THE DETERMINATION OF CEREBRAL BLOOD FLOW IN MAN BY THE USE OF NITROUS OXIDE IN LOW CONCENTRATIONS[1]

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Quantitative measurements of the total blood flow to the brain of man have not previously been reported and the few procedures which have been used for the purpose of obtaining relative or qualitative values have recently been subjected to considerable criticism (1).

The method to be described is based on the principle that the rate at which the cerebral venous blood content of an inert gas approaches the arterial blood content depends upon the volume of blood flowing through the brain. Certain aspects of this principle were recognized by Haggard (2) who postulated that the rate at which an anesthetic gas is taken up by the brain depends in part on the rate of blood flow to that organ, and similarly by Ferris, Molle and Ryder (3) who stated that the clearance of nitrogen from the brain during the inhalation of 100 per cent oxygen may be markedly influenced by the magnitude of cerebral blood flow. As far as we are aware, however, the principle has not previously been subjected to mathematical analysis and applied to actual measurements of cerebral blood flow in animals or man. The experiments described in the preceding report (4) afforded an opportunity for calibrating this procedure against direct measurements of cerebral blood flow and thus for refining the technical and theoretical factors to a degree that would not otherwise have been possible.

METHODS. The specific substance which is employed is not of consequence provided that it is physiologically inert in the concentrations employed, capable of diffusing rapidly across the blood-brain barrier, and susceptible of accurate analysis in the blood. It need not even be a gas if it meets all these requirements. In the present experiments nitrous oxide has been employed although other gases may be found to be more suitable. Radioactive gases offer certain unique advantages and their use is being considered.

In the animal experiments the inhaled gas consisted of 40 per cent nitrous oxide in oxygen which was inhaled through the inspiratory valve attached to the tracheal cannula. In the early experiments on man 15 per cent nitrous oxide and 85 per cent oxygen was employed and was inhaled through the inlet tube of an anesthesia mask. Because the presence of nitrogen in the blood introduces cer-

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tain difficulties which will be discussed later, its effects were minimized by the inhalation of 100 per cent oxygen for a period of at least 20 minutes before each determination. It is realized that the high oxygen tensions are likely to alter cerebral blood flow but these experiments were designed to aid in the development of the method rather than to establish normal values. In later experiments a mixture of 15 per cent nitrous oxide, 21 per cent oxygen and 64 per cent nitrogen was employed and the analytical error due to nitrogen was eliminated by the calculation discussed below. The 15 per cent nitrous oxide has few detectable physiological effects in most normal subjects; some individuals may experience slight dizziness or cutaneous numbness after breathing the mixture for 10 to 15 minutes. Even 40 per cent nitrous oxide has no characteristic effect on the cerebral blood flow of anesthetized monkeys as measured by the bubble flow meter.

Arterial blood was obtained by femoral puncture in man and from a femoral or carotid cannula in animals. Cerebral venous blood was collected from a metal cannula in the torcular Herophili in dogs, from both internal jugular bulbs in monkeys, and from a needle in the right internal jugular vein in man using the technique described by Myerson et al. (5). In a typical experiment in man, 19 gauge needles fitted with obturators were inserted into the femoral artery and internal jugular vein after infiltration with procain solution. The obturators were removed and each needle was connected to a manifold by means of annealed silver tubing of 1 mm. bore. Simultaneous arterial and venous samples were then obtained at intervals during 20 minutes of inhalation of the nitrous oxide-oxygen mixture. In practice it should be necessary to take only 4 such pairs of samples at 2, 4, 6 and 10 minutes. Blood samples were taken into 10 cc. syringes wetted with heparin and containing 1 cc. of mercury. These syringes were fitted with a short length of rubber tubing and a clamp and after the samples had been obtained the capillary of the tip was filled with mercury. They were then kept with the tips up in a refrigerator so that the blood was entirely sealed between mercury and glass. Analyses for oxygen and carbon dioxide were performed within 3 hours and for nitrous oxide within 24 hours. The samples were analyzed in the Van Slyke-Neill manometric apparatus by the method of Orcutt and Waters (6) with certain modifications: the blood was transferred from the syringe to the chamber of the manometric apparatus over mercury to avoid all contact with air and the reagents used were kept free of air over mercury. For the nitrous oxide analyses, carbon dioxide and oxygen were absorbed simultaneously by the addition of 2 cc. of the usual hydrosulfite-anthraquinone reagent and where 15 per cent nitrous oxide was employed 2 cc. of blood were analyzed. Analyses were done in duplicate and consistent checks within 0.05 vol. per cent were obtained with the modified technique. In these analyses nitrous oxide is not determined as such but as residual gas after absorption of oxygen and carbon dioxide. Although the error due to nitrogen can be removed by calculation, in the first 3 experiments on man and in all the animal experiments denitrogenation was employed beforehand and the nitrous oxide made up in oxygen to render the error due to nitrogen negligible.

