THE RATE OF ELIMINATION OF DISSOLVED NITROGEN IN MAN IN RELATION TO THE FAT AND WATER CONTENT OF THE BODY

ALBERT R. BEHNKE, ROBERT M. THOMSON AND LOUIS A. SHAW

From the Department of Physiology, Harvard School of Public Health, Boston, Mass.

Received for publication July 26, 1935

Quantitative studies of the dissolved nitrogen in man have been previously made only for short periods of time, chiefly in determinations of cardiac output (Bornstein, 1919). Measurements of nitrogen absorption and elimination not only give an approximation of cardiac output, but also afford a representation of the absorption and elimination of all chemically inert gases, specifically the inhalation anesthetics. In connection with the decompression of divers studies of the dissolved nitrogen are of immediate practical importance.

This paper presents the application of certain principles from studies of the dissolved nitrogen in dogs (Shaw, Behnke, Messer, Thomson and Motley, 1935) to measurements of nitrogen in man.

METHOD. Inhalation of pure oxygen results in elimination of the gaseous nitrogen dissolved in the tissues of the body. Oxygen can be breathed for a period of 4 hours in a closed system consisting of a helmet, cooling coil, spirometer, and soda lime cannister. Analysis of periodic samples of the circulating oxygen supplies the data for calculations of nitrogen elimination. The volume of the system was 40 liters so that the oxygen percentage at the end of an experiment did not fall below 90 per cent. The term “nitrogen” is applied to the residual gas in the Van Slyke apparatus after oxygen absorption with hyposulphite.

The nitrogen measurements were made on 3 healthy men of medium build who interrupted their usual activities to breathe oxygen at weekly intervals while resting on a cot.

RESULTS. Figure 1-A is typical of the results from 25 experiments on the 3 men. The solid line represents the actual measurements of nitrogen elimination over a period of 4 hours on subject A. The broken line, drawn from calculations based on the experimental results, represents the nitrogen eliminated during the first 5 minutes (when oxygen replaced the air in the lungs and in the apparatus) and during the period following

1 This research was aided by the Miriam Smith Rand Fund.
2 Member of the United States Naval Medical Corps.
the fourth hour. Since these calculations indicate clearly the manner in which nitrogen is eliminated, they will be given in detail.

The elimination or absorption of nitrogen with changes in pulmonary nitrogen tension is a function of the circulatory rate and can be represented by one or more exponential equations of the form,

\[ Y = A(1 - e^{-kt}) \]

expressing the relationship that the nitrogen is eliminated from the body at a rate which is a constant percentage of the amount present at any given time. \( Y \) represents the value for nitrogen eliminated during the time interval, \( t \); \( A \), the total nitrogen; \( k \), the rate of change in the slope of the curve; and \( e \), the natural base of logarithms. The expression \( 1 - e^{-kt} \) gives the percentage decrease of the total nitrogen during the time interval, \( t \).

In terms of \( k \), equation 1 becomes

\[ k = \log_e \frac{A}{A - Y} \cdot \frac{1}{t} \]
The value of $A$ in terms of $Y$ can be expressed as

$$A = \frac{(Y_1)^2}{2Y_1 - Y_2}$$

provided that the time, $t_2$, corresponding to the value for $Y_2$ is twice that of $t_1$ corresponding to the value for $Y_1$. In subject A, for example, the average experimental value for the 5 minutes following the rinsing period of 5 minutes was 116 cc.; and for the 10 minutes following the rinsing period, 187 cc. (table 1, columns 4 and 5). Substituting these values in equation

