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U. S. ARMY
MEDICAL
RESEARCH &
NUTRITION
LABORATORY

FUNDAMENTAL PARAMETERS INFLUENCING
THE ACCUMULATION AND ELIMINATION OF
CARBOHYDRATE BY ADULT HUMAN BEINGS

UNITED STATES ARMY
MEDICAL RESEARCH AND DEVELOPMENT COMMAND
PARAMETERS INFLUENCING THE ACCUMULATION AND ELIMINATION OF CARBON MONOXIDE BY ADULT HUMAN BEINGS

OBJECT:

To devise the basis of a mathematical system for accumulation; elimination of carbon monoxide by human beings.

SUMMARY:

During the past two decades various types of experiments have been published by different schools of investigators dealing especially with the accumulation of carbon monoxide and its combination with hemoglobin in adult human beings. The various parameters which influence carbon monoxide accumulation, as well as its elimination, have not been completely understood or adequately described. This may perhaps have occurred because of particular interest in one, or at the most two, out of several parameters. When, however, a fairly complete set of parameters are derived, it becomes possible to develop a mathematical system of accumulation;elimination which can be tested with data published by several laboratories. The system can be solved by a person acquainted with algebraic methods, and one is able to predict the level of carboxyhemoglobin as a function of time from the initial level of carboxyhemoglobin, the concentration of inspired carbon monoxide and oxygen, respiratory flow rate, total body hemoglobin, etc. total pressure of gas breathed. These findings suggest that future physiological investigations, using carbon monoxide as a tracer, should include the measurement of further parameters than often included to date. Examples are given of the method of calculation, and this is used to illustrate the importance of each parameter. Although scarcely any data are available on elimination of carbon monoxide, it is further shown how the system may predict the rate of elimination, especially when using the newest method of treating carbon monoxide poisoning by means of artificial ventilation with pure oxygen at a total ambient pressure of two atmospheres.

RECOMMENDATIONS:

None.

APPROVED:

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As the industrial revolution advances and spreads, more carbon monoxide than formerly becomes produced through the incomplete combustion of carbon compounds. Indeed, it would well be true that the chances of exposure to carbon monoxide poisoning have been increasing ever since the time of the first fire-maker. With the advent of modern physiology it soon was pointed out by Claude Bernard that carbon monoxide has a greater affinity than oxygen for hemoglobin. Its consequent toxicity, being much like that of anemic anemia, attracted the attention of physiologists interested in, among other things, the hazards of coal mining and other industrial and engineering operations (1). Automotive vehicles used in recent wars produce carbon monoxide, and in the absence of adequate ventilation this gas can accumulate in the vehicle. Many tests pertaining to military aspects of carbon monoxide were published in 1945 - 1946 (2). Just recently, about one-third of 186 victims of fatal crashes in the U. S. Air Force had tissue and blood saturation levels in excess of 30 per cent carboxyhemoglobin even in the absence of fire and more especially when flying at altitudes where a considerable proportion of cabin air would have been breathed (3). During 1954 - 1956 carbon monoxide poisoning accounted for 310 admissions for medical treatment in the U. S. Army. There were 97 deaths due to carbon monoxide. These figures are lower than actual because, if exposure had occurred in moving vehicles, the cases would have been reported as some type of motor vehicle accident (29). The indicated title of a Russian report can be cited as showing interest in carbon monoxide poisoning in outer space travel (30).
What levels of carboxyhemoglobin are dangerous? Even non-smokers have traces of carboxyhemoglobin. In those who smoke much tobacco the carboxyhemoglobin often ranges from 5 to 8 per cent of their total hemoglobin, and this can rise to 12 per cent in persons who smoke heavily for two-thirds or more of a day. Brief breathing of air rich in carbon monoxide can then continue for up to six hours in a more dilute mixture will maintain a level of 15 per cent carboxyhemoglobin in a recumbent subject at a simulated altitude of 15,000 feet (4). A heavy smoker (JL), who was a skillful observer, started this test with a level of 6.8 per cent carboxyhemoglobin which soon rose to 15 per cent. He reported no symptoms during the first hour, "but thereafter appeared headache which became progressively more severe, increasing and almost constant nausea, mental confusion, restlessness, pallor, cold extremities and a state of mild shock. These symptoms increased in severity as time passed". The carboxyhemoglobin level was always close to 15 per cent, and the combined oxyhemoglobin and carboxyhemoglobin level was 83 per cent, thus leaving 17 per cent as reduced hemoglobin on the systemic arterial side. Another subject (RM), while at 10,000 feet and at a level of 15 per cent carboxyhemoglobin suffered from "steadily increasing headache and recurrent nausea" during the final hours of exposure, even though in this case the combined arterial oxygen and carbon monoxide saturation was 97 per cent. At sea level with nearly complete arterial saturation with oxygen and carbon monoxide, J. S. Haldane considered that a brief exposure achieving 30 per cent carboxyhemoglobin was dangerous to himself, especially if engaged in exercise (1). Some valuable observations were reported by Smith and Sharp while using their improved method of treating carbon monoxide poisoning (5). Here, the carbon monoxide is removed with great rapidity
by causing the affected patient to breathe pure oxygen through a mask at a total ambient pressure of two atmospheres. On arrival, one of their patients, a 79-year-old woman, "was breathing spontaneously and all reflexes were present, but she could be roused only with difficulty. A man, aged 47, ... was in a deep coma, ashen-grey, with widely dilated pupils and opaqueness of the upper limbs. Spontaneous respiration was absent and no pulse could be detected ... (He) would normally have been classified as marturian". The carboxyhemoglobin was 76 per cent in the woman and 50 per cent in the man soon after the time of arrival. In general it appears that carboxyhemoglobin levels of 15 per cent should be avoided, especially if maintained for a prolonged period of time during which complete mental alertness is required.

Advantage has been taken of the physiological properties of carbon monoxide. Tracer quantities were used in the first successful measurements of blood volume in living human beings, and with Sjöstrand's unique refinements this method continues to be used (6). The alveolar pressure of oxygen was estimated approximately from the distribution of carbon monoxide between inspired air and arterial blood (7). In recent years many physicians have become interested in gas exchange diffusion between the lung and the blood (7). From basic kinetic data, together with rates of accumulation, Roughton in 1945 deduced that at rest the duration of exposure of capillary blood to alveolar air was three-quarters of a second involving 60 ml of blood (8).

Although much information had been gathered during a century of study, the assumption was nearly always made that carbon monoxide was neither produced nor destroyed in the living body. In 1949, using the
long-lived C$^{14}O$, it was shown that mice could excrete this to C$^{14}O_2$ (9). In the same year it was reported that the catabolism of haemoglobin produces carbon monoxide (10). Green plants, algae and even dry leaf powders, when wetted, make carbon monoxide in the presence of sunlight and oxygen (11). Some opposing reactions and their rates apparently have not been considered in so far as these can influence levels of blood carboxyhaemoglobin. In what follows it is proposed to examine the chief events affecting a system which describes both the accumulation and elimination of carbon monoxide. Certain predictions can be made, and these can be checked with the results obtained in previous studies of adult human beings.

**DERIVATIONS**

**Steady State Equilibrium of CO in**. Upon being exposed to air containing a fractional concentration of carbon monoxide (F$P_{1,CO}$), the quantity of CO inspired per minute ($\dot{V}_T F_{1,CO}$) equals the total of that which is expired ($\dot{V}_T E_{1,CO}$), that which enters the body ($\dot{V}_I CO$) and that which builds up at a certain rate to a definite concentration in the functional residual capacity of the lungs ($\dot{V}_F P_{A,CO}$).

$$\dot{V}_T F_{1,CO} = \dot{V}_T E_{1,CO} + \dot{V}_I CO + \dot{V}_F P_{A,CO} \ldots \Delta l \text{ min}^{-1}.$$  

This is also true for all other inspired gases including oxygen

$$\dot{V}_T F_{1,O_2} = \dot{V}_T E_{1,O_2} + \dot{V}_I O_2 + \dot{V}_F P_{A,O_2} \ldots \Delta l \text{ min}^{-1}.$$  

The last term in each expression should be of particular interest to those who make transient analyses of single breaths (7). It is entirely possible, especially with dilute CO, under steady state conditions, that the last term could be neglected so far as concerns the accumulation and elimination of CO. The last term in the oxygen expression is negligibly small in most cases. Consequently, these last terms will be dropped at this point, although further mention is made of them in the discussion. Next, consider
that \( V_{PA,CO} \) is the exchange between the lung's gas-exchanging space