Derivation of a formula for cerebral blood flow. The familiar Fick formula applied to a single organ like the brain may be expressed as:

$$CBF = \frac{100\ Q_t}{(A - V)t} \tag{1}$$

where CBF represents cerebral blood flow expressed as cc./100 grams of brain/minute.

Q_t represents the quantity of oxygen, expressed as cc./100 grams of brain, consumed in time t.

A and V represent arterial and cerebral venous blood oxygen contents as vol. per cent.

t represents any time interval in minutes.

Although the same basic formula is applicable to any substance which is removed from the blood by the brain, in the case of inhalation of nitrous oxide the arterial and venous contents of that gas both start from zero and increase with

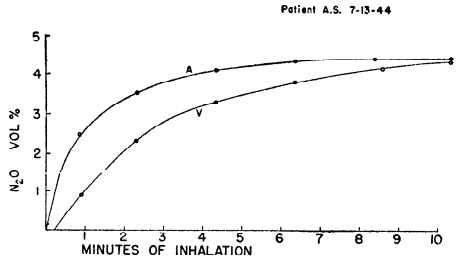

Fig. 1. Arterial and internal jugular blood concentrations of nitrous oxide in a human subject during the inhalation of 15 per cent nitrous oxide in oxygen.

time, the arterial more rapidly than the venous. The course of a typical experiment is shown in figure 1. Obviously A-V is not a constant but rises rapidly to a maximum in the first 30 seconds then decreases progressively. The amount of gas lost per 100 cc. of blood in passing through the brain cannot be calculated simply from $(A\text{-}V)t$ as with oxygen, but is represented by the area between the curves A and V from zero time to time t, i.e. $\int_0^t (A\text{-}V)\ dt$. Equation 1 then becomes:

$$CBF = \frac{100\ Q_t}{\int_0^t (A - V)dt} \tag{2}$$

Where Q_t represents the quantity of N_2O (expressed as cc./100 grams of brain) taken up by the brain from the beginning of inhalation to time t.

A and V represent the N_2O content of arterial and cerebral venous blood expressed as vol. per cent.

The quantity $\int_0^t (A\text{-}V)\ dt$*:* This may be ascertained by direct serial determina-

tions of arterial and venous N_2O contents (as has been done in fig. 1), but if the manner in which $(A\text{-}V)$ varies with time could be found, it could be calculated on the basis of fewer analyses. Since the rate of change of $(A\text{-}V)$ at any specific time is determined by the rate of uptake of N_2O by the brain, which is in turn a function of the magnitude of $(A\text{-}V)$ at that time, $(A\text{-}V)$ should be an exponential function. Plotting $(A\text{-}V)$ semi-logarithmically against time (figs. 2, 3, 4) it is

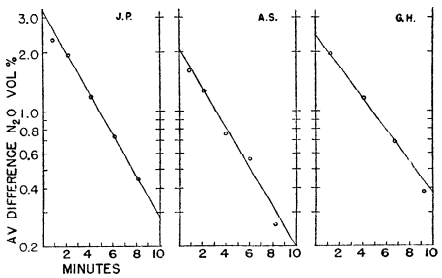

Fig. 2. Cerebral arteriovenous nitrous oxide differences in 3 patients, plotted semi-ogarithmically against time of inhalation.

