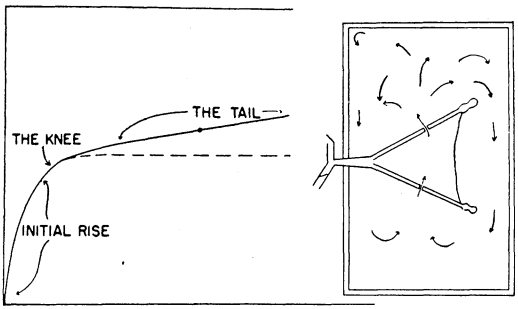

FIG. 4. The effect of enclosing the leaking bellows within a sealed room; representing respiration, pulmonary blood flow, tissue saturation and recirculation. The curve is characteristic of the alveolar or arterial tension curve of any inert gas breathed by the body at a constant inspired tension. The rate of the initial rise is largely a function of ventilation, the height of the knee is determined by the size of the leak (pulmonary blood flow and blood solubility of the gas). The rate of rise of the tail is a function of the size of the leak and the size of the room (mass of muscles and fat and fat solubility of the gas).

into the picture of the bellows as shown in figure 4. The bellows have been placed into a hermetically sealed room, so that gas from the bellows leaking out is diluted by air in the room which represents the body tissue. As time goes on, however, the concentration in the room builds up, and therefore, instead of fresh air coming back through the leak, more and more gas in question comes back to the bellows, so that if enough time elapses the gas in the room and in the bellows will eventually equal the inspired concentration. This washout of the room is a much slower process since the room is much larger than the bellows; therefore, the tail of the curve rises comparatively slowly. The rate at which the tail rises depends upon: (1) the size of the leak, that is, a rapid cardiac output, although it depresses the knee of the curve, speeds the latter part of the curve; (2) the size of the room, that is, a large mass of muscles and fat plus a large fat solubility will make it more

difficult to increase the gas tension in the body and will therefore slow the rate at which the tail approaches the inspired tension.

In figure 4 is shown an example of the general nature of the alveolar or arterial tension curve of every inert gas. The shapes of these curves may vary one from the other depending upon physical factors, but they all have the following similarities: a characteristic initial rise dependent upon lung washout; a point of inflection (the knee) which corresponds to the point at which the slower process takes over, and the slowly rising tail which depends upon the rate at which the body becomes saturated with the gas at the inspired tension. In a given individual with a single value for all the physiologic constants, that is cardiac output, minute volume of respiration, lung volume, body fat, and so forth, any differences among the rates of induction with different anesthetics must depend upon differences in the solubility of the anesthetic gases in blood and fat.

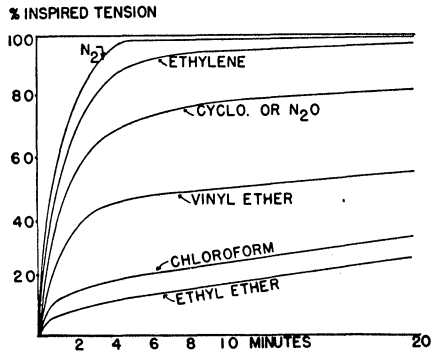

FIG. 5. The effect of solubility in blood of the inert gas on its alveolar or arterial uptake curve, all physiologic factors remaining constant. This demonstrates roughly why rate of induction or recovery is largely a function of blood solubility.

In figure 5 are shown diagrammatically the arterial curves of seven different gases with different blood solubilities. These curves could have been obtained in the same individual, each gas being administered in concentration just enough to produce deep anesthesia if continued long enough. In the case of nitrogen and nitrous oxide more than one atmosphere of pressure might have to be used; the argument however remains the same. Notice that nitrogen, being the least soluble and, therefore, corresponding to a bellows with a small leak, fills the alveoli and reaches arterial equilibrium with inspired tension quite rapidly. Ether, being extremely soluble and corresponding to a bellows with a large leak, builds up little on the initial rise and depends upon recirculation for its equilibration. I have not attempted to show differences in fat solubility which only affect the tail, but actually ether would outstrip the chloroform curve since chloroform is much more soluble

in fat. Nitrous oxide would exceed the cyclopropane curve likewise since cyclopropane is more soluble in fat. It may be noted that the clinically recognized differences in the rates of induction or recovery correspond to the rates at which the anesthetic tension is built up in arterial blood which, in turn, depend upon the solubilities of the individual gases. If the top of the graph were to correspond to the deepest part of the third stage of anesthesia, ethylene would have reached better than 80 per cent of that level in the arterial blood in three minutes, cyclopropane better than 60 per cent while ether would be less than 10 per cent toward that level in the same period of time. It would take hours of breathing such a tension of ether to obtain deep anesthesia. The clinical anesthesiologist already knows how to get around that; he does not start with the tension which he eventually hopes to achieve, but with a much higher tension which, if continued indefinitely, would kill the patient. As the patient approaches that extremely high

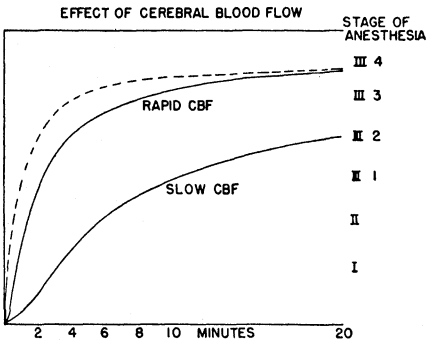

FIG. 6. The effect of a rapid or a slow cerebral blood flow on brain tension of an anesthetic gas and depth of anesthesia with the arterial curve (dotted line) the same for both.

tension, the anesthesiologist delicately lowers the inspired tension until both he and the patient arrive at the same desired level of anesthetic tension.

I have been speaking only of the arterial curve of tension, but this arterial tension of gas still has to get into the brain. That depends largely upon cerebral blood flow. In figure 6 is indicated the effect of different rates of cerebral blood flow on the brain concentration curve of anesthetic gas where the concentration curve in arterial blood (indicated by the dotted line) is the same. Thus, both hyperventilation and the inhalation of 5 per cent carbon dioxide will produce about the same arterial curve with cyclopropane, with a rapid rise and a high knee, but hyperventilation produces a decrease in carbon dioxide tension and therefore a severely depressed cerebral blood flow which results in a deficient supply of cyclopropane to the brain and a slow uptake by the brain. On the other hand, the inhalation of 5 per cent carbon dioxide

accelerates the cerebral blood flow, delivers more cyclopropane per minute to the brain which results in a rapid rise in the brain concentration. Thus, with the rapid cerebral blood flow the patient would arrive at the second plane of stage three in two minutes while it would take twenty minutes to achieve the same anesthetic level with a slow cerebral blood flow. The well known effect of carbon dioxide on induction and recovery from anesthesia thus depends not only upon its effects on the arterial curve of the anesthetic but also, and of equal importance upon its effects on cerebral blood flow.

Much of what has been said about the uptake of anesthetic by the body and the factors governing it apply equally well to the release of anesthetic from the tissues and from the arterial blood; in fact the recovery curve which is achieved by simply stopping the inhalation of the anesthetic would look exactly like the uptake curve turned upside down. That is easy to understand since with the anesthetic removed the patient is nevertheless breathing a constant inspired tension of anesthetic gas. It merely happens that the inspired tension is zero. It is in recovery from the gas that all these factors which have been mentioned are most easily demonstrated since clinically the induction of anesthesia is rarely achieved by the inhalation of a constant tension. In recovery that is practically always the case, however, and therefore what has been said about the differences of the anesthetics from the point of view of their physical properties, and therefore their rates of induction, will apply equally well and even more clearly to the rates of recovery from them.

The ramifications and corollaries of these few principles are extensive. These few fundamental principles, however, may help one in predicting or explaining what various combinations of these physiologic and physical factors actually do in their various clinical associations.

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CONTENTS

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THE THEORY AND APPLICATIONS OF THE EXCHANGE OF INERT GAS AT THE LUNGS AND TISSUES[1]

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The respiratory and circulatory systems of the higher animals constitute a single homeostatic complex whose chief function is the maintenance of an optimal molecular concentration of oxygen and carbon dioxide about each cell. This is accomplished by a highly effective combination of physical diffusion and transport together with reversible chemical reactions. The process of diffusion, which alone is sufficient for the metabolic exchange of unicellular organisms, operates in higher animals only across the microscopic spaces between the blood and pulmonary alveoli or peripheral cells. Between the lungs and the body tissues the molecules of gas are transported by the circulating blood in physical solution and, in the case of oxygen and carbon dioxide, in loose chemical combination with certain blood constituents.

The relative magnitudes and time relationships of these various processes are not obvious in the steady state of metabolic exchange. They become apparent, however, when a new molecular species is introduced into the atmosphere which the organism breathes, and, if the new substance happens to be an inert gas, its behavior in the organism may be explained and predicted on the basis of relatively simple physical laws. For the purpose of this discussion an inert gas will be defined as one which dissolves in the blood and tissues in a manner that can be described by Henry's Law, which suffers no change in chemical identity during its passage through the organism, and which is therefore quantitatively recoverable from the organism at any time (54, 105). This definition would include those volatile anesthetic agents which are not chemically altered in the body even though they produce definite physiological effects.

When an inert gas in abruptly introduced at a constant partial pressure into the inspired air, the tissues of the body do not suddenly acquire the gas at this partial pressure. A number of physical processes intervene, each with its own time rate of change, to delay the eventual saturation of the tissues. First, by means of pulmonary ventilation the gas is inspired, diluted with the functional residual air and distributed to the alveolar membrane. Here diffusion occurs and alveolar gas is equilibrated with pulmonary blood which is then distributed via the peripheral arteries to the individual tissues. A second diffusion step now occurs across the capillary membrane, interstitial fluid and cellular membrane and through the intracellular fluid itself. The venous blood from all the tissues returns to the lungs carrying some fraction of its original gas concentration which is thus contributed to the equilibration process occurring at the alveoli. In this manner the alveolar, arterial, tissue and venous tensions of the inert

[1] Original work reported in this review was supported, in part, by a grant from the National Heart Institute, U. S. Public Health Service.

gas in question gradually rise toward eventual equilibrium with the tension inspired. Although this sequence of processes is fairly obvious, no single mathematical theory has hitherto been elaborated which embraces them all.

Study of the manner in which inert gases are taken up and released by the body has important implications in many different fields. Perhaps the earliest interest was aroused by the problem of caisson disease (9, 19, 104, 133) in which it soon became apparent that the cause and treatment of the disease lay in the factors governing the saturation and desaturation of body tissues with atmospheric nitrogen during sudden and severe changes in ambient pressure. Similar problems have more recently been encountered in aviation medicine (5). The advent of scientific anesthesiology soon led to a realization of the importance of the solubilities of anesthetic gases and the relationship of physiological factors to the rates of induction and recovery. Since physiological parameters such as alveolar ventilation, functional residual capacity, cardiac output, and blood flow to different tissues determine various phases of inert gas exchange, analysis of certain of those specific phases may be made to yield quantitative information concerning the physiological constants themselves.

THEORY

The Physiological Parameters

At the outset it is necessary to formalize the anatomical and physiological factors involved in inert gas exchange, so that an aggregation of millions of separate processes occurring at microscopic levels in the lung or in a tissue may be represented by a single average process taking place uniformly and simultaneously throughout that system. A certain amount of this type of simplification is essential if there is to be any hope of mathematical treatment of the processes involved. The usefulness and applicability of the theory finally derived, however, depend inversely upon the number of simplifications introduced.

Previous authors, in their mathematical treatments, have employed different symbols for the various factors; in order to avoid confusion it appears worthwhile to adopt some standard system of symbols for the following discussion, and to express the derivations of previous authors in the same system. The author has chosen the following to conform, wherever possible, to the system adopted by the Committee on the Standardization of Symbols used in Respiratory Physiology. The following primary symbols represent certain generic factors: V, a volume; P, a pressure; C, a concentration; M, a volume flow of gas per minute; F, a volume flow of blood per minute; Q, an amount; λ, a partition coefficient; D, a diffusion constant; R, a ratio; S, a surface. These primary symbols are modified by the following subscripts: A, alveolar; E, expired; I, inspired; D, dead space; T, tidal; s, shunt; i, a particular tissue; a, arterial; v, venous; b, blood; p, pulmonary. Specific combinations of these symbols and their physiological definition are discussed in the immediately succeeding paragraphs.

Ventilation

This process, although it is obviously cyclic, has been treated as a continuous function by most of those who have taken it into consideration. The inaccuracy

thus introduced is hardly of consequence except where the events occurring in a single breath or in time intervals of a few seconds are being treated. Where interest is confined to the ventilatory process itself it is usually more convenient to represent the process as a series of instantaneous breaths. In this discussion wherever ventilation is taken to be a continuous function, the minute rate of alveolar ventilation (ml. of air washed through the total alveolar volume per minute) will be represented by M_A, the ventilation of the respiratory functional dead space by M_D, and the sum of these by M, the total rate of ventilation (ml./min). In conformity with previous practice inspired air is divided into that fraction remaining unchanged in the physiological dead space and that portion which mixes completely with alveolar gas. Where ventilation is treated as a cyclic process V_T will represent the tidal volume (ml), V_D the physiological dead space (ml) and V_F the effective tidal volume ($V_T - V_D$).

