# *Krypton*$^{85}$ *and Nitrous Oxide Uptake of the Human Brain During Anesthesia*

*S. C. Alexander, M.D., H. Wollman, M.D., P. J. Cohen, M.D., P. E. Chase, M.D., E. Melman, M.D., M. Behar, Ph.D.*

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/25/1/37/282671/0000542-196401000-00007.pdf by guest on 18 April 2024

THE PRODUCTION of anesthesia with an inhalational agent depends on the achievement of an anesthetic concentration of the agent in the brain. Likewise, the speed of induction of or recovery from anesthesia is intimately related to the rate of uptake or loss of the anesthetic agent by the brain. Therefore, measurement of the rate of brain uptake of anesthetic gases is of considerable importance. However, the kinetics of inert gas exchange in the brain of man have not been well studied.

Ideally, the measurement of the rate of brain uptake of an anesthetic agent should begin with the induction of anesthesia. However, during induction alterations of cerebral blood flow (CBF) can occur, either through an effect of the anesthetic agent itself or through secondary effects such as respiratory depression and breath-holding.[1, 2, 3] As an alternative it was decided to measure brain inert gas uptake after anesthesia was established and CBF had become stable. This measurement involves the inhalation of an inert gas in subanesthetic concentrations (15 per cent $N_2O$, or traces of $Kr^{85}$) during anesthesia produced by another agent.

## Methods

Brain $Kr^{85}$ uptake was studied in 13 normal male volunteers whose age ranged from 21–41 years. No premedication was administered. They were anesthetized with halothane in oxygen. Halothane was vaporized by means of a calibrated Fluotec vaporizer and the inspired concentration was maintained at 1.2 per cent. The trachea was intubated following an intravenous dose of 60–80 mg. of succinylcholine and respiration was controlled with a Bird respirator in a nonrebreathing system using a Frumin valve. Ventilation was kept constant at about 12 liters/minute in each subject and arterial $P_{CO_2}$ was controlled by varying the inhaled $CO_2$ concentration with a gas ratiometer.[4] The studies were conducted during hypocarbia ($Pa_{CO_2} \sim 23$ mm. of mercury), normocarbia ($Pa_{CO_2} \sim 37$ mm. of mercury) and hypercarbia ($Pa_{CO_2} \sim 50$ mm. of mercury). Each subject was studied during two of these three conditions. Twelve measurements were made during hypocarbia, six during normocarbia, and six during hypercarbia. Six of twelve measurements made during hypocarbia were made without any other drugs being administered. In all other instances 40–60 mg. of *d*-tubocurare were given intravenously in divided doses. When measurements were made a steady state had been present for at least 10 minutes, as indicated by end-tidal $CO_2$ and halothane concentrations, which were monitored with appropriate infrared analyzers. Arterial $P_{CO_2}$ was determined in a $CO_2$ electrode and minute ventilation ($\dot{V}_E$) was measured with a Wright anemometer. CBF was measured with $Kr^{85}$ by a modification of the inert gas method of Lassen and Munck.[5] Pierce *et al.* have also made measurements of CBF in subjects during thiopental anesthesia using $N_2O$ as the inert gas; suitable data were available in five subjects from that study (subjects 5, 6, 11–13).[2] Arterial and jugular venous concentrations of $Kr^{85}$ and $N_2O$ were measured for periods of up to 28 minutes in these two investigations. These data have been used to calculate brain uptake of those gases at various levels of CBF in the manner outlined below.

Received from the Department of Anesthesia, University of Pennsylvania Schools of Medicine, Philadelphia, Pennsylvania, and accepted for publication September 26, 1963. This paper was presented at the Annual Meeting of the American Society of Anesthesiologists, Inc., Chicago, November 4, 1963.