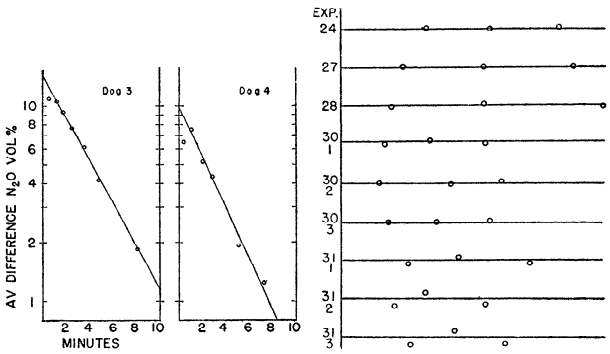

Fig. 3 Fig. 4

Fig. 3. Cerebral arteriovenous nitrous oxide differences in 2 dogs, plotted semi-logarithmically against time of inhalation.

Fig. 4. A representation of the semi-logarithmic plot of the cerebral arteriovenous nitrous oxide difference against time in 9 determinations on monkeys. For convenience the lines have been tilted so that they lie parallel but P and k are given for each line in table 1.

seen that in each case the points fall closely upon a straight line. This confirms the expected exponential nature of the arteriovenous nitrous oxide difference which may now be expressed in the usual mathematical form:

$$(A\text{-}V) = Pe^{-kt} \tag{3}$$

P represents the theoretical value of $(A\text{-}V)$ at zero time and may be obtained from the semi-logarithmic graph by extrapolation to zero time. k which repre-

sents the slope of the straight line semi-logarithmically plotted is obtained from intercepts of the line as follows:

$$k = \frac{\log (A - V)_{t_1} - \log (A - V)_{t_2}}{(t_2 - t_1) \log e} \tag{4}$$

Integrating equation 3 from times 0 to t results in the following expression:

$$\int_0^t (A - V)\, dt = \frac{P}{k} (1 - e^{-kt}) \tag{5}$$

Since the arterial and venous content of N_2O are zero at the beginning of the inhalation, $(A\text{-}V)$ for N_2O does not start immediately at a maximal value but rather rises sharply from zero to a maximum in the first half minute and then decreases exponentially. This divergence from a true exponential form is small and readily corrected for. As seen in figure 5, the actual integral is less than the integral of the simple exponential $OPRS$ by the small triangle NOP the area of

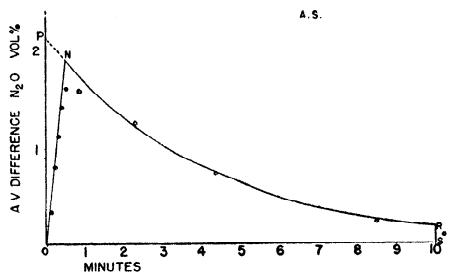

Fig. 5. Cerebral arteriovenous nitrous oxide differences in the subject of figure 1 plotted againt time. Open circles represent values obtained by analysis, closed circles represent values obtained in the first minute from the extrapolated arterial and venous curves. The closeness with which the calculated integral (*ONRS*) fits the experimental values is shown.

which is equal to $P/4$. Thus by subtracting this from the integral derived in equation 5 the true integral is closely approximated (without this correction the error is only about 6 per cent, when corrected the error becomes even smaller). Thus the corrected integral is obtained:

$$\int_0^t (A - V)\, dt = \frac{P}{k} (1 - e^{-kt}) - \frac{P}{4} \tag{6}$$

The closeness with which this calculated integral fits the data can be seen in figure 5. In the three human experiments (G. H., A. S., and J. P.)[2] this calcu-

[2] In these three experiments 8 pairs of samples were taken in order that a valid comparison could be made between the graphic and calculated integrals. The remaining 13 determinations on human beings were based upon the simplified procedure using only 4 pairs of samples. In many experiments there is a tendency for the A-V curve to deviate slightly from that of a simple exponential in the region t = 10 minutes. This is evidence that there is more than one nitrous oxide absorbing phase in the brain. This deviation, however, is slight and it occurs in a region where its effect on the entire integral is negligible, so that there is consistently good agreement between values for the integral obtained graphically and those calculated from the exponential formula (col. 4 and 5, Table 2).

lated integral is 104 per cent, 101 per cent and 104 per cent of the graphic integral respectively.