\( (V_{PA,CO}) \) and their dead space \( (V_{P1,CO}) \)

\[ V_{PA,CO} = V_{PA,CO} - V_{P1,CO} \]

This also holds true for oxygen, and when introduced into the short forms of the first two expressions, the gas rates entering the body becomes

\[ \dot{V}_{CO} = (V_{P1} - \dot{V}_{P1})P_{CO} - \dot{V}_{PA,CO} \] \hspace{1cm} (1)

\[ \dot{V}_{O2} = (V_{P1} - \dot{V}_{P1})P_{O2} - \dot{V}_{PA,O2} \] \hspace{1cm} (2)

The rates of entry of CO and O2 into the body can also be viewed according to the following general equations,

\[ \dot{V}_{CO} = D_{CO}(P_{A,CO} - P_{B,CO}) \] \hspace{1cm} \( \text{mmol} \text{ min}^{-1} \text{liter}^{-1} \)

\[ \dot{V}_{O2} = D_{O2}(P_{A,O2} - P_{B,O2}) \] \hspace{1cm} \( \text{mmol} \text{ min}^{-1} \text{liter}^{-1} \)

in which the flux, either positive or negative, is dependent on the pulmonary diffusing capacities \( (D_{CO} \text{ and } D_{O2}) \) and the difference in pressure of the gas in the alveoli \( (P_{A,CO} \text{ and } P_{A,O2}) \) and of that in the pulmonary capillary blood \( (P_{B,CO} \text{ and } P_{B,O2}) \). J. S. Haldane wrote that the pressures of CO and O2 are interrelated: \( P_{B,CO} = (x/y)P_{B,O2} \) where \( x \) is the fractional saturation of hemoglobin in arterial blood due to CO, \( y \) is that due to O2, and \( z \) is a partition coefficient here accepted to be constant and equal to 230 (12). The Haldane relationship and the two equations immediately above are solved together resulting in the expression

\[ \dot{V}_{CO} = D_{CO}(P_{A,CO} - (z/y)(P_{A,O2} - \dot{V}_{O2}/D_{CO})) \] \hspace{1cm} (3)

where the constant, \( z = D_{O2}/D_{CO} = 1.23 \), accounts for the difference in diffusibility of O2 and CO on the basis of molecular size (7). The gas pressures are then written as the product of the total ambient pressure and the fractional concentration of the particular gas, and the
symbol \( S = \frac{S_p C}{V} \) is introduced. Upon equating equations 1 and 2, the value of carbamyl-globin \( (x) \) can be stated. However, several approximations are necessary in order for \( x \) to be stated in terms of parameters which henceforth will be considered as fundamental. The first assumption that \( y = 1 - x \), which implies that systemic arterial blood is fully saturated with \( CO \) and \( O_2 \), results in the expression

\[
x = \left[ 1 + \frac{SF_{A,02} - d^{-1}(V_I - V_D)F_{I,02} + d^{-1} \dot{V}_A \dot{F}_{A,02}}{Sm_{A,CO} - e \cdot (V_I - V_D)F_{I,CO} + s \dot{V}_A \dot{F}_{A,CO}} \right]^{-1}
\]

provided \( \dot{V}_{O_2} \) is expressed as in equation 2. Next observe, whereas \( \dot{V}_A = \dot{V}_B - \dot{V}_D \), only slight error is introduced by writing \( \dot{V}_A = \dot{V}_I - \dot{V}_D \), and during steady state equilibrium of the single \( CO \) flux system \( \dot{V}_{CO} = 0 \), implying that \( F_{A,CO} = F_{I,CO} \), whence the above expression can be written

\[
x_{eq} = \left[ 1 + \frac{SF_{A,02} - d^{-1}(V_I - V_D)F_{I,02} - F_{A,02}}{Sm_{F_{I,CO}}} \right]^{-1}
\]

Concerning equation 2, the data of others (13,14) when plotted as in Figure 1 above that \( v = \dot{V}_{O_2}/\dot{V}_A = 0.0498 \) (highly correlated, \( r = 0.962 \)), which implies that \( \dot{V}_{O_2} \) is directly proportional to \( \dot{V}_A \) at \( \dot{V}_{O_2} \) rates of less than 2,500 ml min\(^{-1}\). These results show that \( F_{A,02} = F_{I,02} - a \), both while at rest and during exercise when \( \dot{V}_{O_2} \) rates are less than 2,500 ml min\(^{-1}\).

From the above, it now becomes possible to write

\[
x_{eq} = (1 + \beta/(\alpha \dot{V}_A))^{-1}
\]

where \( \alpha = Sm_{F_{I,CO}} \) and \( \beta = S(F_{I,02} - a) - d^{-1} \dot{V}_A \). Further, from data on the same adult men and women as shown in Figure 2, \( \dot{V}_A = 0.835 \dot{V}_B - 1120 \) (very highly correlated, \( r = 0.996 \)).
The equation for \( \dot{x}_1 \) implicitly requires that, of the CO which enters and leaves the body, practically all of it combines with hemoglobin and that none is oxidized, hydrated, or otherwise broken down, or even produced, or else that such opposing rates are equal. Early tests with radioactive tracers employed \( ^{14} \text{C} \) prepared in a cyclotron from \( \text{B}_2\text{O}_3 \). Because of the 21 minute half life of this isotope, the tests lasted for only one hour, and less than one-tenth per cent of the \( ^{14} \text{C} \) which disappeared from the blood was expired as \( ^{14} \text{CO}_2 \) (15). A contrary conclusion was later arrived at (9) by exposing mice in controlled tests in a 12.5 liter chamber initially containing close to 10 ml of CO gas together with traces of the long-lived \( ^{14} \text{C} \). Depending on the number of mice, from one-half to two-thirds of the CO disappeared in the course of four days. The rate of conversion of \( ^{14} \text{C} \) to \( ^{14} \text{CO}_2 \) was reported to be \( 0.29 \times 10^{-3} \) ml ar\(^{-1} \) g\(^{-1} \) of body weight. In tests of recovery of total CO following three hours of equilibration of fresh whole blood of rats, dogs and human beings (12), the rate of disappearance was \( 1.6 \times 10^{-3} \) ml min\(^{-1} \) g\(^{-1} \) of total COHb. If in the mice tests the total hemoglobin was 0.01 of the body weight and this was one-third saturated with CO, the rate of conversion of \( ^{14} \text{C} \) to \( ^{14} \text{CO}_2 \) would have been \( 1.6 \times 10^{-3} \) ml min\(^{-1} \) g\(^{-1} \) of total COHb.

Sjöstrand measured the small quantity of CO which was expired by adult human beings who breathed CO free air (10). He concluded, as Lemberg indicated on biochemical grounds, that the daily breakdown of hemoglobin produces CO. At a mole ratio of 4:1 with \( 1/120 \) of the total \( \text{Hb} \) hemoglobin producing CO daily, this would furnish \( 0.007 \times 10^{-3} \) ml min\(^{-1} \) g\(^{-1} \) of hemoglobin. This rate, just recently verified (27), slightly opposes the oxidation rate discussed above. Thus, \( \dot{v}_{\text{CO}, \text{CO}_2} = \dot{v}_{\text{Hb}, \text{CO}} \).
where $x$ is the proportion of CO in Hb, $r = 1.8 \times (10^{-3})$, and $o = 6 \times (0.00073) \times 10^{-1}$.

At equilibrium under steady state conditions of the postulated triple flux system, $P_{A, CO} = P_{I, CO} = \dot{V}_{HB, CO, CO_2}^{-1}$. Consequently, the equilibrium statement for the triple flux begins as

$$x_{o, 3} = \frac{\beta}{\alpha - \gamma (T_{x_{o, 3}} - 0)}$$

which takes the form of a quadratic equation

$$x_{o, 3} = \frac{\alpha + \beta \cdot \gamma (o + r)}{2 \gamma r} - \left[ \left( \frac{\alpha + \beta \cdot \gamma (o + r)}{2 \gamma r} \right)^2 - \frac{\alpha + \gamma_3}{\gamma} \right]^{1/2}$$

where $\alpha$ and $\beta$ are defined under equation 4 and $\gamma = n(1 + 3 \times 10^{-1}) \Sigma Hb$.