Of considerable importance is that volume of gas (V_A) in the lungs within which each functional tidal volume is ultimately distributed. For the cyclic process this is simply the end inspiratory alveolar gas volume and corresponds to the functional residual capacity[2] (41) plus the effective tidal volume. When ventilation is treated as a continuous process the volume of distribution of inspired gas (V_A) can be shown to correspond closely to the functional residual capacity plus one half the effective tidal volume (*i.e.*, the mid-inspiratory alveolar gas volume).

Blood Flow

The inspired inert gas is not only mixed with alveolar gas but is also distributed into the functional pulmonary blood flow (F_p, ml./min). This represents the portion of the cardiac output which is effectively exposed to alveolar gas. The remaining portion (F_s) represents mixed venous blood shunted past the alveoli through intracardiac communications or unventilated portions of the lung. This normally represents an insignificant fraction of the cardiac output (80) but in certain diseases may assume great importance.

The total left ventricular output (F) is now distributed to the various tissues of the body in a system of parallel circuits, blood flow through a particular tissue being represented by F_i. The liver is a notable exception to the parallel circuit description, as Morales and Smith (91) have pointed out, and represents an organ interposed in series between the abdominal viscera and the heart.

The venous outflow from each tissue, which is assumed to be equal to the arterial inflow, is now mingled with that of all the others and returned to the heart as the mixed venous blood. The concentration of any stable substance in mixed venous blood is therefore the average of its respective concentrations in the venous blood from the several tissues, each weighted by a factor $\left(\frac{F_i}{F}\right)$. Since some tissues are closer to the heart than others, the venous bloods from different tissues are represented in the mixed venous blood at the heart with some degree of time staggering (90). Thus blood from the myocardium may complete its

[2] Functional residual capacity is defined as the total gas volume in the lungs and respiratory dead space at the end of a normal expiration.

circuit back to the right atrium perhaps twenty or thirty seconds sooner than blood from the toes. Where the time periods under theoretical consideration are of the order of many minutes or hours such a time difference in arrival is probably not important and has usually been neglected. It assumes greater significance, however, when events at the very onset of inert gas uptake are to be examined. The time interval between the outflow of blood from the lungs and the first appearance of that blood in the mixed venous return to the lung is an important and controversial point in some methods for measuring cardiac output.

Solubility and Partition Coefficients

Since an inert gas will distribute itself in the various phases (air, blood, tissues), at equilibrium, according to its respective solubility in each, such physical constants constitute important parameters in the exchange process. Solubility of gases in liquids has usually been expressed in two alternative manners. The Bunsen solubility coefficient (α) represents the amount of a particular gas, expressed as ml. reduced to standard temperature and pressure (0°, 760 mm Hg), which is dissolved at complete equilibrium in 1 ml. of a particular liquid when equilibrium has occurred at a specified temperature and a partial pressure for the particular gas of 760 mm Hg. Henry's Law has been shown to apply to the blood solubility of several of the inert gases (50, 61, 109) and probably applies to all (*i.e.*, concentration of gas in liquid is proportional to its partial pressure). The Bunsen coefficient, therefore, yields directly the amount of gas dissolved by 1 ml. of liquid after equilibration at any partial pressure (P) as $\frac{\alpha P}{760}$. The Ostwald solubility coefficient (λ) (sometimes designated α') is similar to the Bunsen coefficient except that the volume of gas dissolved in 1 ml. of liquid is not converted to standard temperature. Thus λ is also the partition coefficient of the gas between the liquid and gas phase after equilibration at any pressure, *i.e.*, λ represents the ratio of the equilibrium concentration of the inert gas in the liquid (expressed in any units) to its concentration in the gas phase (expressed in the same units). It is easily shown that when a quantity of an inert gas Q_x dispersed in another gas is equilibrated with a volume (V_b) of a liquid, the final concentration of x in the liquid will be $\frac{\lambda Q_x}{\lambda V_b + V_a}$ and in the gas phase $\frac{Q_x}{\lambda V_b + V_a}$ where V_a is the final volume of the gas phase and λ the particular partition coefficient. This concept is important in describing inert gas exchange at the lungs. Since both α and λ for a particular gas:liquid system vary with temperature, the particular temperature must be stated; throughout this discussion, unless otherwise noted, values for these coefficients are at 37° C. These two coefficients are related to each other at any temperature (t) as follows:

$$\alpha_t = \lambda_t \left(\frac{273}{t + 273} \right) \tag{1}$$

Another partition coefficient describes the ratio at equilibrium between the concentration of a particular gas in a certain tissue and its concentration in the blood. Throughout this discussion, unless otherwise noted, λ will refer to the blood:gas partition and λ_i to a tissue:blood partition. Values for these coefficients for the different gases have been obtained by numerous investigators and are summarized in Table I. The values for blood:gas partition in general

TABLE I

*Values for partition coefficients at 37°–38° C. of some inert gases**

GAS	WATER / GAS	BLOOD / GAS	TISSUE / BLOOD	OIL / WATER
Hydrogen	0.018 (79)			3.1 (79)
Helium	0.0097 (79)	0.0098 (61)		1.7 (79)
Nitrogen	0.0144 (125)	0.0147 (125)	brain 1.1 (24) liver 1.1 (24) fat 5.2 (21)	5.2 (123)
Argon	0.0295 (79)			5.3 (79)
Neon	0.011 (79)			
Krypton	0.051 (79)			9.6 (79)
Xenon	0.097 (79)			20.0 (79)
Radon	0.17 (79)			125 (79)
Ethylene	0.089 (50)	0.140 (50)	brain 1.2 (60) heart 1.0 (60)	14.4 (98)
Nitrous Oxide	0.440 (109)	0.466 (71) 0.473 (97) 0.474 (109)	brain 1.0 (71) heart 1.0 (38)	3.2 (98)
Cyclopropane	0.204 (98)	0.457 (98)		35.0 (98)
Acetylene	0.850 (50)	0.795 (119) 0.842 (50)		
Divinyl ether	1.32 (103)			41.3 (103)
Chloroform	4.6 (89a)	7.3 (89a)	brain 1.0 (94, 122) liver 0.9 (94)	110 (87)
Ethyl ether	15.5 (53)	15.0 (53) 14.9 (107) 14.4 (65)	brain 1.14 (56)	3.2 (98)
Acetone		333 (130)		

* Parenthetical figures are references to the literature.

agree well with those for water:gas. This is largely fortuitous and results from the fact that the solubility of most gases is higher in the erythrocyte and lower in plasma (13, 87, 96, 109, 125), the solubility in water lying between the two. For this reason some investigators have found the blood:gas partition to vary with the percentage of red cells in the blood (71, 125). There are comparatively few values for the solubility of gases in tissues probably because of the technical difficulties involved in their determination. Those which are tabulated have been obtained *in vivo* after equilibration of the whole animal or *in vitro* by the use of finely divided tissue. It is interesting to note that except for adipose tissues the tissue:blood partition coefficients are close to unity.

Diffusion Processes and Diffusion Coefficients

The diffusion process has been assigned roles of varying importance in the exchange of foreign substances, from a practically exclusive one (120) to one of insignificance (64). For an exhaustive discussion of diffusion processes in biological systems the reader is referred to the excellent review by Jacobs (63). Stated in mathematical terms, Fick's law of diffusion in its most general sense is,

$$dQ = -DS \frac{\partial C}{\partial x} dt \tag{2}$$

where dQ represents the amount of a substance diffusing in time dt across a plane of area S under an instantaneous concentration gradient $\frac{\partial C}{\partial x}$ and D is the diffusion coefficient for the substance at a definite temperature in a definite medium; its units are cm^2 per unit of time.

This general equation may be solved to yield useful values for specific geometrical systems or boundary conditions. Since the solution itself depends to a great extent upon the boundary conditions assumed for the system under examination, these particular assumptions become of great importance.

Perhaps the simplest assumption which can be made for the lung or the tissues is to consider diffusion as occurring in parallel streams across a membrane where the concentrations on each side of the membrane, though different and variable with time are uniform at any instant. Such a treatment would apply to the situation in which two aqueous compartments, whose contents were continuously and perfectly stirred, were separated by a watery membrane. In such a situation the diffusion process would take place only within the membrane itself and if the membrane were sufficiently thin (of the order of 10 μ) a steady state of diffusion would almost instantly (Jacobs, p. 63) ensue which would be described by the following particular solution of Fick's equation:

$$\frac{dQ_1}{dt} = -\frac{DS}{H}(C_1 - C_2) \tag{3}$$

that is, the rate of loss of the diffusing substance from the compartment of higher concentration (C_1) would be equal to the specific diffusion coefficient for the substance in the material of the membrane multiplied by the ratio of the area to the thickness (H) of the membrane and multiplied by the concentration difference between the compartments.

This situation is somewhat more complicated where the two compartments may contain different solvents, and the membrane substance itself may constitute still a third phase. Consider first the most complicated system where the two compartments contain different solvents and where the solubility of the gas in question is different in each of the two solvents and in the membrane. Since diffusion occurs only within the membrane the values for concentration in equation 3 refer to the concentration in the membrane and not in the com-

partments. Now in the face of the membrane exposed to compartment 1 the concentration is $\lambda_1 C_1$ where λ_1 represents the $\frac{\text{membrane}}{\text{solvent 1}}$ partition coefficient for the gas. Similarly the concentration of gas in the face of the membrane exposed to compartment 2 is $\lambda_2 C_2$ where λ_2 is the $\frac{\text{membrane}}{\text{solvent 2}}$ partition coefficient. Equation 3 then becomes,

$$\frac{dQ_1}{dt} = -\frac{DS}{H}(\lambda_1 C_1 - \lambda_2 C_2) \tag{4}$$

In some cases it is more convenient to think in terms of gradients of partial pressure rather than concentration, especially where different phases are involved. Here if P_1 and P_2 be the partial pressure of inert gas on either side of the membrane, then immediately adjacent to compartment 1 the membrane will have a concentration $\frac{\alpha P_1}{760}$ and adjacent to compartment 2 the membrane concentration will be $\frac{\alpha P_2}{760}$, α being the Bunsen solubility coefficient for the gas in the membrane. Equation 3 then becomes,

$$\frac{dQ_1}{dt} = -\frac{DS}{H}\left(\frac{\alpha P_1}{760} - \frac{\alpha P_2}{760}\right) = -\frac{DS\alpha}{H\,760}(P_1 - P_2) \tag{5}$$

Thus from equation 5 the diffusion rate of a gas from the gaseous state through a membrane is directly proportional to its solubility in the membrane. Therefore carbon dioxide, although its diffusion coefficient is lower, diffuses much more rapidly than does oxygen through the pulmonary membrane since its solubility in the membrane solvent (presumably water) is nearly twenty-five times as great.

Values of D in dilute aqueous solutions have been determined for many gases (62); these diffusion coefficients for hydrogen, nitrogen, oxygen and carbon dioxide at temperatures near 20° C are, respectively, 5.2, 2.0, 1.98 and 1.77 $\times$ 10^{-5} cm^2 per second. Krogh (73) found that diffusion coefficients increased approximately by 1% per degree in the region from 0° to 36° C. The coefficients for diffusion through some body tissues have been determined in the case of a few gases (73) (132); they were found to be one third to two thirds their values in water. Recently a beginning has been made in determining coefficients of other gases in living tissues (111); there is need for further work along such lines.

In the treatment of diffusion in the tissues as occurring across a membrane, usually assumed to be that of the capillary, the surface area of this membrane becomes of great importance. This area has been estimated in various tissues from data obtained by several investigators employing injection technics (29, 34, 45, 74, 75, 76, 110, 126). Such studies give quite accurately the number of capillaries open during the injection; the functional surface, however, must be

inferred by means of an assumption as to capillary diameters during life. Table II summarizes some of these findings and deductions.