The quantity Q_t: The amount of nitrous oxide absorbed by the brain from the beginning of inhalation to time t is calculable by assuming that the mean brain tension of the gas is equal to its tension in the blood leaving the brain. If this assumption were correct then:

$$Q_t = V_t \ S \tag{7}$$

Where V_t = nitrous oxide content of cerebral venous blood as vol. per cent at time t.

S = ratio of solubilities of N_2O in brain and blood, i.e., $\frac{\alpha \text{ brain}}{\alpha \text{ blood}}$ where solubility is expressed as cc. N_2O/cc. blood and cc. N_2O/gram brain at 760 mm. N_2O tension and 38°.

Although the assumption that the mean brain tension of nitrous oxide is equal to the cerebral venous tension is only approximately true in the first few minutes of inhalation, it becomes increasingly valid as equilibrium progresses to completeness. It is now pertinent to determine the time after which the assumption is sufficiently valid that its use introduces no appreciable error into the calculation. By substituting in equation 2 the values for Q_t and $\int_0^t (A\text{-}V)dt$ obtained in equations 6 and 7 respectively, and rearranging, the following relation appears:

$$\frac{CBF}{S} = \frac{100 \ V_t}{\frac{P}{k}(1 - e^{-kt}) - \frac{P}{4}} \tag{8}$$

Throughout the course of 10 or 20 minutes of nitrous oxide inhalation the left hand member of equation 8 should remain constant whence the constancy of the right hand member constitutes a test for the validity of the assumption expressed in equation 7. These calculations have been made in the case of the three detailed human experiments and in the two experiments on dogs and the results are presented in figure 6. It is seen that in each case the quantity $\frac{100 \ V_t}{\frac{P}{k}(1 - e^{-kt}) - \frac{P}{4}}$ decreases somewhat throughout the early periods of inhalation but appears to reach a fairly constant value in about 10 minutes, after which it decreases only a few per cent over protracted periods. From this it is inferred that mean brain tension of nitrous oxide at first is somewhat lower than the corresponding cerebral venous tension but that after 10 minutes they have come sufficiently close to make the assumption of equation 7 sufficiently valid for present purposes.[3]

[3] It is now possible to calculate for each of the earlier V_t's a factor (r) by which it must be multiplied in order that the quantity $\frac{100 \ V_t \ r}{\frac{P}{k}(1 - e^{-kt}) - \frac{P}{4}}$ may at all times be equal to the

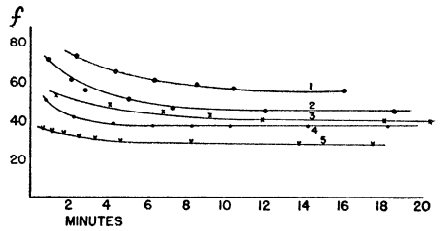

Fig. 6. The function $\left[\frac{100\ V_t}{\frac{P}{k}(1 - e^{-kt}) - \frac{P}{4}}\right]$ plotted against time for experiments on 2 dogs and 3 human subjects. After 10 minutes it is practically constant in each case. Curve 1—patient A. S., 2—dog 4, 3—patient G. H., 4—patient J. P., 5—dog 3.

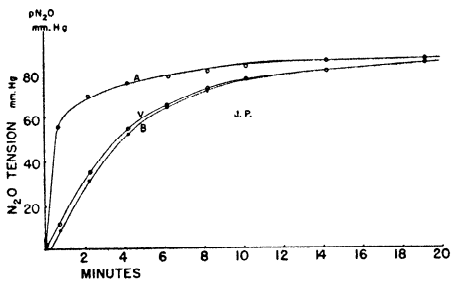

Fig. 7. Curves showing the arterial and internal jugular blood tensions and the mean brain tensions of nitrous oxide in a human subject during inhalation of 15 per cent nitrous oxide in oxygen. Values for mean brain tensions were calculated as explained in the text.

Equation 2 with proper substitutions from equations 6 and 7 now becomes the working formula for calculating cerebral blood flow by this method:

$$CBF = \frac{100\ V_t S}{\frac{P}{k}(1 - e^{-kt}) - \frac{P}{4}} \tag{9}$$

where t is 10 minutes or greater.