\begin{table}
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
\textbf{SUBJECT} & \textbf{WEIGHT} & \textbf{HEIGHT} & \textbf{AGE} & \textbf{SURFACE AREA} & \textbf{NITROGEN ELIMINATION} & \textbf{CARDIAC OUTPUT} \\
\hline
 & & & & & \textbf{Calculated} & \textbf{Experimental} & \\
 & & & & & (1) & (2) & (3) & (7) & (8) \\
\hline
A & 132 & 63 & 32 & 1.62 & 45.5 & 188 & 257 & 4.7 & 3.6 ± 0.5 \\
 & & & & & A-1 & 95 & 165 & 259 & \\
 & & & & & A-2 & 124 & 188 & & \\
 & & & & & A-3 & 130 & 208 & 293 & \\
 & & & & & Av. & 110 & 187 & 276 & \\
B & 124 & 63 & 30 & 1.57 & 33.0 & 143 & 233 & 3.33 & 3.5 ± 0.5 \\
 & & & & & B-1 & 93 & 158 & 248 & \\
 & & & & & B-2 & 97 & 160 & 253 & \\
 & & & & & Av. & 90 & 159 & 251 & \\
C & 143 & 68 & 33 & 1.77 & 38.0 & 165 & 269 & 4.0 & 3.9 ± 0.5 \\
 & & & & & C-1 & 100 & 170 & 298 & \\
 & & & & & C-2 & 111 & 184 & 278 & \\
 & & & & & C-3 & 119 & 189 & 271 & \\
 & & & & & Av. & 110 & 184 & 282 & \\
\hline
\end{tabular}
\end{table}

$3, A = 299$. With this value for $A$, the rate of change per minute in the slope of the curve, $k$, can be calculated from equation $3$ as 0.008. With values for $A$ and $k$, the nitrogen eliminated during the rinsing period of 5 minutes ($Y$) can be obtained from equation 1. Since the experimental curve is extrapolated 5 minutes to the left of the point of origin at which actual measurements of nitrogen began, $t$ has a minus sign, or,

\begin{align*}
Y &= 299 \left(1 - e^{-(0.008 \times (-5))}\right) = 299 \left(1 - e^{-(0.008 \times (-3))}\right) \\
&= 299 \left(1 - e^{0.48}\right) = (-) 188 \text{ cc.}
\end{align*}
Using the same procedure, the calculated value for the first minute of oxygen breathing is 45.5 cc. Dividing this value by 0.96, the solubility coefficient of blood in vitro equilibrated with air (nitrogen tension did not exceed 580 mm.) at body temperature (Van Slyke, Dillon and Margaria, 1934), and multiplying by 100 gives 4700 cc., a value which is an approximation of the cardiac output during the first minute. The cardiac output of healthy individuals in the basal state can be predicted according to Grollman (1932) as 2.2 ± 0.3 liters per square meter of body surface, giving in the case of subject A 3.6 ± 0.5 liters. The value of 45.5 for the nitrogen eliminated during the first minute of oxygen breathing is, therefore, probably correct within the limits of experimental error. The calculated values for nitrogen elimination during each minute up to the sixth are given in table 1, column 1. The measurements of Campbell and Hill (1931) of the nitrogen elimination during the first 5 minutes corroborate the values in column 2, table 1.

A check on the method of calculation is obtained by extrapolating the experimental curve to the right and comparing the predicted value of nitrogen elimination for 20 minutes (column 3, table 1) with the experimental values, column 6. The calculation, \( Y = 299 \left(1 - e^{-0.098\cdot20}\right) \), gives a value of 257 cc. In 6 experiments on subject A, the average of the values for 20 minutes was 265 cc.

It should be pointed out that calculations of nitrogen elimination based on the values for 5 and 10 minutes hold good only for periods up to 25 minutes. If the rate of change, \( k \), in the slope of the nitrogen elimination curve for the whole body were constant, then the value for \( A \) would represent the total body nitrogen, and accurate calculations could be made for the whole period of nitrogen elimination. The value for \( k \), however, decreases as a result of unequal blood flow in relation to the nitrogen content of the tissues. At the start of oxygen breathing the average nitrogen tension in the blood is equal to the nitrogen tension in the different tissues of the body, and a maximum load of nitrogen is eliminated per unit of time. As the experiment progresses, the average nitrogen tension of the blood falls below the nitrogen tension in the slowly desaturating or fatty tissues. Consequently the percentage rate of nitrogen elimination decreases. The \( A \) value, based on the quantities of nitrogen eliminated at 5 and 10 minutes, more closely approximates the nitrogen in the body fluids, and does not include the large reservoir of nitrogen in the fat which is given up very slowly. More representative values for the total body nitrogen can be obtained by using the figures for nitrogen eliminated in 1 and 2 hours, or 1.5 and 3 hours. The accuracy of the extrapolated values is usually limited to a period of time corresponding to that of the experimental values used in the calculations.