TABLE 1. Brain $Kr^{85}$ Uptake During Halothane Anesthesia

| Situation | No. of Meas. | $\dot{V}_E$ (l./min.) | | $Pa_{CO_2}$ (mm. Hg) | | CBF (ml./100 g./min.) | | $T_{50\ per\ cent}$ (min.) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. |
| Hypocarbia | 12 | 12.0 | 0.5 | 23.4 | 0.9 | 25.1 | 1.6 | 6.0 | 0.3 |
| Normocarbia | 6 | 13.1 | 0.9 | 37.3 | 0.8 | 50.8 | 2.7 | 3.3 | 0.3 |
| Hypercarbia | 6 | 11.5 | 0.5 | 51.1 | 1.3 | 63.8 | 3.2 | 3.1 | 0.2 |

$\dot{V}_E$ = volume expired/minute; $Pa_{CO_2}$ = arterial $P_{CO_2}$; CBF = cerebral blood flow; $T_{50\ per\ cent}$ = time for brain saturation to reach 50 per cent of final value.

### METHOD OF CALCULATION

As Kety has shown,[6] if an inert gas is inhaled during a steady state, and if appropriate measurements of arterial ($A$) and jugular venous ($V$) gas concentrations are made,

$$C_{B_t} = \text{CBF} \int^{t} (A-V)\,dt \qquad (1)$$

where CBF represents cerebral blood flow in milliliters/100 g. brain/minute and $C_{B_t}$ is the

$$\frac{\text{volume of gas accumulated to time } t}{\text{100 g. brain}}.$$

At any time, $t$:

Percentage brain saturation

$$= \frac{C_{B_t}}{C_{B\infty}} \times 100 \text{ per cent} \qquad (2)$$

where $C_{B\infty}$ represents brain inert gas concentration at infinite time. Therefore, at any time, $t$:

Percentage saturation

$$= \frac{\text{CBF} \int_0^t (A-V)\,dt}{\text{CBF} \int_0^\infty (A-V)\,dt} \times 100 \text{ per cent} \qquad (3)$$

where

$$\int_0^\infty (A-V)\,dt = \int_0^{t_F} (A-V)\,dt + \int_{t_F}^\infty (A-V)\,dt \qquad (4)$$

$t_F$ represents the time at which the final measurements of arterial and venous concentrations are made. CBF, being constant, disappears from the equation; $\int_0^t (A-V)\,dt$ and $\int_0^{t_F} (A-V)\,dt$ are calculated from the measured arterial and venous gas concentrations. The calculation of the integral $\int_{t_F}^\infty (A-V)\,dt$ makes use of the fact that after sufficient time* the arterial-jugular venous differences of both $Kr^{85}$ and $N_2O$ decrease in a predictable exponential manner with time, such that:

$$(A-V)_t = Ke^{-\alpha t} \qquad (5)$$

where $(A-V)_t$ represents the arterial-venous difference at any time, $t$, $K$ is a constant, and $\alpha$ is the rate constant.[5,7] Integration of equation 5 from $t_F$ to infinity yields:

$$\int_{t_F}^\infty (A-V)\,dt = \frac{(A-V)_{t_F}}{\alpha} \qquad (6)$$

The value of $\alpha$ may be obtained from a semilogarithmic plot of the $A$–$V$ differences as a function of time and $(A-V)_{t_F}$ is measured. Thus,

Percentage saturation at any time $t$

$$= \frac{\int_0^t (A-V)\,dt}{\int_0^{t_F} (A-V)\,dt + \frac{(A-V)_{t_F}}{\alpha}} \times 100 \text{ per cent} \qquad (7)$$

Equation (7) has been used to perform the calculation of brain inert gas saturations in this study.

## Results

Table 1 summarizes the pertinent respiratory and circulatory data obtained in the study of brain $Kr^{85}$ uptake. $\dot{V}_E$ did not differ significantly among the three conditions imposed during this study ($P > 0.5$). Arterial $P_{CO_2}$ was maintained at the desired levels by controlling the inhaled $CO_2$ concentration. As CBF increased, the time required for 50 per cent equilibration of the brain, $T_{50\ per\ cent}$, fell.