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final constant value of $\frac{100\ V_t}{\frac{P}{k}(1 - e^{-kt}) - \frac{P}{4}}$. This factor ($r$) is then the ratio of brain nitrous oxide tension to venous nitrous oxide tension and from it the mean brain tension at each time may be calculated. In figure 7 may be seen the curves for arterial, internal jugular and mean brain tensions of N_2O for one of the human subjects calculated in this manner. The rate at which mean brain tension of N_2O approaches that in internal jugular blood is a function of cerebral blood flow and, for comparable blood flows, an index of the "vascularity" of that particular brain, the latter term representing the proportion of vascular diffusion surface to weight of brain tissue. Such an index may have some clinical significance.

The necessary data are obtained in human subjects as follows: simultaneous arterial and internal jugular blood samples are obtained at approximately 2, 4, 6 and 10 minutes following the onset of inhalation of the nitrous oxide gas mixture. The times of taking the samples are accurately measured and the respective arteriovenous nitrous oxide differences are plotted semilogarithmically against time. A best fitting straight line through the earliest three points (where the arteriovenous differences are sufficiently large that analytical error is inappreciable) determines P and k. The t in equation 9 is the time of the last venous sample and should be 10 minutes or longer.

The solubility factor S remains to be considered. It has not yet been possible to determine this factor to a great degree of accuracy. Early attempts to determine it by equilibration of brain tissue homogenates *in vitro* yielded the unexpected finding that the apparent solubility of nitrous oxide in brain decreased significantly with the time of equilibration at 38°. It was concluded that changes take place in brain tissue so treated which alter its capacity for absorbing nitrous oxide and that reliable determinations could be carried out for the present only *in vivo*. For this two different techniques have been employed. In one, a representative sample of brain tissue was removed anaerobically from an anesthetized dog after a protracted period of nitrous oxide inhalation and its content of this gas determined and compared with that of torcular blood obtained simultaneously. The obvious technical difficulties of this procedure have not yet been fully mastered; the values for S thus obtained in 4 different animals were 1.0, 1.0, 1.3 and 1.4, respectively.

Another method is presented in the direct measurement of cerebral blood flow in the monkeys used in the experiments just reported (4) simultaneously with the administration of nitrous oxide and the collection of the necessary blood samples. From the data thus secured S may be calculated by a rearrangement of equation 8:

$$S = \frac{CBF\left[\frac{P}{k}(1 - e^{-kt}) - \frac{P}{4}\right]}{100\ V_t} \tag{10}$$

The values for S thus obtained are presented in table 1. The fairly wide range of values found is probably not evidence that the solubility of nitrous oxide in different brains of the same species varies widely (there is as wide a variation in different determinations on the same animal as between different animals) but is indicative of certain technical difficulties which have not yet been eliminated. The average value for S thus obtained (1.3) compares well with that obtained by the other quite different method in dogs and has been used as a first approximation in the calculations of cerebral blood flow here presented. Since it is hardly likely that the solubility coefficient of nitrous oxide in human brain would vary significantly in the same individual in the course of an hour or so, the method in its present form is applicable to the quantitative measurement of changes in cerebral blood flow induced by various procedures, and if the further assumption that this coefficient will not vary appreciably from one brain to another is tenable

the method may be used to study deviations in the blood flow in different pathological states. Although the true value for S is not expected to lie far from the tentative value of 1.3, the precise evaluation of the absolute cerebral blood flow in man must await more accurate determination of this factor and a knowledge of its variability.