The treatment of diffusion at the tissues as if it occurred only across the capillary membrane into a tissue chamber of spatially uniform concentration has the advantage of simplicity if not verisimilitude. It is perfectly apparent that concentration gradients must exist within the tissue itself during inert gas exchange and it is only by taking them temporarily, at least, into consideration that their importance in the diffusion process may be realized. But in order to take them into consideration one must decide upon some geometrical model of

TABLE II

Capillary density, capillary surface, and maximum diffusion distance in various tissues, from the data of different investigators

TISSUE	SPECIES	REF.	CAPILLARY DENSITY no. per mm²	CAPILLARY SURFACE cm²/cm³	MAXIMUM DIFFUSION DISTANCE μ
Muscle	frog	76	400	190	28
Muscle	horse	76	1400	240	15
Muscle	dog	76	2600	590	11
L. ventricle	human	126	5730	1090	8
R. ventricle	human	126	5680	1080	8
Vent. septum	human	126	4450	850	8
Papillary muscle	human	126	5220	990	8
Heart muscle	mouse	110	5300	1000	8
Cerebral cortex	human	29	1000	190	18
Cerebral cortex	mouse	110	1250	240	16
Cerebellum	mouse	110	1700	330	14
White matter	human	29	300	57	33
Adipose:					
Fat-rich	rat	45	274	52	34
Fat-poor	rat	45	1000	222	18
Liver	mouse	110	4200	800	9
Duodenum	mouse	110	2400	460	11
Pancreas	g. pig	110	1900	360	13
Renal cortex	mouse	110	4500	850	8
Renal medulla	mouse	110	7400	1400	7

the relationship of capillaries to tissue. One possibility is to consign to each capillary a cylinder of tissue equal in length to that of the capillary and with a volume equal to that of the tissue divided by the number of capillaries (12, 74). On the basis of such a model, governing equations and boundary conditions may be set up (93) and solutions eventually achieved. Such a model might be satisfactory if all the capillaries were disposed in parallel and oriented so that all the arterial ends were on one side. Where the arrangement is more or less random with the arterial end of one cylinder adjacent to the venous end of another there would be gradients not only within but also between the cylinders, introducing almost hopeless complexity into an attempt at mathematical treatment. A relatively simple first approximation may be to consider diffusion as occurring

radially from the capillary in only two dimensions and to calculate the length of time for the attainment of a specified degree of equilibrium between the average concentration in the tissue and an assumed constant concentration in the capillary (31). Such a treatment is much closer to the truth than the theory of linear diffusion across a membrane since it assumes radial diffusion and includes the tissue in the diffusion process. Copperman (31) has obtained a series of solutions for the general diffusion equation on this basis and in terms of available tissue parameters. This was accomplished by solving the radial diffusion equation,

$$\frac{\partial^2 C}{\partial r^2} + \frac{1}{r}\frac{\partial C}{\partial r} = \frac{1}{D}\frac{\partial C}{\partial t} \tag{6}$$

with initial conditions: $r = a, C = C_0, a < r \leq R, C = 0$, and with boundary conditions: $r = R, \frac{\delta C}{\delta r} = 0$. For a mean tissue concentration 95% of the final value the exact expression for the time t becomes,

$$\frac{4}{R^2 - a^2} \sum_k \frac{1 - e^{-Dk^2 t}}{k^2 \left\{ \left[\frac{R}{a} \frac{V_0(kR)}{V_0'(ka)} \right]^2 - 1 \right\}} = 0.95 \tag{7}$$

where $V_0(k r) = Y_0(k a) J_0(k r) - J_0(k a) Y_0(k r)$ and where k is given by $V_0'(k R) = 0$. J_0 and Y_0 are the zero order Bessel functions of the first and second kind, respectively. Only the first term in the series is needed for calculation of t. In Table III are presented values for the time in seconds necessary to achieve 95% equilibrium throughout a tissue region of radius R from a capillary of radius $a (= 2.5\ \mu)$ for substances of different diffusion coefficients. Solubility is assumed to be uniform throughout the system. From an examination of the maximum diffusion distances in the various tissues presented in Table II it is apparent that for most tissues and most inert gases, blood:tissue equilibrium, according to this theory, would be nearly complete in about one second.

THE THEORETICAL APPROACH

Since interest was first aroused in this problem there have been only a few mathematical treatments proposed for the description of inert gas behavior in the body. Some of these are highly theoretical, but a large number are frankly empirical, represent merely a formula which best fits the data obtained and have little theoretical justification. The reviewer will attempt to point out in each case the assumptions made, the mathematical results, and their general applicability.

A.) Zuntz (1897), von Schrötter (1906). This theory was apparently first developed by Zuntz (133) and later amplified by von Schrötter (104) to explain the uptake of nitrogen by the body when exposed to an increase in ambient pressure. These authors made the following assumptions. (i) The inspired concentration of nitrogen is immediately transmitted to the alveoli; they therefore

neglected the phase of lung washout. In this special case of exposure to increased ambient pressure, such an assumption is perfectly permissible since the alveolar gas is also compressed and increases in nitrogen concentration along with the inspired air. (ii) The alveolar and arterial nitrogen concentrations remain constant following their instantaneous arrival at the new level. In this they neglected the continuous removal of some alveolar nitrogen by the pulmonary blood flow, which, because of the low solubility of nitrogen in blood, introduces little appreciable error. (iii) The circulation was visualized as a somewhat discontinuous function in which the entire blood volume is equilibrated instantaneously in the lung at the new nitrogen tension, then instantaneously equilibrated with all the body tissues simultaneously. The nitrogen-poor venous blood, representing the mean nitrogen tension of the whole body, is now re-equilibrated at the ambient nitrogen tension in the lungs and the process is repeated until the tissues approximate this tension. Thus, if the blood volume, as they assumed, were 1/11th of

TABLE III

Approximate time in seconds for 95% equilibrium between tissue region of radius R and capillary of radius 2.5 μ for a substance of diffusion coefficient through the tissue of D

$D \times 10^5$	$R = 15\ \mu$	$R = 30\ \mu$	$R = 50\ \mu$
1.0	0.4	2.3	8.3
1.5	0.2	1.5	5.5
2.0	0.2	1.2	4.2
2.5	0.1	0.9	3.8
3.0	0.1	0.7	2.8

the nitrogen capacity (tissues + blood) of the body, then in each circulation the tissues would go 1/11th of the way remaining toward complete saturation, and thus describe a logarithmic function. A serious compromise, however, lies in the treatment of the whole body as a single tissue phase equilibrated uniformly with arterial blood so that at all times the nitrogen concentration is uniform throughout all tissues. In reality, as Boycott, Damant and Haldane (19) have pointed out, each tissue has access only to a particular quota of arterial blood and increases in nitrogen concentration at a rate which may be quite at variance with that of another tissue with a different blood flow. This fact does not alter the exponential form of the solution which still remains as the fundamental basis of modern theories; it is necessary, however, to increase the number of terms to embrace these differences among tissues. (iv) No difference in the solubility of nitrogen in blood or in tissues was assumed; this can readily be adjusted by the inclusion of an appropriate partition coefficient. (v) The assumption that complete equilibrium is reached almost instantaneously between a tissue and its blood so that the tension of nitrogen in the tissue is equal to that in its venous blood implies that diffusion is not a limiting factor in this process and also that all the blood flow through a tissue partakes in the equilibration (that is, that there are no arteriovenous shunts). Although the latter assumption

may be justified by considering only effective blood flow, no evidence was offered to indicate that diffusion at the tissue is indeed a process rapid enough to be considered instantaneous. A similar assumption has been made by subsequent authors (55, 64) and evidence is being accumulated which may eventually justify it (31, 64).

von Schrötter's actual equation is not nearly so useful as the concepts which Zuntz had previously elaborated. On the basis of these fundamental assumptions, plus the Fick principle (40), it is possible to derive a more generally applicable expression for inert gas uptake by a single tissue. For an inert gas the Fick principle may be stated as follows—the amount of inert gas taken up by the tissue per unit of time is equal to the quantity brought to the tissue by the arterial blood minus the quantity carried away in the venous blood, *i.e.*,

$$\frac{dQ_i}{dt} = F_i(C_a - C_v) \tag{8}$$

assuming that arterial inflow = venous outflow = F_i, and defining a tissue to include its contained blood which constitutes only a few per cent of its total volume (V_i).
Also,

$$\frac{dC_i}{dt} = \frac{1}{V_i}\frac{dQ_i}{dt} = \frac{F_i}{V_i}(C_a - C_v) \tag{9}$$

Now from Zuntz' basic assumption that venous blood from a tissue is in equilibrium with the tissue itself with respect to inert gas, then at all times,

$$C_i = \lambda_i C_v \tag{10}$$

λ_i being a specific partition coefficient for the inert gas in question between tissue (including its contained blood) and blood. From equations 9 and 10 is obtained,

$$\frac{dC_i}{dt} = -\frac{F_i}{\lambda_i V_i}(C_i - \lambda_i C_a) \tag{11}$$

which, if C_a, and therefore $\lambda_i C_a$, are constant, has the following solution for the saturation process:

$$C_i = \lambda_i C_a(1 - e^{-kt}) \quad \text{where} \quad k = \frac{F_i}{\lambda_i V_i} \tag{12}$$

and for the desaturation process:

$$C_i = C_{i_0} e^{-kt} \tag{13}$$

where C_{i_0} is the concentration at the onset of desaturation. From equation 10 similar expressions for C_v are obtained:

$$C_v = C_a(1 - e^{-kt}), \quad \text{for saturation} \tag{14}$$
$$C_v = C_{v_0} e^{-kt}, \quad \text{for desaturation} \tag{15}$$

Thus, on the basis of instantaneous diffusion equilibrium between blood and tissue and with a constant arterial concentration of an inert gas, the concentration in a particular tissue will rise toward its equilibrium value as a single exponential function, with a time constant equal to the blood flow through the tissue divided by the relative capacity of that tissue for the inert gas. Since in reality the body consists of n tissues each with an uptake implicit in equation 11:

$$Q_i = V_i C_i = V_i \lambda_i C_a (1 - e^{-k_i t}) \tag{16}$$

the total amount in the body as a whole (Q) for the saturation process is given by:

$$Q = C_a[V_1\lambda_1(1 - e^{-k_1 t}) + V_2\lambda_2(1 - e^{-k_2 t}) + \cdots + V_n\lambda_n(1 - e^{-k_n t})]$$

$$= Q_{\infty 1}(1 - e^{-k_1 t}) + Q_{\infty 2}(1 - e^{-k_2 t}) + \cdots + Q_{\infty n}(1 - e^{-k_n t}) \tag{17}$$

(where the $Q_{\infty i}$ are the quantities of the inert gas in each tissue at complete saturation $= C_a V_i \lambda_i$)
and for the desaturation process, by,

$$Q = Q_1^0 e^{-k_1 t} + Q_2^0 e^{-k_2 t} + \cdots + Q_n^0 e^{-k_n t} \tag{18}$$

where the Q_i^0 are the quantities of the inert gas in each tissue at the onset of desaturation. Since the total quantity eliminated (Q_E) from the body up to any time t must equal the difference between the total quantity present at zero time and the total quantity present at time t,

$$Q_E = Q_0 - Q_t = (Q_1^0 + Q_2^0 + \cdots + Q_n^0) - (Q_1^0 e^{-k_1 t} + Q_2^0 e^{-k_2 t} + \cdots + Q_n^0 e^{-k_n t})$$

$$= Q_1^0(1 - e^{-k_1 t}) + Q_2^0(1 - e^{-k_2 t}) + \cdots + Q_n^0(1 - e^{-k_n t}) \tag{19}$$

B.) Widmark (1919). The Zuntz-von Schrötter assumptions and the above expressions which the reviewer has derived from them are rigorously applicable only to a state in which the alveolar and arterial concentrations of an inert gas are constant throughout the duration of saturation or desaturation, that is, to a gas of infinitesimal solubility in blood introduced abruptly and at its final concentration into the alveolar spaces. Such a treatment is, therefore, of only limited value in the general problem of inert gas exchange. Widmark (130), on the other hand, derived a relatively simple expression for the elimination (and therefore also the uptake) of inert gases by the body, which is applicable only to gases of extremely great solubility in blood. This author concerned himself especially with the elimination of acetone, the blood:air partition coefficient of which he reported as 333. Because of this preponderant solubility in blood, Widmark could reasonably assume in the case of this gas that in one passage through the lungs the blood loses so little acetone that the concentration in arterial blood is practically identical with that in mixed venous blood. He also assumed that the elimination was sufficiently slow so that the tension of acetone in the blood was always equal to that in the tissues. On the basis of these two assumptions, plus the concept that at the lungs the alveolar air was

brought into equilibrium with pulmonary blood, he set up the following differential equation for the elimination of acetone at the lungs:

$$\frac{dQ_x}{dt} = -\frac{M_A C_b}{\lambda} = -\frac{M_A Q_x}{\lambda V_x} \tag{20}$$

where M_A represents alveolar ventilation rate; Q_x, the total quantity of acetone in the body; C_b, the blood concentration; and V_x, the acetone space or the volume of distribution of acetone in the body. Equation 20 may be solved to yield:

$$Q_x(t) = Q_{x_0}e^{-kt} \quad \text{or} \quad C_b(t) = C_{b_0}e^{-kt} \tag{21}$$

where $k = \dfrac{M_A}{\lambda V_x}$

Similarly for saturation at a constant inspired concentration C_I:

$$C_b(t) = \lambda C_I(1 - e^{-kt}) \tag{22}$$

Widmark determined blood acetone concentration during the desaturation process in man and animals and demonstrated a single exponential decay for acetone. He also found, however, that even in the case of a soluble gas like ether ($\lambda = 14.9$), the resulting curve could not be described in terms of a single exponential. Thus Widmark's treatment is of very limited usefulness and is valid only for gases of inordinately high solubility in blood.

C.) Haggard (1924). This theory was elaborated to explain the uptake and elimination of ethyl ether by the body (55). It embraces three of the Zuntz-von Schrötter assumptions (i) that there is a single body tissue mass with a uniform blood flow; (ii) that λ_i is unity; for this particular assumption Haggard obtained empirical data (total quantity absorbed, total weight of the animal, and blood concentration of ether) which appeared to substantiate an average λ_i near unity (54), but possible differences among tissues were neglected; (iii) that there is complete equilibrium between blood and tissue and also between blood and alveolar gas.

In addition, Haggard introduced an important new concept into his theory, one which appears to have been neglected by most subsequent authors. Dealing with a highly soluble gas, he realized that its alveolar concentration would not immediately equal the concentration inspired, but would rise slowly toward that asymptote as the body tissues and venous blood became saturated. Zuntz, who confined his attention to nitrogen could neglect that important fact without making his theory wholly inapplicable; but any mathematical treatment designed to explain the behavior of all inert gases must include this important concept of Haggard.