In Figure 1 the results of the calculations of $Kr^{85}$ uptake by the brain are shown as well as the arterial and jugular venous concentrations. In the nonrebreathing system employed, arterial $Kr^{85}$ concentration reached its final value about seven minutes after inhalation was begun and jugular venous concentration lagged behind the arterial value. At all three levels of CBF the jugular venous concentrations con-

*For $Kr^{85}$ this holds only for $t > 6$–$9$ minutes. For $N_2O$ it seems to hold for $t > 3$ minutes.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/25/1/37/282671/0000542-196401000-00007.pdf by guest on 18 April 2024

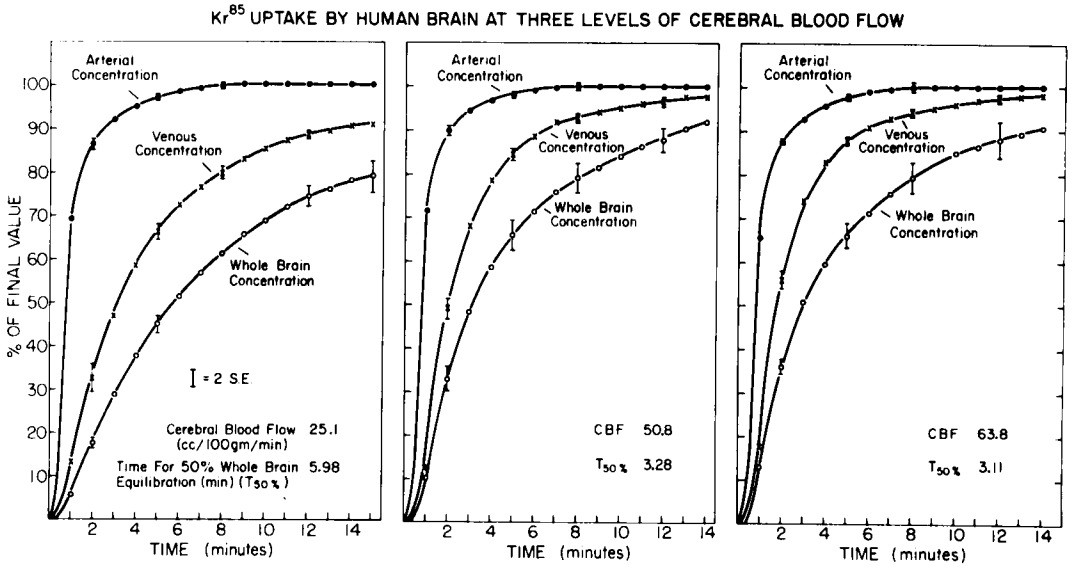


FIG. 1. Arterial, jugular venous, and whole brain $Kr^{85}$ uptake at three levels of cerebral blood flow during halothane anesthesia at constant pulmonary ventilation.

tinued to rise and arterio-venous equilibrium was not obtained during the period of study. Furthermore, brain $Kr^{85}$ concentration approached its final value considerably more slowly than did the jugular venous concentration. For example, after ten minutes of $Kr^{85}$ inhalation during normocarbia, the brain reached only 83.7 per cent of its final concentration while the jugular venous blood had attained 94.9 per cent of its final concentration.

The observed values of $T_{50\text{ per cent}}$, plotted as a function of CBF, are shown in figure 2. This relationship appeared to be hyperbolic and a log-log plot yielded a straight line. A linear regression could therefore be calculated for log $T_{50\text{ per cent}}$ as a function of log CBF. This line is defined by the expression: log $T_{50\text{ per cent}} = 1.78 - 0.73$ log CBF. The linearity of this relationship is statistically significant ($P < 0.001$) and the slope of the line is significantly different from zero ($P < 0.01$).[8] The curve representing this relationship of $T_{50\text{ per cent}}$ to CBF at a mean $\dot{V}_E$ of 12.2 liters/minute is depicted in figure 2.