A critical examination of the method here proposed brings to light several considerations which must be evaluated before the procedure can be regarded as yielding absolute and reliable figures for total cerebral blood flow in man. A discussion of some of these seems pertinent:

1. The derivation assumes that the brain is a homogeneous system with respect to blood flow and nitrous oxide capacity, yet the presence of at least two discrete tissue masses in the brain (white and grey matter) and the cerebrospinal fluid raises a question as to whether such an assumption is warranted. To ascertain the effects of differences in blood flow and in nitrous oxide capacity in different regions of the brain, theoretical biphasic and triphasic schemata have been set up representing variations in rates of blood flow, weights of tissue and nitrous oxide capacity of greater magnitude than are likely to occur in reality. Calculations on these schemata reveal the following: *a*. Where the variations among the phases are considerable the combined (A-V) is no longer a simple exponential function and its rate of decrease (k) instead of remaining constant diminishes with time. The fact that in the experiments which have thus far been performed in animals and man the values for (A-V) conform reasonably well to simple exponential functions is an indication of the relative homogeneity of these brains. *b*. Notwithstanding their more complex nature if these (A-V) functions of heterogeneous systems are treated as simple exponentials by the use of a best fitting straight line through their semi-logarithmic plot at 2, 4 and 6 minutes, values for P and k thus obtained yield a calculated flow within 15 per cent of the true flow. *c*. Even for the most heterogeneous systems the mean flow is accurately calculable by using the true integral for A-V instead of the integral based on the simple exponential. Experimentally such a true integral could be closely approximated by more frequent blood samples or by the continuous withdrawal of blood from the artery and vein at a slow constant rate over a period of ten minutes. Unless subsequent studies yield results markedly different from these early experiments, such procedures seem unnecessary and the brain can for practical purposes be considered homogeneous.

2. In order to obtain true cerebral blood flow by this method it must be assumed that the blood samples from the right internal jugular vein represent mixed cerebral venous blood. The anatomical fact that the torcular in man is often incomplete does not necessarily imply that blood from one jugular is not a representative sample. Riggs (7) has found in an examination of 25 autopsy specimens that torcular blood is distributed both to the right and left lateral sinuses in 15, usually with a preponderance to the right, in 9 cases the torcular communicated entirely with the right and in one case entirely with the left lateral sinus. Gibbs and Gibbs (8) have found in a study of flows in 24 autopsy specimens that on the average 95 per cent of right lateral sinus blood is derived from

the superior sagittal sinus while 84 per cent of the left lateral sinus blood comes from this source. Thus even if the blood of the superior sagittal sinus were entirely different from that in the other channels drained by the lateral sinuses (and there is no evidence that such is the case) the bloods of the two internal jugular veins would still be quite comparable. The final solution to this question awaits the simultaneous determination of cerebral blood flow by the present method using blood from each internal jugular vein, but regardless of how the question is decided it is still true that the method yields a measurement of blood flow per unit weight of brain tissue for that part of the brain which is represented by the venous samples.

3. The values for S may not be the same for brain and blood in different pathologic states. Although this may be true it seems reasonable that S by its dependence on gross physico-chemical structure would hardly vary as widely as cerebral blood flow and oxygen consumption. Furthermore it may be possible by employing a radioactive gas with penetrating gamma radiation to ascertain the value for S under varying *in vivo* conditions.

4. There are two sources of error peculiar to the specific gas and the analytical method employed and not applicable to the general principles involved. Even 15 per cent nitrous oxide is not perfectly devoid of physiological effects (vide: its use as an analgetic (9)) while the fact that the analysis measures only residual gas after oxygen and carbon dioxide absorption necessitates a correction where the usual atmospheric tensions of nitrogen are present. Both of these considerations would be eliminated by a proper choice of gas and analytical technique but until these are available, the error due to nitrogen may be eliminated by the following calculation:

If a subject breathing room air begins to breathe a mixture of 21 per cent oxygen, 15 per cent nitrous oxide and 64 per cent nitrogen and if the slight difference in diffusion rates of nitrogen and nitrous oxide be neglected then at all times the total partial pressure of inert gas in arterial and venous bloods should be the same:

$$pN_2O + pN_2 = 570 \text{ mm.} \tag{11}$$

where 570 represents the total partial pressure of inert gas in alveolar air at standard barometric pressure. The observed inert gas content in vol. per cent (V_0) will be the sum of the contents of nitrous oxide and nitrogen:

$$V_{N_2O} + V_{N_2} = V_0 \tag{12}$$

but tension and content of a gas in blood bear the following relation:

$$p = cV \tag{13}$$

where $c = \dfrac{760}{100\alpha}$

whence equation 11 becomes:

$$c_{N_2O}\, V_{N_2O} + c_{N_2}\, V_{N_2} = 570 \tag{14}$$

and solving simultaneous equations 12 and 14 we obtain:

$$V_{N_2O} = \frac{c_{N_2} V_0 - 570}{c_{N_2} - c_{N_2O}} = \frac{585\ V_0 - 570}{567} \tag{15}$$

the numerical values for c having been calculated from solubility coefficients appearing in the literature (10, 11) ($\alpha^{38°}_{N_2O} = 0.416$, $\alpha^{38°}_{N_2} = 0.013$). In order to obtain V_0 from the manometric reading on the blood gas analysis apparatus it is necessary to use a factor which lies between the factor for nitrogen and nitrous oxide and depends on the proportion of each gas in the mixture. By a method of suc-

TABLE 1

Data from 9 experiments on monkeys including values for S and a comparison between directly measured and calculated cerebral blood flows

EXPT.	P	k	$t_{\frac{1}{2}}$	V_3 VOL. % N_2O	$\frac{100V_3}{\frac{P}{k}(1-e^{-kt}) - \frac{P}{4}}$	S	CEREBRAL BLOOD FLOW CC./100 G./MINUTE	
							*Direct	Calculated†
			min.					
24	12.0	0.182	8.8	13.9	28	1.3	37	36
27	12.4	0.198	9.0	13.4	27	1.6	42	35
28	8.7	0.102	16.6	11.5	17	1.0	17	22
30 I	8.1	0.154	6.1	9.5	32	1.4	46	42
30 II	7.6	0.287	5.2	8.9	48	1.3	60	62
30 III	4.7	0.089	7.1	7.6	23	1.3	31	30
31 I	14.6	0.266	6.2	11.3	28	1.4	38	36
31 II	7.5	0.230	4.9	10.4	51	1.5	76	66
31 III	8.3	0.138	7.0	9.3	26	1.2	32	34
						1.3		

* Direct measurements were obtained by use of the bubble flow meter (12).

† Calculated measurements were obtained by means of the proposed method using the average value of 1.3 for S obtained from these data as described in the text.

cessive approximations and making use of equation 15 the relationship between V_0 and V_{N_2O} has been determined and is expressed in the regression:

$$V_{N_2O} = 1.03\ V_0 - 1.07 \tag{16}$$

Where V_0 is the observed inert gas content in vol. per cent obtained from the manometric reading by using simply the factor for N_2O.

Thus by the use of equation 16 a gas mixture containing atmospheric tensions of oxygen may be employed with 15 per cent nitrous oxide and 64 per cent nitrogen and from the manometric reading of residual gas the vol. per cent of nitrous oxide may be calculated. In 8 of the subjects (table 2) such a mixture was used and the nitrous oxide blood concentrations calculated by equation 16.

The final test of the mathematical analysis and the theoretical assumptions involved here lies in a comparison of this method with direct determinations of cerebral blood flow. Making use of this method in the form which has been suggested for man (equation 9) and employing only 3 pairs of blood samples for each

TABLE 2

Cerebral blood flow and cerebral oxygen consumption in eleven patients determined by the proposed method