A definition of $DOO$ is required in order to complete both the single flux, $x_{o, 3}$, and the triple flux, $x_{o, 3}$, equations. It would be desirable to write this according to parameters already employed, such as rate of alveolar gas flow and total hemoglobin. Figure 3a shows a plot of average values of $DOO$ and $\dot{V}_A$ at rest and at exercise for individual men and women studied by other investigators (14, 17). In all cases, $DOO$ increases with $\dot{V}_A$. On the average, $DOO$ increases by 0.915 al $m^{-1} \text{ml}^{-1}$ of Hg when $\dot{V}_A$ increases by 1,000 al $\text{ml}^{-1}$. From this value of the slope, the mean intercept on the ordinate can be found for each person, thus indicating the value of $DOO$ when $\dot{V}_A = 0$. The values of the intercepts are high for large men, low for small men, and even lower for women of larger body surface area than some of the small men. Sjöstrand found for each square meter of surface area 44.4 ml of total hemoglobin whereas women had only 32$^1 g$ of total hemoglobin (6). Figure 3b shows that, on the average, the intercepts on the
ordinate of Figure 1a increase in proportion with the quantity of \( ZH \) as predicted from body surface area of men and women. This suggests on empirical grounds that in adult human beings

\[
D_C = 0.243 \times E_b - 11.5 + 0.915 \times 10^{-3} \hat{V}_A
\]

On theoretical grounds, Roughton and Forster (18) wrote that \( D_{CO} = D_{W}^{-1} + (dV_C)^{-1} \) from which it follows that \( D_X \) and \( V_C = c^{-1}(1 - r)^{-1} D_{CO} \) and that \( r = D_{W} D_{CO}^{-1} \). The mean value of \( r^{-1} \) for six men breathing room air can be computed from their data to be close to 0.41. On the average, \( r \approx 0.45 \). When our prediction of \( D_{CO} \) is introduced, \( V_C = 0.110 E_b + 0.00234 \hat{V}_A - 29.4 \). Because \( E_b \) was not measured or reported by them, \( V_C = 46.7 \hat{V}_A + 0.00234 \hat{V}_A - 29.4 \) where \( A \) is male body surface area in square meters. From this, if \( \hat{V}_A \approx 5,000 \), for their six subjects \( V_C = 69 \) as compared with 59 as by a steady state method in which they actually determined \( D_{CO} \) and \( \theta \). Of further interest, our prediction of \( D_{CO} \) allows \( V_C \) to increase with the types of exercise which cause \( \hat{V}_A \) to increase (8). An idea of the precision is shown in Figure 4 which compares predicted values with those reported from three laboratories (18, 19, 20) in addition to the two laboratories (14, 17) from whose data the prediction equation was built. Here, the standard deviation of the difference is \( \sigma_D = 5.0 \). If that of actual measurements is \( \sigma_D \approx 3.0 \), it follows that for prediction the \( \sigma_D = \sqrt{25 + 9} = 5.8 \) which, though less precise than an actual measurement, is suitable for the present purposes. Among the parameters which influence \( D_{CO} \), at least two of these of considerable importance are total body hemoglobin as well as rate of ventilation of the lungs during the change from rest to exercise.
To ascertain the validity of \( x_{o,1} \) or \( x_{o,3} \) recall that the 1946 Pensacola studies of the U.S. Navy (4) were performed by first breathing 0.7 to 2.0 per cent CO in air for about three minutes, until it was guessed that COHb levels were such as to be similar to those which eventually would have been achieved while breathing a more dilute mixture of CO in air. Once having thus reached a particular level of COHb, this was steadily maintained by breathing the dilute CO for periods of four to seven hours, during which arterial and venous levels of COHb were equal, fairly steadily maintained, and thus can be termed \( x_o \), "measured". Table 1 lists basic data and the computed values of \( \alpha \), \( \beta \), and \( \gamma \) for each of the total six tests on the three men. The filled circles in Figure 5 compare the \( x_{o,1} \) values predicted from \( \alpha \) and \( \beta \) with the \( x_o \), "measured" values. The crosses in Figure 5 do the same for \( x_{o,3} \) values from which it becomes obvious, if the triple flux system operates in human beings, that the opposing rates have similar values, i.e. \( x_{o,3} \approx c \) such that 
\[ \alpha \approx \frac{1}{2}(x_{o,1} - c). \]
In support of this, Krabbefer's experiments (16), that portion dealing with rate and the oxidation of \( \text{CO} ^ {14} \), can be cited as showing that \( r \% 0.3 \times 10^{-3} \) instead of 1.8 \times 10^{-3}. At this stage, \( x_{o,1} \) seems perfectly satisfactory for the prediction of equilibrium levels of COHb under steady state conditions. Although granting the possibility that CO is produced and also destroyed by the living body, it becomes unnecessarily complicated when the influence of such processes are considered, as was done in the derivation of the equation for \( x_{o,3} \).

Accumulation of carbon monoxide, i.e. \( x(t) = \text{COHb} \) as a function of time. In the early 1940's suitable methods were devised for measuring low levels of COHb (19). These were employed in tests performed on adult human males, who mostly were physically qualified for military service. Because of the dangers involved, \( x \) was never allowed to rise
much beyond a level of one-thirtieth of the total available hemoglobin. In some laboratories only a single blood sample was withdrawn, usually from a vein, and this was done at a definite time from 3 to 300 minutes after starting to breathe a known dilution of CO in either air or "pure" O₂. Realizing that smokers began with a moderately high level of COHb, one laboratory withdrew two blood samples, one at the start and the other at the end of the test (21). Usually, the pressure was that at sea level. A few tests were made at the low pressures obtaining in chambers for the simulation of altitude. The subjects were seated, recumbent, and sometimes engaged in the exertion of "hard work". They wore a mask, tightly covering the nose and mouth, into which was delivered the desired gas mixture at a rate stated as expiratory flow. One laboratory reported the measured blood volume of each subject (19). Another guessed at the blood volume on the basis of an older method of prediction based on body surface area (21). The hematocrit was never reported, and only in one set of tests were the O₂ and CO capacity of a milliliter of blood actually measured and reported (4).

In other words, none of the tests obtained and reported measurements of all of the necessary parameters. Probably, those which in all cases were reliably reported are as follows: $P_I, CO; P_I, O₂; \tilde{V}_H; P_e$ and $x$. In one case $x_0$ was reliable (21); for the other case (19) we have guessed at $x_0$ according to the memory of one of the subjects ($P_U$) as to whether the others were smokers of tobacco. In one set of tests (19) the reported blood volume was perfectly suited for finding $\Sigma S$ except that the CO capacity was not listed, so we have assumed that each subject had a capacity of 0.2 ml of CO per ml of blood. For the other set of tests (21) we have used Sjöstrand's value of 475 g. of hemoglobin for
each square meter of male body surface (6). Further, certain parameters were never measured, and we have had to apply the interrelation of $\dot{V}_A$ and $\dot{V}_{O_2}$ with $\dot{V}_H$; very recently, similar interrelations were published dealing with the control of respiration and circulation (22). However, the reader should realize that this may apply in rest and exercise but certainly not during hyperpnoea. In the latter case the present study of a system is deficient for the accumulation and elimination of CO. The sole remaining parameter is $D_{CO}$ which we derived above in order to complete expressions for $x_{H_1}$ and $x_{H_2}$. As a consequence of the way in which $D_{CO}$ was correlated with $\dot{V}_A$ and $\dot{V}_H$, it follows that the prediction of $D_{CO}$, though suitable for adult human beings, certainly should not be applied to infants, small children, and experimental animals which have $\dot{V}_H$ of 200 g. or less together with low values of $\dot{V}_A$. In order to write a more thorough prediction, there is need for further experiments on the actual values of $D_{CO}$, $\dot{V}_H$, and $\dot{V}_A$.

It is easy to make the above critical remarks after having perused the findings of competent investigators who, while exploring the accumulation of CO, naturally placed more emphasis on some parameters and excluded others of less current interest. In recognition of this, in the tabulation of the results of 51 tests from the literature, we have indicated, where necessary, the assigned values (Tables 2 and 3). The reader who follows these tabulated values can compute or predict $x$ and see this compared with the measured value (Figure 6).