Table 2 summarizes the information on the uptake of $N_2O$ obtained from an analysis of the data collected by Pierce *et al.* in the study of CBF during thiopental anesthesia.[2] In that investigation, arterial $P_{CO_2}$ was controlled by varying ventilation, and consequently $\dot{V}_E$ was lower during normocarbia (4.7 liters/minute) than during hypocarbia (14.9 liters/minute) ($P < 0.001$).

Figure 3 illustrates the arterial $N_2O$ values obtained in that investigation. The concentrations continued to rise slowly after 15 minutes during both normocarbia and hypocarbia. During normocarbia, the mean increase in arterial $N_2O$ concentration from 15–25 min-

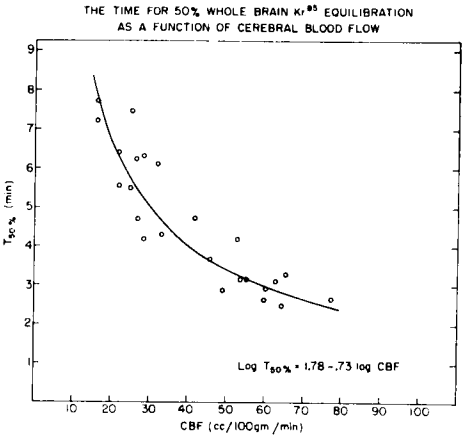


FIG. 2. A demonstration of the hyperbolic relation between the rate of brain $Kr^{85}$ uptake and cerebral blood flow during halothane anesthesia.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/25/1/37/282671/0000542-196401000-00007.pdf by guest on 18 April 2024

TABLE 2. Brain $N_2O$ Uptake During Thiopental Anesthesia

| Situation | No. of Meas. | $\dot{V}_E$ (l./min.) | | $Paco_2$ (mm. Hg) | | CBF (ml./100 g./min.) | | Observed $T_{50\ per\ cent}$ (min.) | | Predicted $Kr^{85}$ $T_{50\ per\ cent}$ (min.) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | S.E. | Mean | S.E. | Mean | S.E. | Mean | S.E. | |
| Hypocarbia | 5 | 14.9 | 1.7 | 16.6 | 0.5 | 14.1 | 0.7 | 7.9 | 0.3 | 8.7 |
| Normocarbia | 5 | 4.7 | 0.9 | 40.9 | 0.9 | 25.0 | 1.7 | 7.1 | 0.5 | – |

Predicted $Kr^{85}$ $T_{50\ per\ cent}$ during hypocarbia was obtained by extrapolation of $Kr^{85}$ data to a CBF of 14.1 ml./100 g./minute (fig. 2).

$\dot{V}_E$ during thiopental anesthesia with normocarbia was much lower than during the study of brain $Kr^{85}$ uptake (table 1); therefore, predicted $Kr^{85}$ $T_{50\ per\ cent}$ is not compared with observed $N_2O$ $T_{50\ per\ cent}$ during this phase. (See table 1 for abbreviations.)

utes was 0.3 volume per cent ($SE_m$ 0.03, $P < 0.01$); during hypocarbia the mean increase was smaller (0.1 volume per cent, $SE_m$ 0.02) but statistically significant ($P < 0.05$). The decreased $\dot{V}_E$ during normocarbia is reflected in the lower $N_2O$ concentrations obtained during this stage. Despite the rise in CBF of 10.9 ml./100 g./minute during normocarbia ($P$ of difference $< 0.001$), $T_{50\ per\ cent}$ did not change significantly ($P > 0.25$). The value of $T_{50\ per\ cent}$ obtained for $N_2O$ during hypocarbia is compared with the value extrapolated from the equation relating $T_{50\ per\ cent}$ for $Kr^{85}$ to the rate of cerebral blood flow (fig. 2) and good agreement is noted.