SUBJECT	DIAGNOSIS	t	$\int_0^t (A-V)_{N_2O}\,dt$		V_t N_2O	$A-V$ O_2	CEREBRAL BLOOD FLOW	CEREBRAL O_2 CONSUMPTION
			by formula	graphically				
		min.			*vol. %*	*vol. %*	*cc./100 g./min.*	*cc./100 g./min.*
*G. H. BF 44	Multiple sclerosis	11.92	11.1	10.7	4.43	6.2	52	3.2
*A. S. BF 26	Essential hypertension	10.30	7.5	7.4	4.26	4.0	74	3.0
*J. P. BF 29	Gastric neurosis	10.22	11.4	11.0	4.27	10.2	50	5.1
W. G. WM 23	Normal	10.50	9.3	8.4	4.72	6.6	66	4.4
J. F. BM 46	Essential hypertension	10.25	7.9	8.1	4.49	4.6	74	3.4
V. L. WM 42	Hypochromic anemia	9.97	10.0	9.7	4.30	5.3	56	3.0
Repeat 15′ later		10.03	8.7	8.9	3.81‡	5.5	57	3.1
L. F. WF 30	Chronic P.I.D.	8.00	6.0	5.5	2.73	6.2	60	3.7
Repeat 15′ later		8.00	10.5	9.8	4.13‡	6.9	52	3.6
P. G. WM 55	Gastric neurosis	9.90	†	8.70	2.71	7.5	41	3.0
Repeat 15′ later		9.94	†	3.86	1.24‡	7.6	42	3.2
J. T. WM 35	Convalescent monarthritis	9.87	7.5	7.5	4.31	5.3	75	3.9
R. O. BM 20	Convalescent pneumonia	10.15	†	5.5	3.01	4.7	71	3.3
Repeat 15′ later		10.05	†	3.6	2.16‡	5.3	78	4.1
L. H. WF 20	Convalescent rheumatic fever	9.92	8.3	8.0	4.29	7.0	67	4.7
Repeat 15′ later		10.03	6.9	6.7	4.10‡	5.7	77	4.4
Mean¶						6.2	62	3.7
"Normal" values for monkey obtained by means of the bubble flow meter, 11 observations (4), mean						8.0	47	3.7

* In the first 3 determinations the gas mixture employed was 15 per cent nitrous oxide and 85 per cent oxygen and was preceded by 30 minutes' inhalation of 100 per cent oxygen. The remaining determinations were made with a mixture containing 15 per cent nitrous oxide, 21 per cent oxygen and 64 per cent nitrogen and the subject breathed room air before the determination.

† In these two patients a poorly fitting mask produced an eccentric curve of arterial nitrous oxide content with the result that the AV difference was not exponential and the formula could not be used. It was still possible to obtain the integral graphically.

‡ Where determinations were repeated on the same individual 15 minutes later there was still a small amount of nitrous oxide present in the brain and venous blood as determined in blood samples taken immediately before the second period of inhalation. For these determinations V_t represents the difference between the final and the small initial venous concentration.

¶ The authors do not attach any special significance to the mean values in man representing as they do a heterogeneous group. They are included merely as an indication of values to be expected in man with no gross derangements in cerebral function.

The identity of the mean values for cerebral oxygen consumption in man and monkey must be construed as fortuitous, since apprehensiveness and disease in the human subjects and light anesthesia and the operative procedures in the monkeys would be expected to modify the results. That the values obtained by these two different methods are of the same order of magnitude is, however, certainly significant.

determination, 9 measurements have been performed on rhesus and spider monkeys for comparison with simultaneous cerebral blood flow determinations obtained directly by means of the bubble flow meter (12). A value of 1.3 obtained from these data as described previously has been assigned to S. The comparison is presented in table 1. Over a wide range of blood flows (17 to 76 cc./100 g./min.) there is good agreement between the direct measurements and those calculated by the present method. The mean deviation of the calculated values from the direct measurements is ± 10 per cent. Technical difficulties peculiar to this preparation would tend to make the error greater than that which would occur in man where blood loss resulting from the sampling would be negligible and where venous samples could be taken rapidly without fear of drawing blood from regions other than the brain. It is fair to state that not many indirect clinical measurements in widespread use today have been subjected to the rigorous test of comparison with direct measurement.

By means of equation 9 and using the value for S of 1.3 the cerebral blood flow and cerebral oxygen consumption have been calculated for 16 determinations in 11 human subjects.[4] The data are presented in table 2. It is worthy of note that these values for cerebral blood flow and oxygen consumption per 100 grams of brain are in excellent agreement with those obtained in this laboratory in the rhesus monkey by an entirely different method (4). These 16 experiments on human subjects are included here to indicate the feasibility of applying the method here described to clinical investigation.

SUMMARY

A method is described applicable to unanesthetized man for the quantitative determination of cerebral blood flow by means of arterial and internal jugular blood concentrations of an inert gas during the first ten minutes of its inhalation in low concentration.

Certain necessary assumptions are experimentally tested and results of the method in monkeys are compared with those obtained simultaneously by direct measurement of cerebral blood flow.

Sixteen determinations of cerebral blood flow on eleven human subjects by this method have thus far been made and suggest the feasibility of applying this method to clinical investigation.

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