The basis on which $x(t)$ can be predicted rests upon the approach of the accumulation reaction to a steady state equilibrium $x_0$, $x_{H_1}$. Certainly this can not be ascertained from only one or two determinations.
of \( x \) at a given time such that the maximum observed values of \( x < 0.3 \) \( x_0 \). Although there is little information for judging which order of a reaction pertains to accumulation, elimination of CO is claimed to be a first order reaction. From this it may be inferred that accumulation is also a reaction of the first order. Repeated statements have been published concerning the order of elimination (e.g. 2, 15). An especially clear presentation of data is that for a single subject (FWM), who undoubtedly eliminated CO in the order so claimed (17). The subject was certainly an interested person of experience who probably was able to keep \( v_0 \) at a steady rate throughout the period of the one hour test during which \( x \) was measured at intervals by two experts (MSH and FWM). These indications, together with the derived value of \( x_0 \), and the apparent linear relationship of \( x \) with time for the early stage of the process (2), dictated an attempt to write an exponential equation which describes \( x(t) \). The mathematical treatment begins with the general first order equation \( x = A + Be^{-kt} \). The initial and equilibrium conditions determine the constants \( A \) and \( B \), i.e. when \( t = 0 \), \( x = x_0 \) and when \( t = \infty \), \( x = x_0 \), resulting in the expression

\[ x = x_0 - (x_0 - x_c)e^{-kt} \]  

(5).

It is now necessary to define \( k \), which determines the rate of the process, in terms of parameters that have been previously designated as fundamental. This begins with a linear approximation for \( v_{CO} \) during the first part of the accumulation. Various workers (19, 21) have noticed the resulting linear relationship, \( x - x_0 = \beta t \), and have substantiated it with their data.

A digression will clarify this linear relationship which ultimately will be solved simultaneously with equation 5 for \( x = x_0 - 1/3(x_0 - x_0) \).
the one-third point being chosen because equation 5 is nearly linear for
the first one-third of its range. \((x - x_0)\) indicates an increase of CO
in the blood equal to \((x - x_0)z\) Z, which, in turn, is equal to the
quantity of CO inspired minus the quantity expired \(\int FY F_{CO} dt - \int F_Y
\int CO dt\), provided the buildup of CO in the lungs' functional residual
capacity is neglected. If the linear approximation \(v_{CO} = \dot{V}_{CO} \) is em-
ployed, the integration of equation 1 gives

\[
\dot{V}_{CO} = (x - x_0)z Z
\]

which implies that \(x = \dot{V}_{CO}/z Z\). Next, a factor is inserted which will
allow the pressure to be other than atmospheric at sea level, resulting
in the expression

\[
\dot{V}_{CO} = \frac{\dot{V}_{CO}}{z Z} f_p = \frac{F - 4T}{7T} Z
\]

Using equations 1 and 2 and accepting \(V_Y Z \dot{V}_{CO} \) and definitions of \(\alpha, \beta, \gamma, \) and \(V, \dot{V}_{CO} \) can be rewritten thus:

\[
\dot{V}_{CO} = (\alpha - \beta - \gamma)Z f_p = \dot{V}_{CO} Z
\]

Noting that \(\dot{V}_{CO} \) is a function of \(x, \beta \) is solved for a point when the
process has completed one-third of its full range, i.e. when

\[
x = x_0 + 1/3 (x_0 - x_0)
\]

At the one-third point

\[
\beta_{1/3} = \frac{\alpha - \beta}{f_p}, \text{ where } \beta = \left[\frac{3}{x_0 + 2x_0} - 1\right]^{-1}
\]

Returning to the first order equation 5, \(k \) can now be found by
solving this equation and the established linear relationship for the
above stated one-third point as indicated below.

\[
t_{1/3} = (1/3)(x_0 - x_0)(\beta_{1/3})^{-1} = \frac{(1/3)(x_0 - x_0)(x_0 + x_0) - k(1/3)}{x_0 - (x_0 - x_0)}
\]

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\[ -k = \frac{\beta_{1/3}}{x_0 - x_0} - 3 \ln \frac{2}{3} \]

Having found an expression for \( k \), it is inserted into equation 5, \( \beta_{1/3} \) being replaced by its equivalent, and the constant term \( -3 \ln \frac{2}{3} \) being symbolized by \( h \):

\[ x = x_0 - (x_0 - x_0)e^{\frac{(c \cdot h - k)P_0 x}{(x_0 - x_0)t}} \]

where, in review,

\[ a = 102 \cdot k^{-1} = 0.0496 \]

\( m = 230 \), partition coefficient

\( z = 1.34 \text{ ml of CO to saturate one gram of hemoglobin} \)

\( h = a^{-1} \ln 0.667 = 0.909 \)

\( d = D_{O_2} k^{-1} = 1.23 \)

\( f_p = (P-47) \times 10^{-1} \), assuming dry gas is breathed at a pressure of 1 atm of Hg.

\[ \alpha = \left( \frac{1}{x_0 + 2x_0} - 1 \right) \]

\[ x_0 = x_0, t = \left( 1 + \frac{a}{\alpha} \right)^{-1} \]

\[ c = 3m b_{LO} \]

\[ b = 3(1 + a^{-1}) \]

\[ y = m(b + 3y^{-1}) \]

\[ S = D_{CO}(P-47) \]

\[ D_{CO} = 0.043 \times 10^{-3} \]

\[ \bar{v}_A = 0.835 \times 10^{-3} \]

Predictions, according to equation 6, of the proportion of the total hemoglobin which would occur as carboxyhemoglobin are compared in Figure 6 with actual determinations reported in \( \bar{v}_A \) tests carried out in two laboratories (Tables 2 and 3). Thirty-six tests (filled circles) were done at a total pressure of approximately one atmosphere.
while breathing a mixture of CO and air (19, 21). Five tests (circles) were done at one atmosphere while breathing CO in 99 per cent O₂. Ten tests were done at total pressures of less than one atmosphere; in two of these, the pressure was so low as one-fifth of an atmosphere, and CO in 98 per cent O₂ was breathed (triangles); in eight of these tests the pressure exceeded one-fifth of an atmosphere and CO in air was breathed (filled triangles). Tables 2 and 3 show that each subject started the test with different levels of COMb, x₀, and during the exposure the COMb rose to a higher level, x, which is shown by the abscissa in Figure 6. The standard deviation of the difference between predicted and reported values of x is σₓ = 0.015. This would represent the precision of prediction if there were no error in the method of measuring the reported values of COMb. Geometric methods, such as those used in the two laboratories, are more precise at low than at high levels of COMb. If so, it follows from \( \sigmaₚ^2 = \sigmaₓ^2 + \sigmaₒ^2 \) that a low levels \( \sigmaₚ \approx 0.015 \), whereas at higher levels, of e.g. 0.3 COMb, \( \sigmaₚ \approx 0.020 \). The mean deviation, \( \bar{x} = 0.021 \), combined with \( \pm 2 \sigmaₚ \), was used to draw the two dashed lines in Figure 6. The intercept on the ordinate of the uppermost line indicates that the precision of prediction is approximately 0.05 at the various levels of COMb involved in the total 51 tests. Of more importance, however, the predictions appear to be valid at different total pressures and concentrations of inspired O₂.

**Influence of Fundamental Parameters**

In order to illustrate the influence of the fundamental parameters included in equation 6, it is believed advisable to show, with an example, how to compute x. Then, by graphic means, it is proposed to show the relative importance of each parameter (Figs. 7 - 11).
The procedure for calculating both \( x_u \) and \( x \), although algebraic, is somewhat lengthy. An example using likely values for the variables, will illustrate the procedure.

**Given:**
- \( P = 7.60 \) mm Hg
- \( V_g = 10,000 \) ml per minute
- \( P_f,0 = 0.00 \) ml per ml
- \( P_f,0 = 0.20 \) ml per ml
- \( 2Hb = 800 \) gram
- \( x_o = 0.060 \) proportionate initial saturation with CO.