## Discussion

The rate of inert gas uptake by the brain is influenced by many factors, the most important of which are cardiac output, the rate of cerebral blood flow, alveolar ventilation and the solubility of the gas in blood and brain.[6] This discussion will deal in detail with the latter three factors.

*Cerebral Blood Flow.* The uptake of such dissimilar agents as xenon and chloroform has been demonstrated to be essentially a flow-limited process in the dog brain.[9] Further, several investigators have demonstrated that inert gas uptake is not diffusion-limited.[10, 11] The present calculations of $Kr^{85}$ uptake by the human brain at three levels of CBF at a constant ventilation extend these observations of the flow dependence of inert gas uptake by the brain. As CBF decreases below a normal value of about 44 ml./100 g./minute,[12] the rate of brain equilibration decreases sharply. An elevated CBF increases the rate of approach to brain equilibrium; however, since the relation of CBF to the rate of brain saturation is hyperbolic, an increase in CBF changes the rate of brain equilibration less than an equal decrease in flow rate.

As shown in figure 1, complete brain $Kr^{85}$ equilibration is never achieved during the experimental periods of this study at any level of cerebral perfusion observed, and brain saturation lags behind venous saturation at all times. Even in those subjects with the highest blood flow, brain $Kr^{85}$ saturation reaches only 91 per cent after 14 minutes of inhalation, while jugular venous blood is 98 per cent equilibrated. This slow saturation of the brain and its lag behind the jugular venous blood is at variance with earlier experimental work which indicated a more rapid saturation of the brain with an inert gas.[13] However, there is reason to believe that *mean whole brain* saturation should follow the pattern found in this investigation. Jones and also Pittinger and his co-workers found evidence that the cerebral circulation was at least a two-compartment system.[9, 10, 14] Later, Kety and his associates elegantly demonstrated that brain flow is heterogeneous and varies greatly from one region to another.[1] Although there is a wide range of flow rates throughout the brain, in general one may assume two compartments, gray matter with the highest rate of flow and white matter, the more slowly perfused compartment. Therefore, the difference between whole brain and venous saturation (fig. 1) is accounted for by the early equilibration of the rapidly perfused areas of the brain; the failure of the

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/25/1/37/282671/0000542-196401000-00007.pdf by guest on 18 April 2024

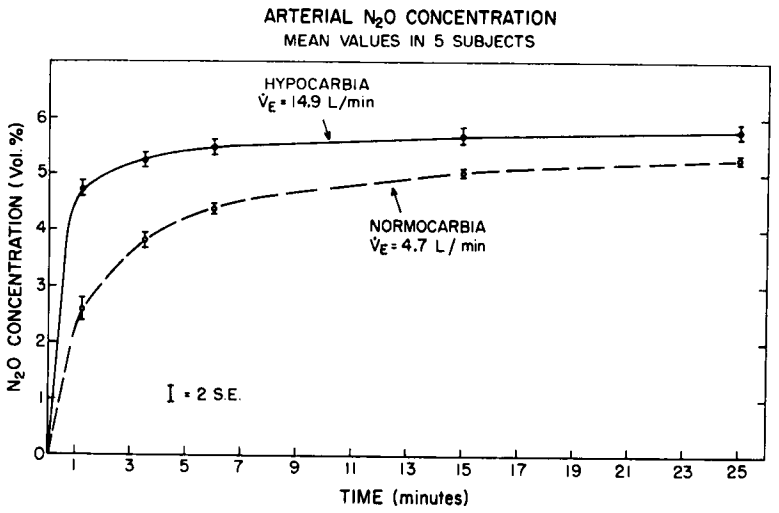


FIG. 3. Arterial $N_2O$ concentration values obtained by Pierce *et al.* in the study of cerebral blood flow during thiopental anesthesia.[9]

whole brain to attain complete equilibrium even at a very high level of CBF after 14 minutes of $Kr^{85}$ inhalation may be explained by the incomplete saturation of slowly perfused areas.