The curve for total nitrogen, curve \( A \), figure 1, can be conveniently rep-
NITROGEN ELIMINATION AND FAT AND WATER OF BODY

represented by two exponential equations on the basis of a high value for $k$ during the first hour and a lower value for $k$ after the first hour. If that portion of the curve after the first hour be extrapolated to the left on the basis of its $k$ value, then curve C, figure 1, can be drawn. The difference between the nitrogen values for curve C and those of curve A are represented by curve B. Curve A is thus the sum of two components, B and C, or

$$Y = (B) \cdot 458 \cdot (1 - e^{-0.098t}) + (C) \cdot 382 \cdot (1 - e^{-0.0085t})$$

where $Y$ is the total nitrogen eliminated from the body during time, $t$.

The designations "fat" and "water" to curves B and C follow from the relation of nitrogen to its solvents. Since fat contains between 5 and 6 times more nitrogen than water (Vernon, 1907) and since the capacity of the blood to carry nitrogen is about the same as water, nitrogen removal from fat and lipoids will take 5 to 6 times longer than nitrogen removal from body fluids. It is a reasonable assumption, then, that the original nitrogen in the body fluids is eliminated at the end of the first hour according to curve B, figure 1.

The nitrogen solvents of the body. While the division of nitrogen in relation to its solvents is given approximately by curves B and C, figure 1, a more exact division follows from the quantitative analysis for water and fat in a dog used in the experiments of Shaw et al. (1935). The water was removed from the tissues of dog D by careful drying after preliminary treatment with 95 per cent alcohol. The fat and lipoids were extracted with carbon tetrachloride. The results: weight of dog, 12.234 kgm.; weight of fat, 1.889 kgm. (15.43 per cent); weight of dry solids, 3.117 kgm.; weight of water by difference, 7.228 kgm. The solubility of nitrogen in omental dog fat, 38°C., 570 mm., was found to be 5.57 cc. per 100 grams—a value in agreement with the extensive studies of Campbell and Hill (1931). The solubility of nitrogen in water, 38°C., corrected to 570 mm., is 0.954 volume per cent (Van Slyke, Dillon and Margaria, 1934). Multiplying the solubility values by the weights of fat and water in the dog:

$$7.228 \times 9.54 = 69 \text{ cc. of nitrogen dissolved in the water.}$$
$$1.889 \times 55.7 = 105 \text{ cc. of nitrogen dissolved in the fat.}$$

Total nitrogen = 174 cc. or 14.2 cc. per kilogram.

The measurements of the nitrogen content of dog D, including the calculated value for nitrogen eliminated during the first 7 minutes (rinsing period), totalled 167 cc. With the exception of a small amount of nitrogen dissolved in hemoglobin, the nitrogen solvents of the body are water and fat.

The total nitrogen content of subject A divided by the body weight, 60
kgm., gives 14 cc. of nitrogen per kilogram, or the same value as that for dog D. Further, the time required for nitrogen elimination in man, 98 per cent in 6 hours, is twice the time required for the dog, and corresponds in the resting state to the ratio of the cardiac output per kilogram of dog to the output per kilogram of man. If the water content of the body is 65 ± 5 per cent of the total weight and if 70 per cent (the usual figure in metabolic studies (Lavietes, D'Esopo and Harrison, 1935)) is used, then the product of the weight of the water, 42 kgm., and the solubility of nitrogen in water, 9.5 cc. per kilogram, gives a value of 400 cc. The nitrogen in the fat and lipoids is 440 cc. (840–400). Dividing 440 by 55.7 gives an estimation of the amount of fat, 7.9 kgm. or 13.2 per cent of the body weight.