Haggard treated the ventilation as continuous and recognized and corrected for the respiratory dead space. He then proceeded in a manner reminiscent of Zuntz to treat the phenomena in a discontinuous manner. In the first minute

of inhalation of ether at a constant inspired concentration (C_I), the arterial concentration of ether is given by,

$$C_a = \frac{M_A C_I \lambda}{\lambda F + M_A} \tag{23}$$

(In this he neglected dilution of C_I by the functional residual air and assumed that all the cardiac output (F) is equilibrated with alveolar gas.) The quantity of ether absorbed in one minute (Q_1') is,

$$Q_{1'} = FC_a = \frac{FM_A C_I \lambda}{\lambda F + M_A} \tag{24}$$

The quantity of ether exhaled in the first minute ($Q_{E_1'}$) is,

$$Q_{E_1'} = M_A C_I - Q_{1'} = \frac{M_A^2 C_I}{\lambda F + M_A} \tag{25}$$

Assuming that there is a time of one circulation, it would be V_b/F minutes; therefore the quantity of ether absorbed in the first circulation (Q_1) is obtained from equation 24:

$$Q_1 = V_b C_a = \frac{V_b M_A C_I \lambda}{\lambda F + M_A} \tag{26}$$

This quantity is now, after the manner of von Schrötter, equilibrated with all the tissues of the body ($V_n + V_b$); therefore the amount remaining in the blood and brought back to the lungs at the end of the first circulation (Q_{v_1}) is,

$$Q_{v_1} = \left(\frac{M_A C_I \lambda V_b}{\lambda F + M_A}\right)\left(\frac{V_b}{V_n + V_b}\right) = \frac{M_A C_I \lambda V_b^2}{(\lambda F + M_A)(V_n + V_b)} \tag{27}$$

Now in the second circulation, the quantity of ether carried away from the lungs (Q_2) equals the quantity inhaled plus the recirculated quantity (Q_{v1}) distributed between the total blood and air and multiplied by the outflow of blood:

$$Q_2 = \left[\frac{M_A C_I V_b}{F} + \frac{M_A C_I \lambda V_b^2}{(\lambda F + M_A)(V_n + V_b)}\right]\frac{\lambda F}{\lambda F + M_A} \tag{28}$$

This concluded Haggard's formal analysis. He then stated that this process repeated indefinitely is one in which the body, in equal intervals of time, goes a constant fraction of the way toward full saturation. This is the form of a single exponential rise so that Haggard's conclusion is the same as von Schrötter's: $Q = Q_\infty(1 - e^{-kt})$.

Haggard's derivation, although fairly adequate for ether, contains an important oversimplification which precludes its general applicability to any inert gas. Equation 28 neglects the quantity of ether remaining in the lungs at the end of the first circulation and therefore treats the lungs as collapsing com-

pletely at each expiration. In the case of a gas as soluble in blood as is ether, little indeed remains in the residual air and this neglect of the pulmonary dilution phase of inert gas exchange introduces only a slight error. This error becomes increasingly great, however, as the inert gas in question decreases in solubility. Even on the assumption of a single tissue phase made by both Zuntz and Haggard, rigorous treatment must yield an expression containing at least two exponential terms determined by tissue *and* lung dilution. It is interesting to note that each of these authors obtained a single exponential by neglecting lung dilution for reasons quite different, and, in each specific and quite limited application, almost justifiable.

Haggard's derivation, however, permitted him to draw the following important conclusions regarding the uptake of ether and other inert gases: (i) The shape of the curve of saturation vs. time for the body is independent of C_I. (ii) From equation 24 he demonstrated that rate of uptake is proportional to $\frac{M_A}{\lambda F + M_A}$ if M_A alone changes, and therefore for very soluble gases (λ large) the rate of absorption is practically proportional to ventilation. For relatively insoluble gases, he pointed out, this dependence on ventilation decreases. (iii) From the same equation he concluded that rate of uptake is proportional to $\frac{\lambda F}{\lambda F + M_A}$ if F alone changes, and, therefore for very soluble gases the rate of uptake is relatively independent of F, becoming increasingly dependent as λ decreases.

D.) Teorell (1937). This author developed a mathematical theory to describe the kinetics of distribution of substances injected into the body (120, 121). He was not directly concerned with the distribution of inhaled gases and none of his derivations is directly applicable to this problem. His point of view, however, must be taken into consideration since it stands in direct antithesis to that of Zuntz. Whereas the latter neglected the diffusion process as a limiting factor in blood:tissue exchange, attributing the rate entirely to circulation, Teorell considered diffusion to be the sole determinant in this exchange and did not include circulation in his derivation. His differential equation for transfer from tissue depot to blood has the form,

$$\frac{dQ_i}{dt} = -k'\left(\frac{Q_i}{V_i} - C_b\right) = -\frac{k'}{V_i}Q_i = -kQ_i \qquad (29)$$

with the assumption that C_b can be neglected. k' represents a permeability coefficient including the diffusion constant for the substance as well as membrane surface and thickness, so that the solution : $Q_i = Q_0 e^{-kt}$ is independent of blood flow. Teorell offered no empirical justification for excluding this important parameter and it is difficult to reconcile his concept with the observation (67) that removal of Na^{24} from an injection site is quite sensitive to local circulation and with the even more cogent results of Jones (64) who found identical values for k of two gases of widely differing diffusion constants.

E.) Morales and Smith (1944–48). These authors have made the most ex-

haustive analysis to this date of the theory of inert gas exchange. In a series of papers (90, 91, 92, 93, 112, 113) they have treated practically all aspects of the problem by a fairly complete mathematical analysis. Their basic approach is perhaps best illustrated by their most recent publication (93) which treats the exchange problem at a single homogenous tissue. With few simplifying assumptions they have set up the following differential equations for the quantities of gas (Q_b) in the blood compartment of a tissue and in the tissue volume itself (Q_i):

$$\frac{dQ_b}{dt} = V_b \frac{dC_b}{dt} = F_i(C_a - C_v) - D_i S_i(C_b - C_i/\lambda_i) \tag{30}$$

$$\frac{dQ_i}{dt} = V_i \frac{dC_i}{dt} = D_i S_i(C_b - C_i/\lambda_i) \tag{31}$$

where D_i is a permeability coefficient for the particular gas and the particular membrane and S_i is the area of the diffusion interface. This treats diffusion as occurring across a definite membrane into a tissue space of uniform concentration C_i.

To evaluate C_b, the mean concentration in tissue capillary blood, they have assumed that it is some constant fraction between C_a and C_v, *i.e.*, $C_a - C_b = r(C_a - C_v)$, and substitute appropriately in equation 30 to get,

$$V_b \frac{dC_b}{dt} = \frac{F_i}{r}(C_a - C_b) - D_i S_i(C_b - C_i/\lambda_i) \tag{32}$$

Equations 31 and 32 are simultaneous differential equations in C_b and C_i and may be solved for each. In order to do this conveniently they have assumed a constant arterial concentration. The solution for C_i is especially pertinent:

$$C_i = \frac{Q_i}{V_i} = \lambda_i C_a(1 + A_1 e^{k_1 t} - A_2 e^{k_2 t}) \tag{33}$$

where $A_1 = \dfrac{k_2}{k_1 - k_2}$ $\qquad A_2 = \dfrac{k_1}{k_1 - k_2}$

and k_1 and k_2 =

$$-\frac{1}{2}\left[\frac{F_i}{V_b r} + \frac{D_i S_i}{V_b}\left(1 + \frac{V_b}{\lambda_i V_i}\right)\right]$$

$$\pm \frac{1}{2}\left\{\left[\frac{F_i}{V_b r} + \frac{D_i S_i}{V_b}\left(1 + \frac{V_b}{\lambda_i V_i}\right)\right]^2 - \frac{4F_i D_i S_i}{\lambda_i V_b V_i r}\right\}^{\frac{1}{2}} \tag{34}$$

Thus Morales and Smith, by taking into consideration both blood flow and diffusion in a homogenous tissue, have arrived at an expression for inert gas uptake which contains two exponential terms instead of the single exponential of Zuntz-von Schrötter or Teorell. In an effort to determine whether one of their exponential terms is physically negligible they have reviewed some of the data

of others, seeking reasonable values for the physiological parameters in particular tissues (93) and concluding that "whereas in certain cases the von Schrötter approximation might be quantitatively justifiable, in others it would be very poor indeed". They have justifiably insisted upon their more rigorous treatment of the blood:tissue exchange, at least until better evidence is obtained for its simplification.

In another paper (91) Morales and Smith have shown that, where the tissues of the body can be assumed to exist as a distinct parallel arrangement each with its own blood supply, the content of inert gas in the body as a whole at any time t during saturation may then be given by the expression,

$$Q = Q_\infty - \sum_{i=1}^{i=n} (A_{i,1}\, e^{-k_{i,1}t} + A_{i,2}\, e^{-k_{i,2}t}) \tag{35}$$

where, as is to be expected from equation 33, there are two exponential terms for each tissue and the A's and k's are determined solely by the physiological parameters of that tissue. In the same communication they have derived an expression for inert gas uptake for tissues in series in which the venous blood from one tissue supplies a succeeding tissue with blood. This also leads to a sum of exponentials where the number of exponential terms is twice the number of tissues, where the decay constants are peculiar to the individual tissue, but where the coefficients are determined by the parameters of all the tissues in series:

$$Q = Q_\infty - \sum_{s=1}^{s=n} (A_{s,1}\, e^{-k_{s,1}t} + A_{s,2}\, e^{-k_{s,2}t}) \tag{36}$$

This type of arrangement is seen to an important extent only in the portal circulation through the liver.

In the first paper of the series (112), Smith and Morales derived an expression for inert gas uptake for a limb on the assumption that there is in the limb a single blood chamber supplying all the tissues which remove the inert gas in a competitive manner. It is not unexpected, perhaps, that this assumption leads to a solution in the form of a series of exponential terms of one more than the number of tissues, all of the coefficients and decay constants being determined by the parameters of all the tissues:

$$Q = Q_\infty - \sum_{j=0}^{j=n} A_j\, e^{-k_j t} \tag{37}$$

It is the opinion of this reviewer that this treatment is needlessly cumbersome and no closer to physiological reality than the distinct parallel system, since individual tissues do in general have their own capillary network and any slight admixture of tissues (*e.g.*, fat cells among muscle fibers) may be taken into account reasonably well in mean parameters for the tissue as a whole.

Morales and Smith have also attempted a mathematical analysis of inert gas exchange at the lung (90). Starting with the drastically limiting assumption that at the instant of the first breath the alveolar concentration is suddenly

increased to its final constant value, they derived a set of expressions for four stages of the pulmonary exchange process. Stage (a) persists only for as long a time as the blood spends in the lungs and during this time the partial pressure of the inert gas in the blood is rising exponentially toward that in the alveoli. Stage (b) extends from the end of stage (a) to stage (c), the onset of which is marked by the first return of venous blood containing the inert gas to the lung. Stage (d) begins when the region with the longest roundtrip circulation time just begins to contribute to the venous return to the lung and continues through the remainder of the saturation process. Since this treatment neglects the phase of dilution of inspired air with residual air, and all the ventilatory parameters as well, and neglects the depletion of alveolar gas by carriage of inert gas from the lung in the pulmonary venous blood and the consequent rise of alveolar and arterial blood concentrations as a function of mixed venous concentration, it is applicable only to the special case treated by Zuntz of an insoluble inert gas (N_2) forced into the lung by a sudden increase in ambient pressure or to the special case in which the inspired concentration can be made to vary in order to keep the alveolar concentration constant. It is apparent that the limiting assumptions of this treatment are such as to prevent its applicability generally to the pulmonary exchange of many inert gases.

F.) Kety (1949). This reviewer has had occasion to resort to inert gas exchange theory in the past several years in an effort to comprehend the physiological factors involved in the uptake of nitrous oxide by the arterial blood. Several hundred such curves had been obtained over the early periods of saturation for quite a different purpose (66). It was, however, apparent that the arterial curve varied with important physiological parameters and it seemed desirable to obtain an expression which would demonstrate this relationship. Since all the existing theories save Haggard's assumed a constant arterial concentration and Haggard's treatment was incomplete, it was necessary to develop a theory (70) which comprehended inert gas exchange at the lung.

If the inhaled concentration of an inert gas (C_I, mg./ml.) is held constant and alveolar ventilation is treated as a continuous process represented by M_A (ml./min.), then in a short time (dt), $M'\ dt\ C_I$ mg. of gas are delivered to the alveoli and $M'\ dt\ C_A$ mg. are removed from the alveoli by ventilation. By means of the pulmonary blood flow (F_p ml./min.), $F_p\ dt\ C_v$ mg. of inert gas are delivered during the same time to the alveoli in the mixed venous blood and $F_p\ dt\ C_p$ mg. are removed in the pulmonary venous blood (C_v and C_p representing concentrations of inert gas in mg./ml. in mixed venous and pulmonary venous blood, respectively) thus,

$$\frac{dQ_A}{dt} = V_A \frac{dC_A}{dt} = M_A(C_I - C_A) + F_p(C_v - C_p) \tag{38}$$

This equation neglects the quantity of gas which dissolves in the tissue and blood of the alveolus unless one defines V_A to include not only the alveolar air but also the blood and tissue present in the alveolus with an appropriate partition

coefficient correction (*i.e.*, $V_A = V_{air} + \lambda V_{tissue + blood}$). Recent work indicates that for CO_2 this "phantom" residual air is equivalent to an average of 0.7 l. of blood (37).