Using the definitions set forth immediately following equation 6, it is found, to within three significant digits, that:

\[ \dot{V}_A = (0.85)(10,000) - 1.20 = 7,230 \]
\[ \circ Hb = (0.24)(800) - 11.5 + (0.915)(7.23) = 29.5 \]
\[ \circ S = (1.95)(7.1) = 21000 \]

\( \alpha, \beta, \gamma \) can be determined using \( S \) and the various other equations and constants specified under equation 6.

\[ \alpha = (21,000)(1.00)(0.001) = 4.830 \]
\[ \beta = (21,000)(0.210 - 0.8396) - (0.2468)(7.230) = 3.070 \]
\[ \gamma = (2.0)(1 + \frac{21000}{7.230}) \frac{1800}{719} = 719,000 \]

Now, the desired predictions can be made:

\[ x_u = \frac{1}{1 + \frac{0.070}{4.830}} = 0.611 \]

Since \( x_u = 0.610 \), a value near that of a person who smokes moderately, the exponent of eq 6 may be determined by using the values computed above of \( J, \beta, \gamma \), recognizing that \( f_p = 1.0 \). Whence,

\[ \beta = \frac{1}{2} \cdot \frac{0.611}{0.050} = 0.311 \]
and the exponent of equation 6 is

\[
\frac{(d - m)}{\gamma(x_n - x_0)} t = \frac{4.830 - (0.511)(3.070)(-0.909)}{719.000 (0.611 - 0.050)} \times 0.00875t
\]

Then, the level of carboxyhemoglobin at any time becomes

\[
x = 0.611 - (0.611 - 0.050) e^{-0.00875t}
\]

If \(t = 20\) minutes

\[
x_{20} = 0.611 - 0.561 e^{-0.175}
\]

Since the "natural" antilogarithm of \(-0.175 = 0.339\)

\[
x_{20} = 0.611 - (0.561)(0.339) = 0.140.
\]

It is thus seen that a large man with a moderate ventilation rate, when breathing room air at atmospheric pressure diluted to a level of one-tenth per cent carbon monoxide, could have a carboxyhemoglobin level of approximately 14 per cent saturation after 20 minutes of exposure.

The above type of example can be expanded to illustrate the influence of the various parameters. Allen and Root (12) determined the partition coefficient \(m\) at 37°C. using aerotometers containing fresh whole blood mixtures such that within three hours equilibrium was approached from either direction. Further, the plasma hydrogen ion activity was caused to vary with \(\text{CO}_2\). When the plasma \(pH\) was 7.30 to 7.36, the \(m\) value was 230. At lower and higher \(pH\), i.e. 7.15 and 7.40, \(m\) fell to a value of 170. Sendroy does not believe that \(m\) is affected by plasma \(pH\) (24) and accordingly would treat \(m\) as constant and equal to close to 230, as has been done thus far for the purpose of simplification. Table 4 was prepared to show that if \(m\) were to vary from 170 to 230, this would cause steady state equilibrium levels of carboxyhemoglobin, \(x_n\), to range from 0.54 to 0.61. However, for at least two hours during approach to such
equilibria, the absolute values of carboxyhemoglobin would rise similarly. Even if a were to vary through this range, it would have little influence on \( x(t) \) values for at least two-thirds of the total accumulation. It therefore seems reasonable to accept \( a \) as a constant and presently to ignore the claimed influence of plasma hydrogen ion activity.

On the basis of equation 6, various aspects of accumulation of CO are shown in Figures 7 through 10 which cite assigned dimensions in the legend. From Figure 7 it is clear that air containing 100 parts of CO per million would lead to a steady state equilibrium of 15 per cent COHb. If air contained 1,000 p.p.m., the \( x_0 \), value would rise to 61 per cent COHb. In contrast, if 98 per cent \( O_2 \) contained 1,000 p.p.m., the level would be 20 per cent. The above (Fig. 7) would also have been anticipated approximately by Haldane (1). It is doubtful, however, if the following Figure 8 could have been predicted by him and his colleagues, since full use of the presently derived equation 6 is involved. To reach 10 per cent levels of COHb, when breathing air, would require only 5 minutes if the air contained as much as 1 per cent CO. Sixty-five minutes would be required to reach this level if the air contained 0.1 per cent CO. If the air contained 0.01 per cent CO, it would take 120 minutes for the percentage COHb level to rise only from 2 to 6. The above would occur if the expiratory flow were maintained at an ambient rate of 10 liters per minute. At rates greater and less than this, the curves in Figure 9 show that the approach to steady state equilibrium would occur far more rapidly if the ventilation of the lungs were to increase. Figure 10 shows that with lesser quantities of total body hemoglobin, the rate of approach to steady state equilibrium would
increase. In this example, we can estimate that 70% to combine with 600 grams of hemoglobin, the saturation would be 40 per cent. During a similar process, 700 grams of hemoglobin could combine with a later level of CO. From this, the saturation would be slightly less than equal to 40 per cent. From these illustrations it appears that the most important parameter is $P_{1,CO}$ followed in descending order by $P_{2,CO}$ then $P_3$ and finally $P_{4,CO}$.

Although accumulation of CO can be viewed as set forth above and dangerous situations, or it is to none of the fundamental parameters in physiological tracer experiments can be anticipated, it is wise to emphasise the elimination of CO from the body. This especially should be of interest to physicians who will find the observations of Smith and Sharp (5) to be predictable. Let us consider that their normal male patient could have had a 60 per cent COHb level, i.e. in this case $x_0 = 0.60$, at the start of the treatment at two atmospheres of ambient pressure. Further, accept their finding with the reversion spectrophotometer that, after one hour of treatment, his COHb = 0. Oxygen was breathed through a mask, and $P_{1,CO} = 0.05$ or 10 p.p.m. The arterial blood saturation rate was 10 liters min$^{-1}$ and the total body haemoglobin was 15 grams, all the necessary parameters having been assumed. From equation 6, predict the rapidly descending curve, drawn with a dashed line in Figure 7, which after 60 minutes of treatment, anticipates there to be 1 per cent COHb instead of "none". The dashed curve indicates, with all parameters the same except that the ambient pressure is one atmosphere, that the rate of elimination would be 2.5 times more slow. The third of the dashed curves is of interest to aviation medicine, showing at one-half of an atmosphere
that breathing of 98 per cent oxygen would eliminate CO at a rate of 2.9 times slower than at one atmosphere. Similar effects of ambient pressure on elimination of CO would occur when breathing air, except that at a given pressure, the rate of elimination of CO would be 6.5 times more slow than when breathing 98 per cent oxygen (three continuous curves in Fig. 11). This six-fold relative difference is precisely that cited by Lilienthal (2) for findings in two laboratories. However, there truly were absolute differences in elimination half-time between the two laboratories. It is believed that such could have occurred if the subjects of Roughton and Root (25) might have had a low ventilation rate of 5 liters min\(^{-1}\), whereas those of Lilienthal and Fiske (cited in 2) might have had either a ventilation rate exceeding 5 liters min\(^{-1}\) or else a total body hemoglobin lower than 800 grams. Although it would be desirable to refer to other studies of elimination, such as from dogs (26), the present authors have earlier indicated that for equation 6 the derivation of \(V_{CO}\) and the interrelationship of \(V_{O_2}\) with \(V_A\) and \(V_E\) contain knowledge that could presently apply only to men and women. It therefore seems that the same fundamental parameters affecting the accumulation will operate just as effectively upon the elimination of CO from adult human beings.

**DISCUSSION**

A critique of the means employed to obtain a prediction of blood carboxyhemoglobin chiefly concerns the fact that, whereas it was possible to state certain fundamental parameters, it was impossible to find these as having been actually measured and reported in their entirety in the various cited experiments performed with human beings. It is indeed gratifying that, in the tests of predictability, the results on accumulation
(Fig. 6) and elimination of CO (Fig. 11) agreed as well as they did.

This suggests, should future needs arise, that instead of making estimates of various parameters, it will become desirable to measure these with independent methods capable of detecting all of the necessary factors involved in the computation of a given parameter. The presently associated parameters can be listed according to decreasing order of absolute precision of measurement ranging from errors of $\pm 0.5$ per cent to $\pm 5$ per cent, or somewhat more, as follows: $P$, $P_e$, $P_{CO}$, $x$, $P_{I,CO}$, $P_{I,02}$, $\dot{V}_{02}$, $\dot{V}_{CO2}$, $EHB$, $\dot{V}_A$, and $D_{CO}$. These, in part, are associated with the constants $d$ and $s$. Further, in the true statement $x + y + z = 1$, it was convenient to let $s = 0$, where $s$ is the proportion of total functional arterial hemoglobin occurring as reduced hemoglobin. It was not only convenient but also necessary because of lack of full information to interrelate certain of the above basic parameters, thus sacrificing some precision.