*Alveolar Ventilation.* The lack of change in $T_{50\text{ per cent}}$ for $N_2O$ between hypocarbia and normocarbia illustrates the interaction of alveolar ventilation and CBF on brain $N_2O$ uptake. During normocarbia CBF increased 75 per cent and this would tend to increase the rate of brain $N_2O$ uptake. It should be noted, however, that $\dot{V}_E$ in the normocarbic phase was decreased approximately 70 per cent from the level imposed on the hypocarbic subjects. As Kety has shown this decrease in $\dot{V}_E$ would be expected to slow the rate of rise of arterial $N_2O$ content.[6] The arterial uptake of $N_2O$ was indeed slower during normocarbia (fig. 3). The slowed arterial uptake would tend to depress the rate of brain $N_2O$ equilibration. Thus during normocarbia the expected increase in brain $N_2O$ uptake with a more rapid CBF has been offset by the decrease in alveolar ventilation. A fall in cardiac output during hypocarbia would also produce a slower rise in arterial $N_2O$ concentration similar to the pattern seen in figure 3.[6] Although the increased positive pressure ventilation used by Pierce *et al.* to produce hypocarbia may have reduced cardiac output, no data on this parameter are available.

*Blood and Brain Solubility.* Although the brain/blood coefficients of $N_2O$ and $Kr^{85}$ are similar (1.0 and 1.1 respectively), $N_2O$ is approximately 10 times more soluble in blood than is $Kr^{85}$.[5, 13, 15] In order to evaluate the effect of blood solubility on the brain uptake of these two gases, comparisons must be made under conditions of comparable pulmonary ventilation and CBF. $\dot{V}_E$ in the hypocarbic phase of Pierce's study is comparable to the level of $\dot{V}_E$ imposed in the present study. The value of $T_{50\text{ per cent}}$ for $N_2O$ at a CBF of 14.1 ml./100 g./minute (hypocarbia) is 7.9 minutes while the extrapolated value of $T_{50\text{ per cent}}$ for $Kr^{85}$ at a similar level of CBF is 8.7 minutes. Thus, the rate of brain uptake of these two gases seems similar despite the difference in their blood solubility.

*Clinical Implications.* The fact that both brain blood flow and alveolar ventilation affect cerebral gas equilibration has clinical import. An anesthetist may attempt to hasten brain gas uptake or elimination by increasing pulmonary ventilation since arterial equilibration is enhanced by a rise in alveolar ventilation. Under usual clinical conditions, however, an increase in ventilation decreases arterial $P_{CO_2}$ and hence cerebral blood flow is lowered. This diminished brain blood flow could completely negate or even reverse the desirable effects produced by increased pulmonary ventilation. However, hyperventilation can be used to produce a rapid alteration of brain inert gas concentrations if approximately 4 per

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/25/1/37/282671/0000542-196401000-00007.pdf by guest on 18 April 2024

cent $CO_2$ is maintained in the inspired anesthetic mixture to prevent a reduction in arterial $P_{CO_2}$ and a fall in CBF. This inspired $CO_2$ concentration might be maintained either by direct addition to the inspired gases or indirectly by removing the $CO_2$ absorber from the anesthetic circuit in a semiclosed system with the appropriate flow rates. Under these conditions, the production of pulmonary hyperventilation while preventing a reduction in CBF would permit a rapid, efficient change in brain inert gas content. Such a method would be particularly advantageous during the administration of the more soluble anesthetics such as halothane, diethyl ether, trichloroethylene or chloroform, if the possible elevation of arterial $P_{CO_2}$ was shown not to be otherwise harmful.