If one assumes diffusion equilibrium between alveolar gas and pulmonary venous blood then $C_p = \lambda C_A$, where λ is an appropriate partition coefficient. If one is not willing to make such an assumption, another relationship can be obtained by employing a derivation similar to that of Bohr (14): Let C_b represent the variable blood concentration of inert gas along a pulmonary capillary of length L, and x a variable distance along the capillary. Further, let s' and v' represent the diffusion surface and the capillary blood volume, both per unit length of capillary, f the average linear velocity of blood in the capillary, and D' the diffusion coefficient per unit area for the gas across the alveolar membrane. Now assume that the concentration in the gas phase (C_A) is uniform from one end of the capillary to the other.

As an element of blood moves in the capillary from x through dx, it takes up a quantity of gas according to the law of diffusion through a membrane:

$$dQ_b = D's'dx(\lambda C_A - C_b)dt \tag{39}$$

which is also equal to the gain in concentration in the blood (dC_b) multiplied by the volume of blood under consideration ($v'dx$). But $dx = fdt$, whence,

$$dC_b v'fdt = - D's'dx(C_b - \lambda C_A)dt$$

and,

$$\frac{dC_b}{dx} = - \frac{D's'}{v'f}(C_b - \lambda C_A) \tag{40}$$

whence

$$(C_b - \lambda C_A)_x = (C_b - \lambda C_A)_0 \, e^{-(D's'/v'f)x} \tag{41}$$

At $x = o$, $C_b = C_v$; at $x = L$, $C_b = C_p$, therefore,

$$C_p - \lambda C_A = (C_v - \lambda C_A)e^{-(D's'/v'f)L} = (C_v - \lambda C_A)e^{-(D'S/F)} \tag{42}$$

where $\frac{S}{F}$ is the ratio of diffusion surface to volume flow of blood for the capillary or the lung as a whole. From equation 42 it is readily shown that

$$C_v - C_p = \theta(C_v - \lambda C_A) \tag{43}$$

where $\theta = 1 - e^{-\frac{D'S}{F}}$ and is probably close to 1 under most circumstances.

The value of $(C_v - C_p)$ obtained in equation 43 may now be substituted in equation 38 to yield:

$$\frac{dC_A}{dt} = \frac{M_A}{V_A}C_I - \frac{M_A + F_p\theta\lambda}{V_A}C_A + \frac{F_p\theta}{V_A}C_v \tag{44}$$

For the case of saturation with an inert gas where at $t = o$, $C_A = C_v = o$, the following solution is obtained,

$$C_A = A_1 C_I(1 - e^{-kt}) + A_2 e^{-kt} \int C_v e^{kt}\, dt \tag{45}$$

where $A_1 = \dfrac{M_A}{M_A + F_p\theta\lambda}$ $\quad A_2 = \dfrac{F_p\theta}{V_A}$ $\quad k = \dfrac{M_A + F_p\theta\lambda}{V_A}$

Equation 45 represents only a partial solution for the alveolar concentration in terms of physiological parameters since the mixed venous concentration (C_v) remains undefined. It is useful, however, in explaining the differences among the uptake curves of different gases (69) and in assigning appropriate weights to the pulmonary parameters, and it has a certain heuristic value in suggesting means for determining some of the constants involved.

In order to define the arterial concentration (C_a) with close adherence to physiological reality, it is necessary to consider the possibility of venous to arterial shunts by-passing the alveoli. If the ratio of effective pulmonary blood flow (F_p) to total cardiac output (F) be designated as R_p then it is apparent that

$$C_a = R_p C_p + (1 - R_p)C_v \tag{46}$$

which, combined with equation 37 yields,

$$C_a = R_p\theta\lambda C_A + (1 - R_p\theta)C_v \tag{47}$$

When extra alveolar shunts and diffusion limitation become negligible, equation 47 reduces to $C_a = \lambda C_A$ which should be subject to experimental demonstration. It is interesting that in the case of a single inert gas (as opposed to oxygen (80)) the effect of an extra alveolar shunt would be indistinguishable from that of a diffusion barrier, although the two could be differentiated by employing two gases with markedly different diffusion coefficients. In such a case θ would be different but R_p the same for the two.

Since mixed venous concentration (C_v) in equation 45 remains undefined and since it obviously represents the weighted sum of the venous concentrations from all the separate tissues, it is important now to discuss blood:tissue exchange. A special case of this exchange (the clearance of injected sodium ion from a tissue depot) has previously been published (67); a more general derivation, however, is desirable. The Fick principle, applied to a particular tissue (i), yields as before (equation 8) the equation,

$$\frac{dQ_i}{dt} = V_i \frac{dC_i}{dt} = F_i(C_a - C_{v_i})$$

On Zuntz' assumption that diffusion equilibrium is instantaneous, it has been shown that this reduces to a single exponential expression for C_i. It is now proposed to take the diffusion process into consideration in the manner previ-

ously employed at the lung. The assumption is now made that there is some mean tissue concentration of inert gas (C_i) which remains constant during the passage of blood from the arterial to the venous end of the capillary. Since the capillary volume represents less than 5% of the volume of most tissues, marked changes in the blood concentration along the capillary would be reflected in only a slight change in mean tissue concentration. In a manner exactly analogous to that used at the lung the following relationship can be shown to exist for $C_a - C_{v_i}$:

$$C_a - C_{v_i} = m_i(C_a - C_i/\lambda_i) \qquad \text{where } m_i = 1 - e^{-(D_i' S_i / F_i)} \tag{48}$$

which substituted into equation (8) yields,

$$\frac{dC_i}{dt} = \frac{m_i F_i}{V_i \lambda_i}(\lambda_i C_a - C_i) \tag{49}$$

which has the following special solutions:
If C_a is constant and positive (saturation process),

$$C_i = \lambda_i C_a(1 - e^{-k_i t}) \tag{50}$$

If C_a is constant and zero (desaturation process),

$$C_i = C_{i_0} e^{-k_i t} \qquad \text{where } k_i = \frac{m_i F_i}{V_i \lambda_i} \tag{51}$$

These solutions are the same as those derived previously (equations 12 and 13) for similar cases from Zuntz' assumptions except that the k_i now includes a diffusion dependent factor (m_i). This result is to be contrasted with the two term exponential of equation 33 obtained by Morales and Smith by means of a more rigorous derivation. The loss of one exponential term resulted from the assumption that changes in mean tissue inert gas concentration, during the time of passage of an element of blood through the tissue, were negligible in comparison with the concentration change occurring in the blood itself. Although less exact than the expression of Morales and Smith, equations 44 or 45 may be more useful if this assumption can be justified for any particular tissue. Experimental data obtained in two tissues at least (muscle and liver) appear to fit the single exponential form (67, 127), and it is suggested that this less rigorous treatment may be adequate. Where the arterial concentration is variable with time, which unfortunately is often the case, the respective solutions for equation 49 are somewhat more complicated:
For saturation,

$$C_i = \frac{m_i F_i}{V_i} e^{-k_i t} \int C_a e^{k_i t}\, dt \tag{52}$$

For desaturation

$$C_i = C_{i_0} e^{-k_i t} + \frac{m_i F_i}{V_i} e^{-k_i t} \int C_a e^{k_i t}\, dt$$

In a manner similar to that employed at the lung it is possible to set up expressions for C_v assuming the presence of some degree of arterial to venous shunting of blood. Let R_i represent the ratio of effective capillary flow through the tissue to the total capillary plus shunt flow and $C_{v'}$, the resultant venous concentration, then clearly,

$$C_{v_i}' = R_i C_{v_i} + (1 - R_i)C_a$$

whence, from equation 48,

$$C_{v_i}' = R_i \frac{m_i}{\lambda_i} C_i + (1 - R_i m_i)C_a \tag{53}$$

which, in the absence of tissue arteriovenous shunts and with instantaneous diffusion ($R_i = 1 = m_i$) resolves to $C_{v_i} = C_i/\lambda_i$.

Now it is apparent that mixed venous blood entering the lung is a weighted average of the venous blood from the several tissues, so that, neglecting the time stagger mentioned previously,

$$C_v = \frac{F_i}{F} C_{v_i}' + \frac{F_2}{F} C_{v_2}' + \cdots + \frac{F_n}{F} C_{v_n}' \tag{54}$$

so that by means of equations 52 and 53 mixed venous blood has been defined in terms of tissue parameters and arterial blood and by equations 45 and 47 arterial blood has been defined in terms of cardiorespiratory parameters and mixed venous blood. If it were possible to eliminate the blood concentration variables common to both expressions it should be possible to arrive at an expression for the complete lung:blood:tissue exchange of an inert gas entirely in terms of physiological parameters. It is possible to do this to a degree of verisimilitude and, unfortunately, of complexity which is dependent only on the number of assumptions made. The simplest solution is achieved by assuming, with Zuntz, that all the body tissues comprise a single homogeneous tissue mass (V_T) regarding blood flow and gas solubility, and further that equilibrium between alveolar gas and arterial blood and between blood and tissue is complete and, finally, that the blood:tissue partition for the inert gas in question is unity. On the basis of these assumptions m_i and λ_i drop out of equation 49, $C_i = C_v$ and $F_i = F = F_p$. The simultaneous differential equations 38 and 49 now give the following solution for the saturation process:

$$C_A = C_I(1 - A_1 e^{-k_1 t} - A_2 e^{-k_2 t}) \tag{55}$$

where,

$$k_1 \text{ and } k_2 = \frac{1}{2}\left\{\frac{M_A + \lambda F}{V_A} + \frac{F}{V_T} \pm \left[\left(\frac{M + \lambda F}{V_A} + \frac{F}{V_T}\right)^2 - \frac{4M_A F}{V_A V_T}\right]^{\frac{1}{2}}\right\}$$

$$A_1 = \frac{M_A/V_A - k_2}{k_1 - k_2} \qquad A_2 = 1 - A_1$$

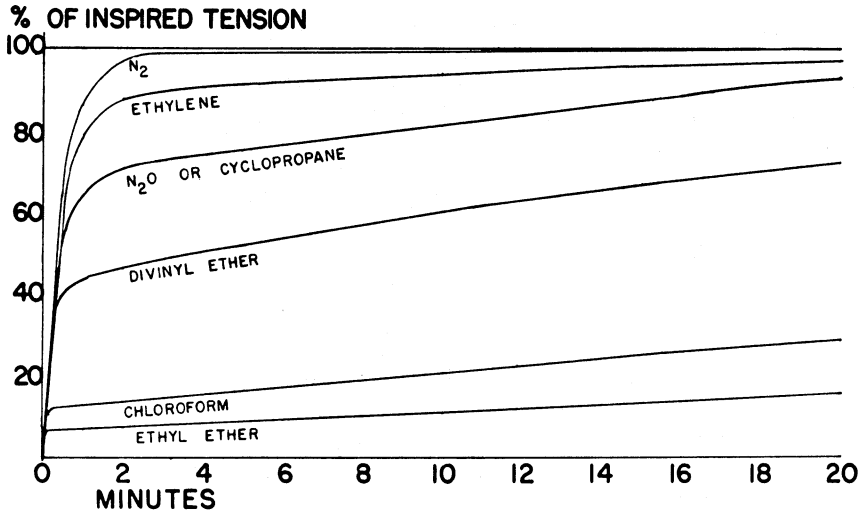

FIG. 1. Alveolar or arterial tensions of several inert gases (expressed as percent of a constant inspired tension) at various times as calculated from equation 55 using values for λ given in Table I. The physiological parameters are assumed to remain constant and to have the following respective values: $M_A = 6$ l./min., $F = 6$ l./min., $V_A = 3$ l., $V_T = 70$ l.

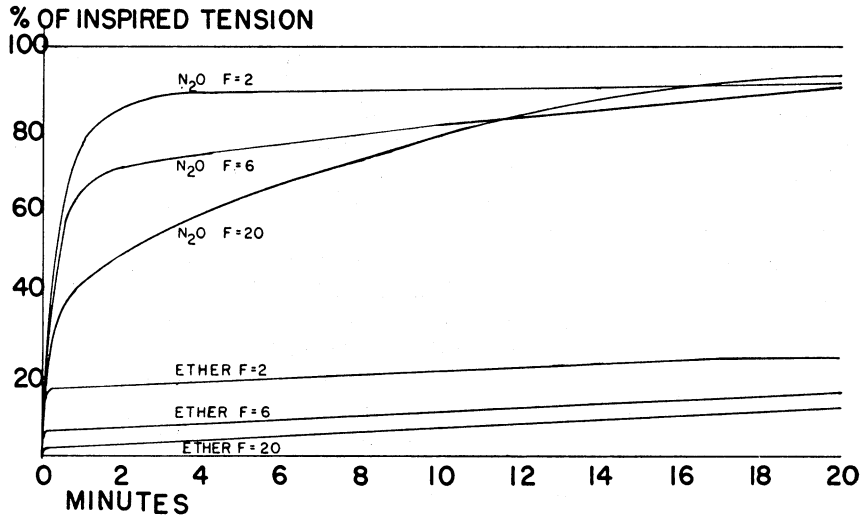

FIG. 2. The effect of variations in cardiac output on the alveolar or arterial tensions of two inert gases as calculated from equation 55 with other physiological parameters remaining constant: $M_A = 6$ l./min., $V_A = 3$ l., $V_T = 70$ l.

Equation 55, although inexact, is nevertheless more complete and general than any previous treatment of this problem. It is applicable to any inert gas regardless of its solubility in blood and in fact can be used to describe the uptake

of gases of different solubility (Fig. 1) which it does rather faithfully especially in the early phases of saturation. It is also useful in predicting the effect of changes in some of the important physiological parameters on the uptake of any specific inert gas (Figs. 2, 3).