The error involved in equating $\dot{V}_T$ and $\dot{V}_B$ is negligibly small. Within fairly wide limits $\dot{V}_{O2} = 0.0496 \dot{V}_A$; if $\dot{V}_{CO2} \approx 0.83 \dot{V}_{O2}$, it can be shown that $\dot{V}_T = 1.009 \dot{V}_B$, thus eliminating the necessity of collecting information on $\dot{V}_{CO2}$. Further, from the interrelation of $\dot{V}_{O2}$ and $\dot{V}_A$ (Fig. 1), it becomes possible to dismiss, though with certain misgivings (hyperpnea, $O_2$ debt, etc.), the necessity of reporting values of $\dot{V}_{O2}$. Hence, three basic parameters can be expressed in terms of $\dot{V}_A$, which is very closely related to $\dot{V}_C$ (Fig. 2), a parameter easily measured and often reported. Although specialized investigators to date have not reported on the relationship of $\dot{V}_{CO}$ with $EHB$ and $\dot{V}_A$, their data are highly suggestive of such, at least to within a presently suitable
degree of precision which could certainly be improved in future studies. Therefore, the nine presently appreciated parameters decrease to six in number and consist of the following: \( P, t, \dot{V}_1, CO, \dot{V}_I, O_2, \dot{V}_2, \) and \( \dot{V}_E. \) These certainly should be accurately measured and reported in studies using CO as a tracer. Among these, the only one which is difficult to comprehend is \( \dot{V}_E \) because this obviously includes non-circulating hemoglobin (or its equivalent). Several schools of investigators have indicated that the non-circulating hemoglobin is about 15 per cent of the circulating hemoglobin. A means of reporting \( \dot{V}_E \) would be to measure the total circulating hemoglobin by one of various methods and then multiply this by a factor of 1.15 (26).

Concerning the CO build-up in the functional residual capacity of the lungs, it was stated early in the above derivations that \( \dot{V}_{ACO} \) approaches zero as the exposure time increases. The quantity of gas

\[
\left( \int_0^t \dot{V}_{ACO} \, dt = [\dot{V}_{ACO}]_t - [\dot{V}_{ACO}]_0 \right)
\]

which builds up the CO concentration in the lungs may be appreciable, especially if the inspired CO concentration is high. This is apparent when it is noted that at equilibrium \( \dot{V}_{ACO} \) approximately equals \( \dot{V}_I, CO, \) and that this particular equilibrium is rapidly approached in the lungs. If the exposure is of long duration, the quantity does not have much effect since it is small compared to the total CO in the blood. For high inspired concentrations necessarily having short exposure times, the quantity becomes significant. In most of the data referred to by the authors, the exposure times were probably sufficiently long to permit disregard of this quantity. In the few cases where the exposure times were short, the
data were such that estimation of this quantity was impossible. Hence, it was neglected, although a thoroughly complete system should contain the term, $V_{F_{A}, CO}$.

It was stated prior to equation 4 that $x + y = 1$. This would be true if the $O_2$ and $CO$ pressures were sufficiently high so that hemoglobin became fully saturated with $O_2$ and $CO$ on its passage through the lung capillaries, and a shunt never existed which bypassed these capillaries. The relationship should correctly be stated as $x + y + z = 1$ where $z$ perhaps could be defined as functions of $P_{A}, O_2$ and $P_{A}, CO$ together with a shunt factor. Altogether this would slightly affect the computation of $x_{e, 1}$. For subject JL in Table 1, since $s = 0.17$, $x_{e, 1} = \left[0.83 + 1.519/(0.2615)^{-1}\right]^{-1} = 0.151$ instead of the value 0.147 which was computed on the assumption that $s = 0$. This subject had an exceedingly large proportion of reduced hemoglobin in the systemic arterial blood, due to his being exposed for several hours to a simulated altitude of 15,000 feet, yet the calculation of $x_e$ is scarcely affected in this instance.

There have now been mentioned many refinements to the present system which certainly seem important. It was intended to make the system as simple as possible, and many approximations were necessarily made to keep it so. The present lack of measured parameters certainly could lead to inadequate interpretations. For example, when two possible refinements (the production and oxidation of $CO$) were included, the resulting expression for $x_{e, 1}$ was much more complicated and did not agree with reported values. It is believed, however, that if all factors were taken into account, and the parameters necessary for their calculation were adequately determined, the complete system could be
improved beyond its present capabilities. The design and execution of experiments which should enable investigation of these various ideas are being considered. Minute quantities of $^{14}C$ could be safely used, and its accumulation and elimination from the human body could be detected continuously with a vibrating reed electrometer.

ACKNOWLEDGMENT

This survey of selected literature and the building of a prediction system started at the recent annual meetings of the Federated Societies of Experimental Biology when Mr. Allan Claghorn (Linde Company), who has long been interested in standards for breathing gases, asked in brief "Would 100 p.p.m. of CO be dangerous to SCUBA divers or should this never exceed 20 p.p.m.?" At a total of three atmospheres with an ambient flow of 10 liters min$^{-1}$ a fairly large man starting at 2 per cent carboxyhemoglobin could reach an equilibrium level of 12.9 per cent when breathing 100 p.p.m. of CO. After 100 minutes of exposure the level would be only 3.4 per cent. After 1,000 minutes this would rise to 10.2 per cent. Carboxyhemoglobin levels so low as these could elevate the threshold for vision in dim light (28), but it is doubtful if other physiological functions would be seriously affected during periods of time spent in such diving.
REFERENCES

1. Bajdane, J. S.: Respiration, 1922, Yale University, New Haven, Conn.


30. Letter dated 15 August 1961 to Commanding Officer, USAREUR from Chief, Preventive Medicine Division, Office of the Surgeon General, Headquarters, Department of the Army.

TABLE 1. Prediction of steady state equilibria, $x_{o1}$ and $x_{o2}$, and comparison with "measured" value (based on data of Lilienthal, Riley, Preuss, and Franks, 4).

<table>
<thead>
<tr>
<th>Subject</th>
<th>JL1</th>
<th>JL2</th>
<th>H1</th>
<th>H2</th>
<th>CP1</th>
<th>CP2</th>
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<tr>
<td>P</td>
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<td>598</td>
<td>523</td>
<td>523</td>
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<td>$e_{A1}^{10^{-3}}$</td>
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<td>10</td>
<td>10</td>
<td>10</td>
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<td>10</td>
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<tr>
<td>$e_{EM}$</td>
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<td>800</td>
<td>800</td>
<td>800</td>
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<td>$P_{i,00}$</td>
<td>$10^{-4}$</td>
<td>$1.5(10^{-4})$</td>
<td>$10^{-4}$</td>
<td>$0.5(10^{-4})$</td>
<td>$0.5(10^{-4})$</td>
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<td>0.2105</td>
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<td>mean. $x_{o}$</td>
<td>0.151</td>
<td>0.235</td>
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</table>

**Symptoms** | Yes | - | Yes | - | - | - |

* Values assigned by present authors but not given by investigators.
TABLE 2. Prediction of COHb as a function of time, $x$, in nineteen brief tests performed on five men at three different pressures, with a ten-fold range in alveolar gas flow and when breathing either air or oxygen containing as much as 5,000 parts per million of CO (based on data of Forbes, Sargent, and Houghton, 19).

<table>
<thead>
<tr>
<th>Subject</th>
<th>$P$ in kPa</th>
<th>$v_A(10^{-3})$ in ml min$^{-1}$</th>
<th>$\Sigma Hb$ in g</th>
<th>$v_{I, O_2}$ in ml m$^{-1}$</th>
<th>$v_{I, CO}(10^{-3})$ in ul ml$^{-1}$</th>
<th>$t$ in min</th>
<th>$x_0$</th>
<th>$x_1$</th>
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<th>reported $x$</th>
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<td>762</td>
<td>0.21</td>
<td>3.41</td>
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<td>0.143</td>
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<td>PK</td>
<td></td>
<td>52.3</td>
<td>851</td>
<td>0.208</td>
<td>1.49</td>
<td>3</td>
<td>0.746</td>
<td></td>
<td>0.115</td>
<td>0.127</td>
</tr>
<tr>
<td>PK</td>
<td></td>
<td>39.0</td>
<td></td>
<td>0.98</td>
<td>1.46</td>
<td>12</td>
<td>0.275</td>
<td></td>
<td>0.207</td>
<td>0.182</td>
</tr>
<tr>
<td>PK</td>
<td>412</td>
<td>9.9</td>
<td>911</td>
<td>0.21</td>
<td>3.56</td>
<td>6</td>
<td>0.864</td>
<td></td>
<td>0.107</td>
<td>0.112</td>
</tr>
<tr>
<td>JC</td>
<td></td>
<td>10.8</td>
<td>911</td>
<td></td>
<td></td>
<td></td>
<td>0.862</td>
<td>0.01</td>
<td>0.073</td>
<td>0.067</td>
</tr>
<tr>
<td>JB</td>
<td></td>
<td>10.7</td>
<td>762</td>
<td>3.87</td>
<td></td>
<td></td>
<td>0.876</td>
<td>0.05</td>
<td>0.123</td>
<td>0.117</td>
</tr>
<tr>
<td>JE</td>
<td>140</td>
<td>8.4</td>
<td></td>
<td>0.98</td>
<td>4.94</td>
<td></td>
<td>0.583</td>
<td></td>
<td>0.058</td>
<td>0.077</td>
</tr>
<tr>
<td>WP</td>
<td></td>
<td>7.7</td>
<td>866</td>
<td></td>
<td></td>
<td></td>
<td>0.578</td>
<td>0.01</td>
<td>0.019</td>
<td>0.048</td>
</tr>
</tbody>
</table>