The relatively high fat and lipid content of the spinal cord in comparison with the brain is undoubtedly partly responsible for the susceptibility of this tissue to injury from nitrogen bubble formation in compressed air illness. In an extraction of the fat and lipid substances from the brains and spinal cords of 5 dogs with carbon tetrachloride, 100 grams of brain substance contained 4.8 grams of fatty material, while 100 grams of spinal cord tissue contained 27.8 grams of fatty material. The quantity of nitrogen absorbed by the spinal cord per unit weight is, therefore, about 2.5 times that absorbed by the brain. This fact, in addition to the poorer blood supply, accounts for the more rapid injury of the cord from nitrogen bubble formation compared with the brain.

Discussion and applications of the experimental results. Determination of cardiac output. The experimental results in this paper do not permit any conclusions with reference to the accuracy of Bornstein's nitrogen elimination method for the determination of cardiac output. They suggest, however, the advisability of further study of this comparatively simple method either in the original or in a modified form. The main objections specifically applicable to the method, listed in the careful study of Marshall, Harrop and Grollman (1928), were essentially removed by their own experiments or by the work of subsequent investigators. The observation that constant values for nitrogen elimination cannot be obtained on untrained individuals may not necessarily invalidate the method.

The absorption and elimination of inhalation anesthetics. The inhalation anesthetics are generally regarded as chemically inert, and consequently an index of their absorption and elimination will be given by the nitrogen elimination curves, A, B, and C, figure 1. For example, the time required for the body to come into equilibrium with a given tension of ether is represented by figure 1, curve A, since the ratio for ether, \( \frac{\text{solubility in fat}}{\text{solubility in water}} \), is
4.3—about three-quarters that of the corresponding ratio for nitrogen. If ether elimination follows the nitrogen curve, then about 6 hours will be required for complete elimination following withdrawal of the anesthetic.

The absorption and elimination of anesthetics only slightly soluble in lipoids should follow curve B, while the elimination of members of the aliphatic group will be proportional to their solubility in lipoids.

The decompression of divers. The application of the experimental results to the problems of deep sea diving will serve to emphasize certain fundamental concepts.

The nitrogen elimination experiments on dogs (Shaw et al., 1935) supported three accepted generalizations, although the significance of the third is not usually realized. The principles may be briefly restated: a, with the same pressure head the rate of nitrogen absorption (saturation) is equal to the rate of nitrogen elimination (desaturation); b, nitrogen absorption obeys Henry's law; and c, the time required for complete desaturation of the body is independent of the quantity of nitrogen absorbed, i.e., the same equation with the same constants applies to all experiments irrespective of the amount of nitrogen diffusing.

If these principles are applicable to nitrogen absorption and elimination in man, curve A, figure 1, represents not only the nitrogen leaving the body when the partial pressure of nitrogen is lowered, but also the nitrogen absorbed when the partial pressure of nitrogen is raised. Curves B and C, figure 1, indicate the uptake of nitrogen at increased pressures by the body fluids and lipoids respectively.

The importance of the third principle and the understanding of its implications require further discussion. If, for example, the barometric pressure is raised to 2 atmospheres, the nitrogen absorbed after successive exposures of 30, 60 or 360 minutes will not only be eliminated in the same period of time but also at the same percentage rate when the barometric pressure is again lowered to 1 atmosphere. These statements indicate that the nitrogen solvents, fat, lipoids and water, are so distributed that on decompression after partial saturation the diffusion of nitrogen from the rapidly saturating body fluids into the slowly saturating lipoids and fat tends to equalize the partial pressure of nitrogen in the different tissues of the body. Thus, when the body is only in partial equilibrium with an increased nitrogen tension the lipoids and fat act as nitrogen absorbents when the pressure is lowered, and serve as buffers against bubble formation in the blood stream. Fat men with adequate circulations are, therefore, better suited for short exposures to excess pressure than lean men.