Equation 55 neglects the different blood flows to the various tissues and treats the body as a single tissue mass with a blood flow equal to the cardiac output. It neglects possible differences in gas solubility in the several tissues and treats diffusion as an instantaneous phenomenon. It therefore represents a special case of a more exact and general equation which can be derived and which is given in the following section.

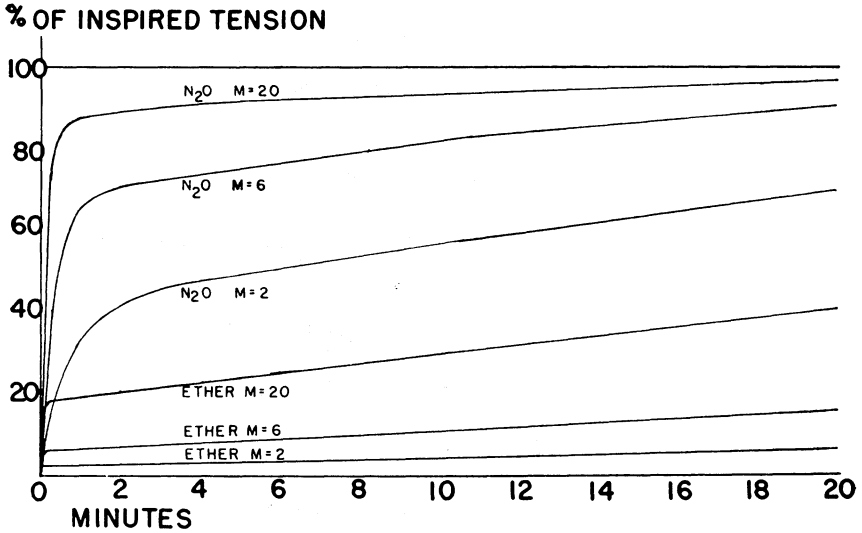

FIG. 3. The effect of variations in alveolar ventilation on the alveolar or arterial tensions of two inert gases as calculated from equation 55 with other physiological parameters remaining constant: $F = 6$ l./min., $V_A = 3$ l., $V_T = 70$ l.

G.) Copperman (1950). Starting with the respiratory and tissue exchange equations derived above, Copperman (31) has combined them and obtained for the first time a general equation entirely in terms of physiological parameters and based on a minimum of simplifying assumptions. Its only restriction is that the inspired concentration of inert gas be held constant, but the alveolar, arterial and venous concentrations are permitted to vary as they will. In the expression derived here he has chosen to neglect the presence of shunts at the lung and tissues ($R_p = 1 = R_i$) and to assume instantaneous diffusion at the lung ($\theta = 1$) but retaining the diffusion process at the tissues. He obtains therefore from equation 8,

$$\frac{dC_i}{dt} = \frac{F_i}{V_i}(\lambda C_A - C_{v_i}) \tag{56}$$

and from a Bohr derivation as in equation 42,

$$\frac{\lambda_i \lambda C_A - C_i}{\lambda_i C_{v_i} - C_i} = e^{D_i' S_i / F_i} = \psi_i \qquad \psi > 1 \tag{57}$$

Copperman has also treated blood-tissue diffusion in a somewhat more rigorous fashion (Table III) than that employed here and suggests that in reality diffusion at the tissues is practically an instantaneous process for most gases.

From equations 56 and 57, C_i is eliminated to yield,

$$\frac{dC_{v_i}}{dt} + r_i C_{v_i} = \frac{\lambda}{\psi_i}\frac{dC_A}{dt} + \lambda r_i C_A \tag{58}$$

$$\text{where } r_i = \frac{F_i(\psi_i - 1)}{V_i \lambda_i \psi_i} > 0$$

The $(n - 1)$ tissue venous concentrations are related to the mixed venous concentration as before by,

$$\sum_{i=1}^{n-1} F_i C_{v_i} = F C_v \tag{59}$$

Finally C_v and C_A are related by the equation for respiratory exchange (equation 38):

$$\frac{dC_A}{dt} = \frac{M_A}{V_A}(C_I - C_A) + \frac{F}{V_A}(C_v - \lambda C_A) \tag{60}$$

Simultaneous solution of equations 58, 59 and 60 yields a solution of the form,

$$C_A = A_0 + \sum_{j=1}^{n} A_j e^{k_j t} \tag{61}$$

where A_0 can be shown to equal C_I and the k_j's are the n roots of the following equation,

$$\lambda \sum_{i=1}^{n-1} \frac{F_i}{\psi_i}\frac{k_j + \psi_i r_i}{k_j + r_i} = M_A + \lambda F + V_A k_j \tag{62}$$

where it can be shown that each k_j is negative and real.

The n arbitrary coefficients A_j are determined from initial conditions: For the saturation process, at $t = o$, $C_A = C_{v_1} = C_{v_2} = \cdots C_{v_{n-1}} = 0$ and the following definition is achieved,

$$A_j = -\frac{\prod_{i=1}^{n-1}\left(1 + \frac{k_j}{r_i}\right)}{\prod_{\substack{i=1 \\ i \neq j}}^{n}\left(1 - \frac{k_j}{k_i}\right)} C_I \tag{63}$$

The A_j's are shown to be real and, in every particular case examined, to be negative, although a rigorous proof that they are always negative has not been obtained. The alveolar concentration of an inert gas inhaled at a constant

concentration has therefore the form:

$$C_A = C_I(1 - A_1e^{-k_1t} - A_2e^{-k_2t} - \cdots - A_ne^{-k_nt}) \qquad (64)$$

where the coefficients A_1 to A_n and the decay constants k_1 to k_n are related in an obvious manner to corresponding coefficients and decay constants defined by equations 62 and 63 entirely in terms of physiological parameters. It is immediately apparent that these A's and k's are not specifically referable each to a particular tissue, but that all are determined by all the parameters. It may be possible by appropriate assumptions to simplify these expressions so that each coefficient and decay constant refers to a particular tissue. It will always be necessary, however, to justify such assumptions by experimental proof.

THE EMPIRICAL APPROACH

A wealth of experimental data pertinent to the problem of inert gas exchange has been accumulated since the earliest interest in the role of nitrogen in decompression sickness. In reporting their results most investigators made use of some mathematical expression which they or others had previously derived or which they found by trial from their data. With one notable exception (117) these expressions have assumed the exponential form, as indeed, have all the theoretically derived equations.

Inert Gas Exchange in the Body as a Whole

Campbell and Hill (21) in 1931 reported measurements on the elimination of nitrogen by the lungs effected by the breathing of practically pure oxygen. They distinguished between the nitrogen present in the residual air at the beginning of oxygen inhalation and that subsequently eliminated from the body tissues via the pulmonary circulation by means of an initial flushing of the lung during one minute of hyperventilation, and measured the residual volume of the lung in this manner. Although they did not attempt a mathematical analysis of the nitrogen elimination process they report that its rate decreased with time and suggested that the slower rates represented regions with poor blood supply and therefore slower diffusion. They also observed that after exposure to several atmospheres of nitrogen the quantity of that gas eliminated in the denitrogenation process was proportional to original saturation pressure, *i.e.*, the conditions of Henry's law were satisfied for the uptake of nitrogen by the body.

In the United States much of the early and fundamental work on the exchange of nitrogen and other inert gases was done by Behnke and his associates (4, 6, 7, 108). By means of considerably improved technics they studied the elimination of nitrogen during oxygen breathing of several hours duration (6). Total nitrogen elimination beginning after an initial 5-minute period for lung washout was found to fit the expression,

$$Q_E = A_1(1 - e^{-k_1t}) + A_2(1 - e^{-k_2t}).$$

The following values for the constants were obtained in one experiment: $A_1 = 458$ ml., $k_1 = 0.098$ min.$^{-1}$, $A_2 = 382$ ml., $k_2 = 0.0085$ min.$^{-1}$. These investigators have refrained from suggesting an interpretation of the k's in terms of physiological parameters. Their original interpretation of the A's as represent-

ing the quantities of nitrogen initially in the water and fat components of the body, although supported by the reasonable values thus obtained for these components, was a rough approximation. More recent analysis of Behnke's nitrogen elimination data by Smith and Morales (4) has yielded a three term exponential expression:

$$Q_E = 172(1 - e^{-0.13t}) + 353(1 - e^{-0.028t}) + 255(1 - e^{-0.0079t})$$

Underwood and Diaz (124) have reported an interesting series of experiments in which a solution of radon was injected intravenously in dogs and the quantity exhaled over the next several minutes measured by means of a Geiger counter. The elimination was found to fit an exponential decay curve ($k = 0.66$ min^{-1}). They suggest that the elimination curve is actually a series of exponentially decaying functions, without attempting what might have been a fairly taxing theoretical analysis.

A unique expression for the quantity of nitrogen eliminated during breathing of oxygen has been obtained by Stevens and his collaborators (117). In 85 carefully performed experiments on 37 individuals they found that after an initial period of lung washout, the total nitrogen eliminated (Q_E) in time t from 1 to 20 minutes and in some cases up to several hours could be expressed as $Q_E = a\,t^b$, a and b being arbitrary constants. Although this frankly empirical expression enables one to report cumbersome nitrogen elimination data in terms of only two numbers, that is probably its greatest value, since there does not appear to be a theoretical basis for the expression used in terms of physiological mechanisms.

Jones has recently summarized the results of extensive experiments performed over the past several years (64); these have included studies with many different gases and of the uptake and elimination by the body as a whole as well as that confined to local regions. In his studies of inert gas exchange for the body as a whole, Jones has assumed expressions for the total quantity exhaled or absorbed up to time t, or in differential form, the time rate of these processes at any instant:

$$Q_E = A_1(1 - e^{-k_1 t}) + A_2(1 - e^{-k_2 t}) + \cdots + A_n(1 - e^{-k_n t})$$
$$dQ_E/dt = k_1 A_1 e^{-k_1 t} + k_2 A_2 e^{-k_2 t} + \cdots + k_n A_n e^{-k_n t}$$

His data fit such expressions to a satisfactory degree. For example, one of the best resolved curves yielded for nitrogen (exclusive of initial lung nitrogen) the following values in units of ml. for the A's and min.$^{-1}$ for the k's: $A_1 = 111$, $k_1 = 0.462$; $A_2 = 193$; $k_2 = 0.087$; $A_3 = 428$, $k_3 = 0.024$; $A_4 = 95$, $k_4 = 0.008$; $A_5 = 600$, $k_5 = 0.0025$.

Jones was able to derive physiological quantities from these empirical constants by assuming first, that each pair of constants is representative of a single tissue or group of tissues having similar perfusion characteristics, and second, that the constants themselves are related quite simply to these physiological parameters. A_i was then taken to denote the total quantity of the inert gas in question in a particular tissue or group of tissues after full saturation at the partial pressure in question, that is $A_i = C_I \lambda \lambda_i V_i$ where C_I is the concentration in inspired air during the saturation process. Similarly k_i was considered to

represent the perfusion rate of the tissue in terms of blood flow and tissue capacity for the inert gas, $k_i = F_i/V_i\lambda_i$. Although he presented no theoretical justification for these simplifications, Jones offered in evidence (i) the fact that among the gases nitrogen, krypton, helium, and xenon no appreciable differences were found in the respective k's obtained and (ii) that the total amounts of inert gas exchanging could be predicted from their solubility in body tissues. Such data are quite pertinent and the number of such experiments could with profit be extended. However, direct and conclusive proof is still to be obtained that the empirical constants (k) of Jones are in fact simply tissue perfusion rates.

The equations 62 and 63 of Copperman indicate that none of the A's and k's of an expression like that of Jones is in general defined exclusively by the parameters of a single tissue or group of tissues. It is probable, however, that Jones, by a combination of relatively insoluble gases and an initial period of hyperventilation, succeeded in achieving arterial concentrations of the inert gases which were practically constant over most of the experimental period. Under such special circumstances the general equation could be approximated by one in which each of the j terms could be referred to a single tissue or group of tissues. It is important to point out, however, that such an approximation is not generally permissible and would not be valid in the case of more soluble gases, *e.g.*, the anesthetic gases.

Inert Gas Exchange in the Individual Tissues or Organs

Early studies on this phenomenon as it occurs within the living body were few in number and confined to experiments in animals which could be sacrificed at intervals during the gas exchange process and the tissues in question analyzed for their content of the inert gas (24). The difficulties of handling and analyzing tissues without loss of these volatile constituents are obvious, and results must often be interpreted with caution.

The recent availability of radioactive isotopes of the elements has made possible a means for studying exchange phenomena in living tissues with a minimum of disturbance to the phenomena themselves. By means of suitably placed and properly shielded detecting instruments, the time course of the uptake or removal of a radioactive substance in particular parts of the body may be obtained if the emanations are sufficiently penetrating (64, 67, 113, 123, 127). Such technics, although admirably suited to the problems of local inert gas exchange, are not entirely free from objections. The problem of shielding the detecting device from radiation arising elsewhere than the region of interest is often a difficult one, and safety requirements place a definite limit on the dosages permissible in man. In addition, conversion from radiation intensity in the detecting instrument to concentrations or quantities in the tissues involve complicated calculations, assumptions, or the preparation of satisfactory models. Most investigators have not attempted to calculate absolute quantities involved, since, fortunately, the time constant of an exponential function is independent of the units in which the function is measured.