$x_0$ not given by investigators; assigned by present authors on the basis of whether or not the subjects smoked tobacco.
Table 3. Prediction of COHb as a function of time, \( x \), in tests lasting up to 300 minutes on thirty-two men at two different pressures when breathing air with no little as 90 parts per million of CO (based on data of Pace, N. V., Consolazio, White and Bohnke, 21).

<table>
<thead>
<tr>
<th>Subject</th>
<th>( \dot{V}A (10^{-3}) )</th>
<th>( \times 10^{-3} )</th>
<th>( P_{t, CO} (10^{-3}) )</th>
<th>( t )</th>
<th>( x_{0,1} )</th>
<th>( x_0 )</th>
<th>Pred.</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAB</td>
<td>6.9</td>
<td>875</td>
<td>2.0</td>
<td>20</td>
<td>0.755</td>
<td>0.022</td>
<td>0.191</td>
<td>0.145</td>
</tr>
<tr>
<td>CUV</td>
<td>4.4</td>
<td>796</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.753</td>
<td>0.016</td>
<td>0.142</td>
<td>0.112</td>
</tr>
<tr>
<td>KLI</td>
<td>4.0</td>
<td>817</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.752</td>
<td>0.000</td>
<td>0.114</td>
<td>0.107</td>
</tr>
<tr>
<td>BOL</td>
<td>3.7</td>
<td>706</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.753</td>
<td>0.040</td>
<td>0.157</td>
<td>0.130</td>
</tr>
<tr>
<td>HLA</td>
<td>13.8</td>
<td>761</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.770</td>
<td>0.004</td>
<td>0.302</td>
<td>0.346</td>
</tr>
<tr>
<td>KNU</td>
<td>16.8</td>
<td>854</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.771</td>
<td>0.013</td>
<td>0.326</td>
<td>0.346</td>
</tr>
<tr>
<td>TOH</td>
<td>19.1</td>
<td>862</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.773</td>
<td>0.033</td>
<td>0.365</td>
<td>0.323</td>
</tr>
<tr>
<td>NCB</td>
<td>17.9</td>
<td>883</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.771</td>
<td>0.029</td>
<td>0.355</td>
<td>0.349</td>
</tr>
<tr>
<td>SCH</td>
<td>14.8</td>
<td>777</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.771</td>
<td>0.036</td>
<td>0.337</td>
<td>0.337</td>
</tr>
<tr>
<td>RIT</td>
<td>24.0</td>
<td>1,002</td>
<td>1.5</td>
<td>24</td>
<td>0.719</td>
<td>0.017</td>
<td>0.331</td>
<td>0.349</td>
</tr>
<tr>
<td>SCA</td>
<td>18.5</td>
<td>777</td>
<td>&quot;</td>
<td>20</td>
<td>0.722</td>
<td>0.037</td>
<td>0.302</td>
<td>0.358</td>
</tr>
<tr>
<td>DEM</td>
<td>13.6</td>
<td>740</td>
<td>1.0</td>
<td>30</td>
<td>0.627</td>
<td>0.069</td>
<td>0.289</td>
<td>0.289</td>
</tr>
<tr>
<td>DIB</td>
<td>14.7</td>
<td>777</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.628</td>
<td>0.024</td>
<td>0.241</td>
<td>0.270</td>
</tr>
<tr>
<td>KRI</td>
<td>13.2</td>
<td>731</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.627</td>
<td>0.050</td>
<td>0.290</td>
<td>0.264</td>
</tr>
<tr>
<td>PIT</td>
<td>14.3</td>
<td>861</td>
<td>1.72</td>
<td>15</td>
<td>0.738</td>
<td>0.073</td>
<td>0.236</td>
<td>0.230</td>
</tr>
<tr>
<td>OED</td>
<td>17.5</td>
<td>830</td>
<td>1.87</td>
<td>&quot;</td>
<td>0.760</td>
<td>0.072</td>
<td>0.306</td>
<td>0.265</td>
</tr>
<tr>
<td>WAO</td>
<td>14.5</td>
<td>749</td>
<td>2.18</td>
<td>&quot;</td>
<td>0.787</td>
<td>0.042</td>
<td>0.304</td>
<td>0.338</td>
</tr>
<tr>
<td>SBA</td>
<td>19.7</td>
<td>905</td>
<td>1.42</td>
<td>20</td>
<td>0.707</td>
<td>0.064</td>
<td>0.301</td>
<td>0.261</td>
</tr>
<tr>
<td>CAT</td>
<td>13.8</td>
<td>805</td>
<td>1.41</td>
<td>&quot;</td>
<td>0.702</td>
<td>0.054</td>
<td>0.255</td>
<td>0.261</td>
</tr>
<tr>
<td>JAN</td>
<td>16.5</td>
<td>747</td>
<td>1.29</td>
<td>&quot;</td>
<td>0.690</td>
<td>0.098</td>
<td>0.229</td>
<td>0.248</td>
</tr>
<tr>
<td>HTB</td>
<td>13.5</td>
<td>713</td>
<td>0.90</td>
<td>30</td>
<td>0.604</td>
<td>0.1</td>
<td>0.220</td>
<td>0.247</td>
</tr>
<tr>
<td>LEO</td>
<td>14.4</td>
<td>800</td>
<td>0.90</td>
<td>30</td>
<td>0.601</td>
<td>0.089</td>
<td>0.266</td>
<td>0.236</td>
</tr>
</tbody>
</table>
Table 3 (Cont'd)

<table>
<thead>
<tr>
<th>Subject</th>
<th>( V_A (10^{-3}) ) (al min(^{-1}))</th>
<th>( \Sigma Hb ) (E)</th>
<th>( P_{1,00} (10^{-3}) ) (al min(^{-1}))</th>
<th>( t ) min</th>
<th>( x^1 )</th>
<th>( x )</th>
<th>pred.</th>
<th>reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIN</td>
<td>14.0</td>
<td>7.08</td>
<td>0.94</td>
<td>30</td>
<td>0.612</td>
<td>0.069</td>
<td>0.278</td>
<td>0.295</td>
</tr>
<tr>
<td>SFB</td>
<td>11.9</td>
<td>7.14</td>
<td>0.55</td>
<td>45</td>
<td>0.478</td>
<td>0.036</td>
<td>0.183</td>
<td>0.193</td>
</tr>
<tr>
<td>WAI</td>
<td>13.4</td>
<td>6.83</td>
<td>0.56</td>
<td>&quot;</td>
<td>0.488</td>
<td>0.030</td>
<td>0.196</td>
<td>0.254</td>
</tr>
<tr>
<td>BBH</td>
<td>15.8</td>
<td>7.95</td>
<td>0.57</td>
<td>39</td>
<td>0.491</td>
<td>0.018</td>
<td>0.179</td>
<td>0.200</td>
</tr>
<tr>
<td>MRT</td>
<td>6.7</td>
<td>7.52</td>
<td>0.92</td>
<td>30</td>
<td>0.592</td>
<td>0.018</td>
<td>0.139</td>
<td>0.121</td>
</tr>
<tr>
<td>MAB</td>
<td>5.8</td>
<td>7.40</td>
<td>0.09</td>
<td>240</td>
<td>0.129</td>
<td>0.000</td>
<td>0.045</td>
<td>0.063</td>
</tr>
<tr>
<td>SCH</td>
<td>5.2</td>
<td>7.95</td>
<td>&quot;</td>
<td>180</td>
<td>0.126</td>
<td>0.033</td>
<td>0.055</td>
<td>0.078</td>
</tr>
<tr>
<td>PIZ</td>
<td>5.8</td>
<td>8.16</td>
<td>&quot;</td>
<td>270</td>
<td>0.127</td>
<td>0.004</td>
<td>0.046</td>
<td>0.073</td>
</tr>
<tr>
<td>MAB</td>
<td>5.7</td>
<td>7.68</td>
<td>0.18</td>
<td>300</td>
<td>0.226</td>
<td>0.058</td>
<td>0.130</td>
<td>0.165</td>
</tr>
<tr>
<td>MRT</td>
<td>4.6</td>
<td>7.10</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0.225</td>
<td>0.035</td>
<td>0.110</td>
<td>0.150</td>
</tr>
</tbody>
</table>

\( P = 523 \text{ mm } Hg = 10,000 \text{ ft.} \) standard altitude with \( V_A \) shown as the flow at that altitude; all other subjects were at sea level; \( Hb \) was assigned to be 425 \( g \) (E)\(^{-1}\).