## Summary

A method of calculating whole brain inert gas uptake during periods of stable cerebral blood flow (CBF) has been developed. This method has been used to calculate brain $Kr^{85}$ uptake at three levels of CBF in 13 human subjects during halothane anesthesia at constant pulmonary ventilation. In addition, brain $N_2O$ uptake has been calculated in 5 humans during thiopental anesthesia at two levels of CBF. The rate of whole brain $Kr^{85}$ uptake was shown to vary in a hyperbolic manner with CBF. In addition, alveolar ventilation was demonstrated to be an important determinant of the rate of brain inert gas uptake. At comparable levels of alveolar ventilation and CBF, the rate at which brain $N_2O$ uptake proceeded did not differ markedly from the rate of brain $Kr^{85}$ saturation. Whole brain $Kr^{85}$ saturation lagged behind jugular venous saturation at all times. Complete whole brain $Kr^{85}$ equilibration was never achieved during the experimental periods of this study even at high levels of CBF.

This work was supported (in part) by Grants RG-9070 and 2G-215 (C4) from the United States Public Health Service, National Institutes of Health.

## References

1. Landau, W. M., Freygang, W. H., Rowland, L. P., Sokoloff, L., and Kety, S. S.: The local circulation of the living brain: values in the unanesthetized and anesthetized cat, Trans. Amer. Neurol. Ass. **80**: 125, 1955.
2. Pierce, E. C., Lambertsen, C. J., Deutsch, S., Chase, P. E., Linde, H. W., Dripps, R. D., and Price, H. L.: Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man, J. Clin. Invest. **41**: 1664, 1962.
3. Wollman, H.: Effects of Anesthetics on the Circulation, H. L. Price and P. J. Cohen, Editors, Fort Lauderdale, Charles C Thomas, In Press.
4. Lambertsen, C. J., and Wendel, H.: An alveolar $P_{CO_2}$ control system: its use to magnify respiratory depression by meperidine, J. Appl. Physiol. **15**: 43, 1960.
5. Lassen, N. A., and Munck, O.: The cerebral blood flow in man determined by the use of radioactive krypton, Acta Physiol. Scand. **33**: 30, 1955.
6. Kety, S. S.: Theory and application of the exchange of inert gases at the lungs and tissues, Pharmacol. Rev. **3**: 1, 1951.
7. Kety, S. S., and Schmidt, C. F.: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations, Amer. J. Physiol. **143**: 53, 1945.
8. Batson, H. C.: An Introduction to Statistics in the Medical Sciences. Minneapolis, Burgess Publishing Co., 1956, pp. 58–60.
9. Pittinger, C. B., Conn, H. L., Featherstone, R. M., Stickley, E., Levy, L., and Cullen, S. C.: Observations on the kinetics of transfer of xenon and chloroform between blood and brain in the dog, ANESTHESIOLOGY **17**: 523, 1956.
10. Jones, H. B.: Medical Physics. Otto Glasser, Editor. Chicago, Year Book Publishers, Inc., 1950, vol. 2, pp. 855–951.
11. Pappenheimer, J. R.: Passage of molecules through capillary walls, Physiol. Rev. **33**: 387, 1953.
12. Lassen, N. A.: Cerebral blood flow and oxygen consumption in man, Physiol. Rev. **39**: 183, 1959.
13. Kety, S. S., Harmel, M. H., Broomell, H. T., and Rhode, C. B.: The solubility of nitrous oxide in blood and brain, J. Biol. Chem. **173**: 487, 1948.
14. Pittinger, C. B., Featherstone, R. M., Gross, E. G., Stickley, E. E., and Levy, L.: Xenon concentration changes in brain and other body tissues of dog during inhalation of the gas, J. Pharmacol. Exp. Ther. **110**: 458, 1954.
15. Lawrence, J. H., Loomis, W. F., Tobias, C. A., and Turpin, F. H.: Preliminary observations on the narcotic effect of xenon with a review of values for solubilities of gases in water and oils, J. Physiol. **105**: 197, 1946.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/25/1/37/282671/0000542-196401000-00007.pdf by guest on 18 April 2024