Inert gas exchange in the *brain* has been studied by both technics (24, 64, 71). Campbell and Hill (24) reported a very slow rate for the uptake of nitrogen by the brains of goats exposed to 4, 5, and 6 atmospheres of pressure, observing only 50% saturation in that organ at the end of an exposure lasting 3 to 5 hours (24). Kety, Harmel, Broomell and Rhode (71), employing a similar but perhaps more precise technic, obtained data indicating, on the contrary, practically complete equilibrium with the inspired tension of nitrous oxide within ten minutes. They were also able to demonstrate a very rapid loss of this gas from the exposed brain unless certain precautions were taken and thus probably to explain the low nitrogen contents found by Campbell and Hill. By means of radioactive krypton, Jones (64) has demonstrated a very rapid uptake of this gas by the human brain which yields two time constants of 1.4 and 0.35 $min.^{-1}$, respectively. On that basis one would expect a saturation of better than 98% at the end of 10 minutes, a prediction in good agreement with the results above obtained for nitrous oxide in dogs. This reviewer has made mathematical analyses of arterial and cerebral venous curves of nitrous oxide which confirm Jones' finding of a system of two components, possibly gray and white matter.

Campbell and Hill (24) also obtained results which suggest a slow uptake of nitrogen by the *livers* of goats exposed to increased ambient pressures. Their results are not in accord with expectation on the basis of the known rapid blood flow through the human liver (20) and the rapid clearance rate (0.4 $min.^{-1}$) of radioactive sodium from this organ obtained by Wechsler and associates (127).

The radioactive isotope of krypton ($Kr^{79,81}$) has been used to study the dynamics of inert gas exchange in the *extremities* of man (64, 113, 123) and animals (30). In studies on the normal human hand, Tobias and coworkers (123) found a three component uptake curve with average k's of 0.16, 0.021 and 0.0037 $min.^{-1}$ in a series of 9 cases. In one case Morales and Smith (92) obtained k's of 0.11, 0.058 and 0.02 $min.^{-1}$ for the hand. They calculated theoretical magnitudes for these constants on the basis of known and assumed reasonable values for the physiological parameters and obtained 0.17, 0.03 and 0.003 $min.^{-1}$. Although these theoretical constants agree only within an order of magnitude with the empirical values found by Morales and Smith it is interesting to note that they are in almost perfect agreement with the values found by Tobias. In a series of 7 studies at the popliteal region Tobias found two components with k's of 0.013 and 0.0018 $min.^{-1}$, respectively.

Three important tissues are included in these studies upon the extremities of man: muscle, fat and skin, not to mention bone and bone marrow. Some authors have attempted to relate the k's to these tissue components; in general, however, there are practically no studies on the uptake or removal of inert gases by pure tissues. Whitely and McElroy (128, 129) have reported denitrogenation curves on samples of blood draining *muscle* or *fat*. Although they have not attempted mathematical analyses of their curves there appear to be two exponential components in each, one of which is extremely slow. It is difficult to exclude the possibility of a continuous diffusion of nitrogen from the surrounding air into the tissues as an explanation of this slow component, since apparently

little precaution was taken to exclude it, and since others (4) have demonstrated that this phenomenon may occur in the presence of open wounds. Kety (67) has demonstrated an average clearance rate of 0.05 $min.^{-1}$ for Na^{24} ion injected into the human gastrocnemius muscle, but the relationship between this and the exchange rate of an inert gas has not yet been investigated.

The rate of inert gas exchange through the intact human *skin* was investigated by Behnke and Willmon (8) by means of an ingenious technic. They found, at room temperature and under a gradient of close to one atmosphere, that some 50 ml. of helium were able to diffuse through practically the entire cutaneous surface per hour. Nitrogen diffused through the skin approximately one half as rapidly as helium under similar circumstances. The cutaneous diffusion of these gases was quite sensitive to temperatures above 29° C. and increased rapidly so that at a temperature of 35° C. the total diffusion of helium was 160 ml./hr. By means of their data and the Fick principle these authors calculated a total cutaneous blood flow of 333 ml./min. at 35° C. This is probably an underestimate of the true value since they assumed complete diffusion equilibrium between the ambient helium tension and that in cutaneous venous blood, which is not likely to have occurred through the fairly gross distances involved. Several other gases have also been shown to diffuse through the intact skin (99).

Campbell and Hill (22) studied the uptake of nitrogen by the *bone marrow* and found it to be quite slow (25% of full saturation in one hour). Jones (64) has compared these results with his own obtained by a different method.

The uptake of radioactive krypton from the *stomach* and *intestinal tract* was qualitatively demonstrated by Tobias and his associates (123). This was found to occur fairly rapidly when the gas was introduced into the duodenum, but at a much slower rate from the stomach or colon.

Ferris, Molle and Ryder (39) have recorded several interesting examples of the time course of nitrogen concentration in blood from various sites in man during denitrogenation. These include analyses of arterial, internal jugular and antecubital venous blood and ascitic, cerebrospinal and synovial fluid. The nitrogen concentration in arterial and internal jugular venous blood fell rapidly while the clearance from cerebrospinal fluid was quite slow.

The accumulation and removal of some anesthetic gases from artificial subcutaneous and peritoneal pockets have been examined by one group (105). Cyclopropane was found to appear in and disappear from these pockets at a rate approximately twice that of ethylene. Since the ratio of exposed surface to volume in this situation is extremely small, this would be expected to be a diffusion limited process and as such the respective solubilities of the two gases in water should be the determining factor in the rate of exchange (equation 5). The results found are entirely in accord with the fact that this solubility for cyclopropane is twice that for ethylene (Table I).

The Effects of Changes in the Physiological Parameters on Inert Gas Exchange

Haggard (58) has reported the results of experiments designed to test the effects of varying certain cardiorespiratory factors on the uptake and elimination

of ethyl ether by the body. He showed that pulmonary ventilation was a factor of prime importance in the case of this very soluble gas. Underwood and Diaz (124) also showed that hyperventilation increases considerably the rate of elimination of radon, another soluble gas, while Stevens (117) demonstrated that the elimination of relatively insoluble nitrogen from the body, excluding the initial quantity present in the alveoli (43), was little affected by prolonged hyperventilation. All these findings are compatible with equation 45, the general expression for gas exchange at the lungs.

Exercise has been shown by Behnke and Willmon (7) to increase the rate of nitrogen elimination via the lungs, but largely during the first thirty minutes of the denitrogenation curve. This may probably be explained on the basis that nitrogen, being slightly soluble in blood, achieves a constant and low arterial concentration fairly early so that the subsequent elimination is a function largely of tissue parameters. Furthermore, muscular exercise probably does not increase the exchange processes in adipose tissue which constitute the bulk of the slower components and thus the latter part of the denitrogenation process is not accelerated. Locally, muscular exercise has been shown to increase the rate of gas exchange in the limbs (30) and the clearance of nitrogen (128) or Na^{24} (67) from the active muscles.

The local rate of exchange of inert gas or of sodium can be increased by warming the region (30, 39), by reactive hypermia (67), or by vasodilating drugs (30). Cooling the extremity or the administration of vasoconstrictors (30) has been shown to decrease these rates of exchange. These results may be explained by changes in effective blood flow through the tissue or by changes in the number of functioning capillaries with consequent effects on capillary surface and mean diffusion distance. It is quite difficult to differentiate among those effects which probably occur simultaneously and affect the exchange rate in the same direction.

There remains a wide gap at the present time between the theory of inert gas exchange at the lungs and tissues and empirical data with which to substantiate the numerous assumptions or to test the predictions of theory. Although it is apparent that the exchange processes are everywhere dependent on physiological and physical parameters, much remains to be done in relating those factors rigorously to the phenomena which may be observed in the expired air, the arterial or venous blood, or directly in the various tissues.

THE APPLICATIONS OF INERT GAS EXCHANGE TO MEDICAL PROBLEMS

The earliest interest in this general problem was stimulated by the astute demonstration of the remarkable physiologist, Paul Bert (9), that decompression illness was probably due to the release of dissolved gases from the tissues. The mass of theory and data which has been acquired since that time and which has amply substantiated that observation is well summarized in a number of recent excellent reviews (5, 25, 64).

The practical implications of these phenomena, however, have not been confined to decompression sickness. Their obvious dependence on physiological

factors soon led to numerous attempts to measure these factors by study of various aspects of inert gas exchange as a result of which a number of clinically useful methods have been developed for measurement of pulmonary ventilation, cardiac output, and blood flow through various organs.

A.) *Pulmonary Ventilation*

Examination of the general pulmonary exchange equation developed earlier (equation 45) reveals that for the special case of gases with very low solubility in blood the term containing C_v becomes negligible and

$$C_A = C_I(1 - e^{-(M_A/V_A)t}) \qquad \begin{matrix} \lambda << 1 \\ C_v << C_A \end{matrix} \tag{65}$$

In other words under such circumstances the lungs are acting like bellows, continuously diluting the inspired gas with the mid-inspiratory lung volume. This equation may readily be converted to one which treats ventilation as a discontinuous process (1a, 36, 44). After n breaths of nitrogen-free oxygen, the concentrations of nitrogen in alveolar and expired air would be as follows:

$$C_{A_n} = C_0\left(\frac{V_R}{V_R + V_F}\right)^n \tag{66}$$

$$C_{E_n} = \left(\frac{V_F}{V_F + V_D}\right) C_0\left(\frac{V_R}{V_R + V_F}\right)^n \tag{67}$$

where $C_I = O$, C_0 = initial nitrogen concentration, V_F, V_D, V_R are, respectively, effective tidal, physiological dead space, and functional residual volumes.

Darling, Cournand and Richards (36) include a correction for the small contribution of nitrogen to the alveolar gas from the mixed venous blood. This rate of nitrogen elimination is assumed to remain constant; it was determined empirically and found to vary with surface area of the body, averaging about 200 ml. in seven minutes for a normal adult (33, 35). Measurement of lung volume has been accomplished with the use of hydrogen (11, 88), nitrogen (15, 21, 28, 33, 35, 36, 44, 81) or helium (46, 89, 131) in one or several breaths.

It was soon realized that some unevenness existed even in normal pulmonary ventilation (11, 42) and that this became quite marked in patients with emphysema. Individual measurement of these ventilatory components from analysis of expired air has been accomplished independently by Robertson, Siri and Jones (101a) and by Fowler (44).

B.) *Cardiac Output*

Bornstein (16) was apparently the first to apply the principles of inert gas exchange to measurement of pulmonary blood flow. Starting with Zuntz' concept of gas exchange (133), he reasoned that the quantity of nitrogen eliminated in unit time during oxygen breathing should be proportional to the tissue—alveolar nitrogen gradient and to the pulmonary blood flow or cardiac output. He

devised a technic for measuring the nitrogen eliminated and the mean alveolar nitrogen tension by oxygen rebreathing from a rubber bag and calculating relative values for cardiac output in the same individual under different conditions compared to the resting state.

Krogh and Lindhard (77) soon pointed out that if Bornstein's determination were to be done within a time short enough to prevent the recirculation of blood through the lungs, it would then be possible to obtain an absolute value for pulmonary blood flow. They devised a technic for making measurements within a period of about 15 seconds and in this way hoped to avoid recirculation. Their method employed 10–25% nitrous oxide as the inert gas and consisted essentially in measuring the loss of this gas from the alveoli during an accurately determined period of breath-holding following its introduction into the alveoli by means of one or several deep breaths. By simultaneous measurement of oxygen loss from the alveolar gas they found an increase in oxygen consumption during the determination which they attributed to an increased pulmonary blood flow induced by the procedure itself. On the assumption that only pulmonary blood flow and not the mixed venous oxygen content was altered by the short procedure, they reduced the experimentally determined values for pulmonary blood flow to corrected values by the use of a factor which was the ratio of the experimental to the pre-experimental oxygen consumption. The latter was determined in the usual manner immediately before the nitrous oxide inhalation. Most of the resting values for pulmonary blood flow thus obtained were within 4 to 5 l./min. and showed approximately a four-fold increase during exercise. Krogh and Lindhard's method was followed by a great surge of methods and modifications, all of which utilized the principle of inert gas exchange (17, 18, 27, 78, 76, 82, 83, 84, 85, 86, 114, 116).

After an elaborate evaluation and modification of Bornstein's method (86), Marshall and Grollman developed a technic using ethylene (85), which Grollman subsequently modified by substituting acetylene (49, 51). This method is essentially that of Krogh and Lindhard except that the technic for determining the quantity of inert gas absorbed was improved by introducing a procedure of rapid rebreathing from a rubber bag. Thus the alveolar gas and the gas in the bag were in essential equilibrium throughout the procedure, permitting the calculation of gas removed from the alveolar-bag system to be made from samples taken at 15 seconds and 8 seconds later. The acetylene technic also incorporates the ingenious oxygen correction which Krogh and Lindhard introduced for minimizing the effect of the procedure *per se* on pulmonary blood flow. In 50 young adults, Grollman (51) obtained mean values of 3.87 l./min. for cardiac output (pulmonary blood flow) and 2.21 l./min./m.^{2} for cardiac index.

All the technics above are subject to certain errors and difficulties. The errors associated with analytical methods, correction for change in gas volume during absorption, etc. simply require their recognition and sufficient patience for satisfactory solution. The problem of obtaining representative samples of alveolar air is a real one although it is likely that by the technic of Marshall and Grollman satisfactory uniformity could be achieved in normal subjects. In patients with

pulmonary disease and uneven ventilation even this method might be open to some question. The problems of the uptake of the inert gas by the lung tissue itself and by its contained blood volume (as distinct from its blood flow) and the possibility of loss by diffusion into the other thoracic structures were all considered by Krogh and Lindhard but often overlooked by subsequent investigators. Even the former pair of workers, however, achieved only a partial solution to the problem by a short preliminary period of equilibration.