Table 4. Variation in the partition coefficient, \( \alpha \), and its slight effect on anticipated levels of carboxyhemoglobin, \( x(t) \).

<table>
<thead>
<tr>
<th>( \alpha )</th>
<th>( x_0 )</th>
<th>( x_{10} )</th>
<th>( x_{40} )</th>
<th>( x_{120} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>170</td>
<td>0.538</td>
<td>0.095</td>
<td>0.206</td>
<td>0.384</td>
</tr>
<tr>
<td>190</td>
<td>0.565</td>
<td>0.096</td>
<td>0.210</td>
<td>0.396</td>
</tr>
<tr>
<td>210</td>
<td>0.590</td>
<td>0.096</td>
<td>0.213</td>
<td>0.406</td>
</tr>
<tr>
<td>230</td>
<td>0.611</td>
<td>0.097</td>
<td>0.215</td>
<td>0.415</td>
</tr>
</tbody>
</table>

Given: \( P_{1,02} = 0.21, P_{1,00} = 0.001, P = 760 \text{ mm } Hg, V_E = 10,000 \text{ al min}^{-1}, Hb = 800 \text{ g}, \) and \( x_0 = 0.050. \)
Fig. 1. Relationship between rates of oxygen utilization and of alveolar ventilation in men and women during rest and exercise (based on data of Fiske et al. [1] and Turino et al. [14]).

Fig. 2. Relationship between rates of alveolar and expiratory flow in men and women during rest and exercise (based on data of Fiske et al. [1] and Turino et al. [14]).

Fig. 3.a) Diffusing capacity of the lung for carbon monoxide compared with alveolar flow rate (based on data of Turino et al. [14] and Bates et al. [17], varying mean values during rest and exercise of their men and women subjects).

b) Relationship between diffusing capacity and total hemoglobin (estimated according to Fjæstad, [6]) when alveolar flow approaches zero.

Fig. 4. Comparing predicted diffusing capacities for carbon monoxide with those reported from three laboratories (Bates et al., Tables 2 and 3, ref. 16; Forbes et al., Table 5, ref. 15; Bates et al., Table 11, ref. 20).

Fig. 5. Comparing the predictions of steady state equilibria achieved by a single flux of carbon monoxide, $x_4$, and a triple flux $x_{14}$, with "measured" values of $x_0$ (based on data of Liberton et al. [4]).

Fig. 6. Prediction of blood carboxyhemoglobin as a proportion of total hemoglobin while breathing either air or oxygen mixtures containing traces of carbon monoxide both at sea level and at elevated altitudes (based on data of Forbes et al. [11] and Pace et al. [11]).

Fig. 7. Steady state equilibrium levels of carboxyhemoglobin, $x_{4,1}$, at various concentrations of inspired carbon monoxide in air and $0.06$ percent oxygen. Given: $V_T = 10,000$ ml; $F = 0.3$ as $R = 800$ grams, and $X_0 = 0.05$.

Fig. 8. Accumulation of carboxyhemoglobin as a function of time, $x(t)$, when breathing at the concentrations of carbon monoxide given in Fig. 7 for $V_T = 10,000$ ml; $F = 0.3$ as $R = 800$ grams, and $X_0 = 0.05$. Note that for purposes of comparison Figs. 8 through 10 are drawn on the same scale.

Fig. 9. Accumulation of carboxyhemoglobin as a function of time, $x(t)$, when breathing at a different flow rates. Given: $V_T, CO = 0.1$, $F = 0.3$ as $R = 800$ grams, and $X_0 = 0.05$. 

Fig. 10. Accumulation of carboxyhemoglobin as a function of time, $x(t)$, in accordance with different quantities of total body hemoglobin in grams. Given: $F_{i\text{CO}} = 10^{-3}$, $F_{i\text{O}_2} = 0.21$, $V_g = 10,000$ ml min$^{-1}$, $P = 760$ mm Hg, and $x_0 = 0.02$.

Fig. 11. Elimination of carboxyhemoglobin as a function of time, $x(t)$ when breathing air or 98 per cent oxygen at three different total ambient pressures. Given: $F_{i\text{CO}} = 10^{-3}$, $F_{i\text{O}_2} = 0.21$ or 0.98, $P = 0.5$, 1, or 2 atmospheres, $V_g = 10,000$ ml min$^{-1}$, $EHB = 800$ grams, and $x_0 = 0.02$. 


FIG. 1

OXYGEN UTILIZATION AND ALVEOLAR VENTILATION

\[ \dot{V}_O = 0.0498 \dot{V}_A \]

\( (r = 0.962) \)

During rest and exercise \( \dot{V}_O \) \(10^{-3} \) ml. min⁻¹
ALVEOLAR AND EXPIRATORY FLOW

\[ \dot{V}_A = 0.835 \cdot V_E - 1.120 \]

\( r = 0.996 \)
METHOD OF PREDICTION OF DIFFUSING CAPACITY

**FIG. 3a**

- ml min⁻¹
- mm⁻¹ Hg
- $D_{CO}$

**FIG. 3b**

- g
- $\Sigma Hb$ 'estimated'
- $V_A (10^{-3})$
FIG. 4

PREDICTED AND REPORTED DIFFUSING CAPACITY

\[ D_{CO} = 0.043 \Sigma \text{Hb} - 11.5 + 0.915 \left(10^{-3}\right) V_A \]

REPORTED \( D_{CO} \)
FIG. 5

PREDICTION OF STEADY STATE COHb

- $X_{e,1}$ 'SINGLE FLUX'
- $X_{e,3}$ 'TRIPLE FLUX'

$X_e \text{ 'predicted'}$

$X_e \text{ 'MEASURED'}$
FIG. 6

PREDICTION OF COHb AS A FUNCTION OF TIME

PREDICTED

REPORTED

PRESSURE  AIR  OXYGEN

ONE  < ONE
FIG. 7

COHb EQUILIBRA & INSPIRED CO CONCENTRATIONS

$X_{e1}$

$F_{I, O_2} = 0.21$

$F_{I, O_2} = 0.98$

$F_{I, CO}$
FIG. 8

COHb AT VARIOUS TIMES & INSPIRED CO CONCENTRATIONS

- $F_{ICO} = 10^{-2}$
- $F_{ICU} = 10^{-3}$
- $F_{ICO} = 10^{-4}$

$X(t)$ vs TIME (in minutes)
FIG. 9

COHb AT VARIOUS TIMES & RATES OF VENTILATION

\( \left( F_{i,CO} = 10^{-3} \right) \)

\[
\dot{V}_E \quad \text{LITERS min}^{-1}
\]

\[
\dot{V}_E = 50
\]

\[
\dot{V}_E = 20
\]

\[
\dot{V}_E = 10
\]

\[
\dot{V}_E = 5
\]

TIME ... minutes
COHb AT VARIOUS TIMES AND QUANTITIES OF HEMOGLOBIN

$F_{1,co} = 10^{-3}$

$\Sigma Hb = 600g$

$\Sigma Hb = 800g$

$\Sigma Hb = 1,000g$

TIME minutes
FIG. 11

ELIMINATION OF CO WHEN BREATHING AIR OR OXYGEN AT VARIOUS PRESSURES

- $F_1 O_2 = 0.21$
- $F_1 O_2 = 0.98$
- $P = \frac{1}{2}$
- $P = 1$
- $P = 2$

TIME (minutes)