If the results from the dog experiments are applied further, figure 2-A (from fig. 1-A, subject A) will represent nitrogen elimination after an indefinite exposure (e.g., 99 per cent saturation) to any given excess pressure (e.g., 4 atmospheres), while curve B represents nitrogen elimination
after a 30 minute exposure (62 per cent saturation) to the same excess pressure. Thus the nitrogen elimination curve after partial saturation at a high pressure (62 per cent at 4 atmospheres) is indistinguishable from the nitrogen elimination curve after complete saturation at 2.48 (–0.62 × 4) atmospheres. Actually some tissues with a high fat and lipoid content, after partial saturation at a high pressure may not be completely saturated with nitrogen when the pressure is lowered to 1 atmosphere. For it is probable that the bone marrow, consisting largely of fat (as high as 95 per

cent) encased in bone, and dependent for its nitrogen absorption on a relatively poor blood supply (Campbell and Hill, 1933), requires many hours for complete saturation. The spinal cord may also saturate slowly because of a high fat and lipoid content (28 per cent).

_Duration of exposure to excess pressure with immediate decompression to 1 atmosphere._ It follows as a corollary that the same curve will represent the elimination of a given quantity of nitrogen irrespective of whether the nitrogen is absorbed at a low pressure over a long period of time or at a high pressure for a short period of time. If use is made of the empirical
fact that compressed air illness (excessive nitrogen bubble formation) rarely occurs with immediate decompression, even after prolonged exposures to excess pressures, from 1.3 atmospheres (Haldane, 1922), or from even somewhat higher pressures (Japp, 1909), then the safe exposure time to excess pressures for subject A followed by rapid decompression (2 min.) can be predicted from his nitrogen elimination curve (curve A, fig. 1). The calculations are easily computed by making the product of the excess pressure, $P$, and the per cent saturation of the body, $R$, equal to a constant, $K$, which has a value which lies between 1.3 and 1.5. For example,

$$P \times R = K$$

$$1.3 \times 100 \text{ per cent} = 1.3$$

$$2.6 \times 50 \text{ per cent} = 1.3$$

$$3.9 \times 33.3 \text{ per cent} = 1.3$$

The time for any degree of saturation, $R$, is given by the nitrogen elimination curve. The method of computation is illustrated by figure 3. The results of these calculations have been verified by repeated diving tests (Kagiyama, 1934).

**SUMMARY**

The inhalation of oxygen results in the elimination of dissolved body nitrogen in equilibrium with pulmonary nitrogen.
The nitrogen content of a young, well developed man weighing 60 kgm. is 840 cc., or 14 cc. per kilogram, 98 per cent of which is eliminated with oxygen breathing over a period of 6 hours.

If the assumption is made that the body is 70 per cent water, then 400 cc. of nitrogen are dissolved in water and 440 cc. in the body fat and lipoids. Dividing 440 by the solubility coefficient of nitrogen in fat gives an estimate of 13.2 per cent for the body fat, in contrast with 70 per cent assumed for body water content.

The fat from a well nourished dog of 12.2 kgm., extracted with carbon tetrachloride, comprised 15.4 per cent of the body weight and the water 59.2 per cent. If these values are multiplied by the respective solubility values of nitrogen in fat and water, the nitrogen content of the dog per kilogram is 14.2 cc., or approximately the same as that for man.

Nitrogen elimination follows an exponential type of curve, the slope of which is a function of the cardiac output. The cardiac output in liters can be estimated by dividing the value for nitrogen eliminated during the first minute by the quantity of nitrogen dissolved per liter of blood.

The rate of absorption and the time of elimination of inhalation anesthetics can be estimated from the nitrogen elimination curve on the basis of the ratio
\[
\frac{\text{solubility in fat}}{\text{solubility in water}}
\]

During the decompression of divers who have been exposed for short periods (20 min.) to excess pressures, the fat and lipoids of the body act as nitrogen absorbents and serve as buffers against bubble formation. Under these conditions rapid decompression from relatively high pressures can be safely effected.

REFERENCES

    Quart. J. Exper. Physiol. 23: 197, 1933.
GROLLMAN, A. The cardiac output of man in health and disease. C. C. Thomas,
    Baltimore, Md., 1932. (See p. 87.)
    (See p. 344.)
    This Journal 112: 545, 1935.