An important difficulty in these methods and the one which has been largely responsible for their disrepute up to the present time has been the fact that venous blood carrying some of the inert gas in question returns to the lungs before a single determination has been completed. Although most of the proponents of these methods have insisted that significant recirculation does not occur during their determination others have emphasized the extreme rapidity with which some venous blood returns to the heart. In the dog (59, 115) significant recirculation has been shown to occur in 15 seconds. Baumann and Grollman (2), by direct cardiac puncture in man, found the mixed venous blood concentration of acetylene to be almost 6% of the arterial in samples taken from 12 to 20 seconds after the first inhalation of that gas. In 25 to 30 seconds this had reached 12% and in 33 to 37 seconds, 18% of the arterial level. By less direct procedures Gladstone (47) and Adams and Sandiford (1) have found evidence for recirculation of blood containing acetylene in 10 and 20 seconds, respectively, and quite recently mixed venous blood samples obtained by cardiac catheterization (26) indicated that recirculation begins at about 8 seconds. These investigators (26), in an excellent critical evaluation of the Grollman method, have discovered a number of factors which together explain the discrepancy between that method and the direct Fick determination. They suggest several corrections which may permit the indirect method to yield valid results. Methods have been described recently (1, 48) in which more serious consideration has been given to this problem of recirculation. By means of one such method, Gladstone (48) found in seven individuals a mean cardiac output of 5.4 l./min. which is higher than the values found by Grollman and almost exactly the normal mean of 5.5 l./min. obtained by Cournand (32) by direct cardiac catheterization. With this latter technic for direct comparison and with newer and possibly more precise technics for gas analysis now available the near future will probably see further developments in the estimation of cardiac output and pulmonary blood flow by study of inert gas exchange at the lungs.

C.) *Measurement of Blood Flow to Organs and Tissues*

A technic for the determination of cerebral blood flow in man has recently been developed (64, 72) which makes use of the principles of inert gas (nitrous oxide) exchange at a tissue. The equation for the Fick principle applied to a single organ (equation 8) may be integrated to yield an expression for the mean concentration of inert gas in the organ at any time, u, measured from the beginning of inhalation of the inert gas:

$$(C_i)_u = \frac{F_i}{V_i} \int_0^u (C_a - C_{v_i})\, dt \qquad (68)$$

so that if C_i can be determined at any time and also the integrated values for concentration of the inert gas in arterial and venous blood from the organ, then the blood flow per unit volume of organ can be calculated. Without assuming instantaneous or even rapid diffusion equilibrium, it is nevertheless true, that if the time (u) over which the determination is made is sufficiently long, then, $(C_i)_u = \lambda_i(C_{v_i})_u$. At that time, then,

$$\frac{F_i}{V_i} = \frac{\lambda_i(C_{v_i})_u}{\int_0^u (C_a - C_{v_i})\, dt} \tag{69}$$

This principle can be applied to any organ for which it can be shown (i) that venous samples representative of all the venous drainage from that organ are obtainable, (ii) that there is negligible contribution to the venous blood sampled of drainage from other regions or organs than that under study, and (iii) that the experimental time period (u) is sufficiently long so that the inert gas tension in the venous blood sampled is representative of the mean tension in the organ itself. Evidence has been obtained (71, 72) that these conditions can be met in the case of the human brain. It is apparently also necessary (64) to point out that this principle does not require a constant arterial concentration and all the factors which go into that variable are conveniently eliminated by the simple expedient of measuring the arterial concentration throughout the determination and using the function so obtained in the calculation.

This technic has found successful application not only to measurement of human cerebral circulation (68) but also to the determination of coronary blood flow in dog (38) and man (10). Its application to other regions such as the extremities or the splanchnic area is beset with the difficulty that in such regions extremely slow components (resting muscle, fat) make the time of venous equilibrium impractically long.

In contrast to the technic above which yields a value for blood flow to an organ independently of diffusion factors are the methods which measure the time constants of uptake or clearance of inert gas (64) or other diffusible substances (67) in the various regions of the body. These depend first upon the assumption of constant arterial concentration of the substance in question, a condition which can be approximated by use of poorly soluble gases and hyperventilation (64) or local deposition of the tracer substance (67). In addition, however, in order to employ these time constants as quantitative measures of blood flow per unit volume of tissue it is necessary to assume instantaneous diffusion and the absence of arteriovenous shunts. Although such assumptions have been made and partially substantiated by Jones (64) who uses these constants synonymously with blood flow, it is not really necessary to take so bold a point of view. These uptake or clearance constants of diffusible substances measure a very important homeostatic function—the ability of the local circulatory and diffusion processes to supply substances to and remove them from the tissue cells. From the point of view of the local economy these overall constants are much more important than the quantity of blood flowing through the vessels.

D.) *Application in Anesthesiology*

Since the volatile anesthetics behave like inert gases in the body, the principles of this exchange both at the lungs and the tissues are of fundamental importance to this clinical specialty (3, 52, 69, 118). Whatever the mechanism whereby an anesthetic gas produces its effects, there is little doubt that the intensity of those effects is directly dependent upon the concentration of the anesthetic in the tissues of the brain. Haggard (56) has demonstrated an excellent correlation between anesthetic level and brain concentration of ether as reflected in the concentration in internal jugular blood. A rigorous test of any theory of inert gas exchange in the body is its ability to explain the known differences in rate of induction and recovery among the anesthetics and the observed effects of changes in the various physiological parameters.

In an earlier part of this review, an expression (equation 52) was derived for the concentration of an inert gas in a tissue in terms of the factors which determine it. Thus cerebral concentration is dependent on cerebral blood flow per volume of brain, on factors of diffusion and solubility, and upon the past history of the arterial concentration of that gas. On the basis of recent experience (64, 66, 71), it may be stated that the factors of flow and diffusion in this organ are normally such as to introduce a time lag of the order of 10 minutes for the achievement of complete equilibrium between all parts of the brain and a certain arterial concentration of inert gas. It may be concluded, therefore, that the arterial concentration of anesthetic is the important determinant of rate of induction or recovery where this rate is slow (as in the case of ether); but where induction or recovery is rapid (as with ethylene), cerebral blood flow assumes considerable importance in addition to arterial concentration. Obviously, also, if the cerebral parameters are kept reasonably constant, as they would tend to be in a normal patient in the care of a competent anesthetist, the rise in brain concentration will depend almost entirely upon the shape of the arterial concentration curve.

In the section on theory, an expression was derived (equation 55) which described the alveolar concentration of a foreign gas as a function of time. Since one may assume, without serious error in the case of a normal individual, that the arterial inert gas tension is equal to that in the alveoli, this same equation also describes the shape of the curve of inert gas tension in arterial blood. It is seen that the alveolar curve appears as the sum of two terms, the first representing the process of lung washout, or the initial dilution of the inert gas by the residual gas and the pulmonary blood flow, the second representing the contribution of gas by the recirculating mixed venous blood. Since k_1 is quite large (never less than $\frac{M_A}{V_A}$ and therefore at least 1), this term represents an initial rapid rise toward some fraction of the inspired partial pressure. The remainder of the rise toward the inspired tension of inert gas in governed by the mixed venous blood tension and is a much slower process depending on blood flow, diffusion, inert gas solubility, and volumes of all the tissues of the body.

Thus the alveolar and arterial tension curves for any inert gas inspired at a constant partial pressure have three distinct phases (69): (i) an initial rapid rise occupying 3 minutes or less, (ii) a sharp inflection and (iii) a progressive slow rise reaching the inspired tension only after a period of hours. The rapidity of induction or recovery peculiar to each anesthetic is determined by the fraction of complete saturation or desaturation achieved in the initial rapid rise or fall of the arterial curves and this is given by the coefficient A_1 in equation 55. It is apparent that A_1 is quite sensitive to the solubility of the gas in blood and varies inversely with it. From the known values for λ, assuming normal values for M_A and F_p of 6 l./min. each, and neglecting diffusion lag across the pulmonary membrane, it is possible to estimate the fraction of complete saturation of arterial blood with inspired gas achieved within the first few minutes for each anesthetic, as follows (in order of decreasing value): ethylene 87%, nitrous oxide 67%, cyclopropane 68%, divinyl ether 42%, chloroform 12%, and ethyl ether 6%. This order is also one of decreasing rapidity of induction or recovery with each of the anesthetics named. Data have been reported for ether (56, 102), cyclopropane (100, 101), nitrous oxide (66), divinyl ether (103) and ethylene (95) which qualitatively confirm these predictions from the theoretical equation. There is need, however, for more such data obtained with a constant inspired tension, for all the anesthetics.

It is also possible to predict from equation 55 the effect of variations in the physiological factors concerned on the shape of the arterial curve. Increased respiratory minute volume will increase the height of the initial rise (A_1), especially where pulmonary blood flow or blood solubility is large, and will increase the rate of the whole arterial curve (k), especially where blood flow or solubility are low. This in general confirms the predictions and observations of Haggard (55, 58). Increased pulmonary blood flow will decrease the initial rise especially for soluble gases but will speed the rate of rise of the whole curve and thus shorten the time necessary for complete saturation or desaturation. Increased adiposity will slow the latter portions of the arterial curve especially for the highly fat soluble gases but will not significantly affect the initial phase of induction or recovery. For the effect of some of these variables see Figures 1, 2, 3.

In general, although theory seems capable of explaining many clinically observable facts, the applications of the principles of inert gas exchange to anesthesiology manifest the same tendency which is seen throughout all aspects of the inert gas exchange problem—a tendency for theory to advance far beyond empirically obtainable evidence. It is to be hoped that with the great number of physical technics now available some advance may be made in our comprehension of these phenomena, for intimately associated with them are the basic functions of the circulatory and respiratory systems.

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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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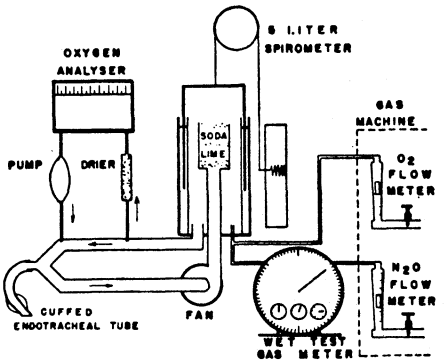

FIG. 1. THE ARRANGEMENT OF APPARATUS USED FOR DETERMINING THE NITROUS OXIDE UPTAKE RATE

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

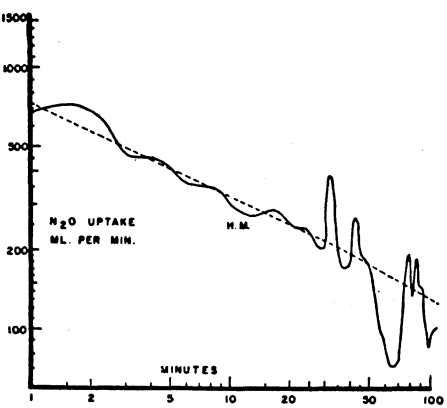

FIG. 2. AN EXAMPLE OF THE OSCILLATIONS IN UPTAKE RATE DUE TO VARIATIONS IN THE INSPIRED CONCENTRATION OF N_2O IN ONE PATIENT DURING 100 MIN. OF ANESTHESIA

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.

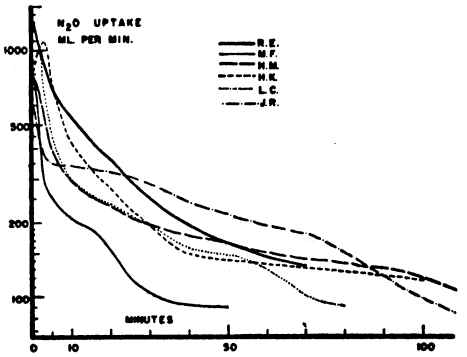

FIG. 3. THE RATE OF UPTAKE OF N_2O BY SIX SUBJECTS DURING ANESTHESIA WITH 80 PER CENT N_2O AND 20 PER CENT O_2.

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 $\dot{N}_2O$ 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.

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

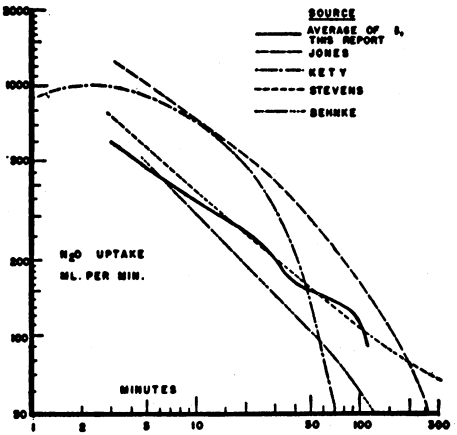

FIG. 4. COMPARISON OF THE AVERAGE OF THE CURVES OF N_2O UPTAKE OF SIX PATIENTS, DISREGARDING BODY SIZE, WITH THE RATE OF UPTAKE OF N_2O AS PREDICTED BY VARIOUS METHODS

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 $\left(30 \times \frac{\text{arterial } N_2O \text{ tension}}{\text{inspired } N_2O \text{ tension}}\right)$.

[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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