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Respiratory System: Nitrogen Elimination

Hardin B. Jones

The characteristic of gas exchange appears to be mainly determined by the quality of blood perfusion through the various tissues of the body. Table 1 shows a comparison of the time constants of inert gas exchange of helium, argon, nitrogen, krypton and xenon. Regardless of the gas used, the similarity of the time constant is apparent. Thus to no discernible extent are the values fixed by diffusion rate or by factors of permeability. Additional evidence that the gas-exchange-rate constants are determined by the blood-tissue-perfusion rates is that the summated circulation to the body tissues calculated from the gas-exchange rates closely approximates cardiac output, and the regional perfusion rates so calculated from gas exchange are uniformly in agreement with other existing measurements.

TABLE 1.—WHOLE-BODY EXCHANGE OF INERT GASES MEASURED FOR 2 INERT GASES DURING SAME EXPERIMENTAL TIME*

	k_1	k_2	k_3	k_4	k_5
N_2	0.69	...	0.022		
Kr	0.69	...	0.022		
N_2	0.49	...	0.028		
He	0.49	...	0.025		
N_2	0.45	0.085	0.020	?	
Kr	0.40	0.090	0.019	?	
N_2	0.53	0.097	0.020	0.0078?	
He	0.50	0.094	0.022	0.00--?	
N_2†	0.46	0.087	0.024	0.0047	?
Xe†	0.35	0.087	0.024	0.0038	0.0008

* Results are given in terms of time constants of the equation: $R = R'e^{-kt} + R''e^{-kt} + R'''e^{-kt} + \ldots\ldots$
† Determined simultaneously using radioactive xenon.

The idea of inert-gas exchange depending on the circulation is not new. Every investigator of the past referred to its probable importance. It has been relatively weighted with a permeability factor in theoretical considerations of gas exchange, and recent extensive theoretical consideration has favored the weighting of the permeability factor (Smith and Morales[1]). The converse effect was established (Jones *et al.*[2]), for it had become apparent that the time constants analyzed from data as on radioactive nitrogen, krypton and argon uptake by the hand gave remarkably similar time constants. Experiments were devised in which whole-body exchange of N_2 and He and of N_2 and Kr were done successively. The subject was denitrogenated by O_2 inhalation for several hours, then he rebreathed a He or a Kr atmosphere; this was followed by a 2d period of O_2 inhalation during which exchange of the noble gas could be measured. The most precise experiment was that with radioactive Xe. In this instance the subject equilibrated with a known amount of radioactive Xe contained in air before beginning O_2 inhalation. Thus both gas-exchange rates were measured exactly simultaneously. The results showed an excellent matching of time constants obtained by semilogarithmic analysis of the curves. Results extracted in these comparative studies show that the time constants obtained in the same circumstances and the same time period are nearly identical. The amounts of the noble gases eliminated in each case are in good agreement with the calculated amount on the basis of solubility in body tissues (water and fat) and the uptake during the saturation period based on known time constants for the subject's gas exchange.

TABLE 2.—RELATIVE DIFFUSION OF GASES AT ROOM TEMPERATURE THROUGH A HYDRATED GELATIN MEMBRANE*

GAS	TEMP. OF MEASUREMENT	K (ARBITRARY UNITS)	REL. DIFFUSION RATES	
N_2	24.1	146.0	N_2 = 1.00	0.36
He	23.8	142.8	2.57	He = 1.0
H_2	24.2	126.0	3.20	1.15
A	23.1	147.5	0.84	0.30
CO_2	23.0	146.0	0.75	0.27
Kr	23.2	147.0	0.58	0.21
Xe	(not measured)		(0.36)	(0.13)

* The membrane was 1% gelatin stretched on Nylon stocking, dried and rehydrated. One side contained a circulating saturated solution of the gas to be measured, and the other a circulating solution of water free from the gas to be measured. Results were calculated in relative terms as

$$K = \frac{\text{volume of gas exchanged} \times \sqrt{\text{molecular weight}}}{\text{solubility in water}}$$

If diffusion or a permeability factor limited gas exchange, it would be expected that the results would be influenced by the predicted diffusion rate of the dissolved gas which, according to Graham's law, is proportional to the reciprocal of the square root of the molecular weight. Diffusion rates of dissolved gases do behave according to Graham's law; this is shown in the consistency of diffusion of dissolved gases through hydrated gelatin (Table 2). Thus over almost an 8-fold range of relative diffusion rates (He to Xe, 1.0–0.13

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relative diffusion units), results in gas-exchange rates for the body give similar time constants and the amounts of gases so exchanging can be predicted from solubility in body tissues. These results leave no alternative but to consider diffusion and transcapillaric permeability as factors not limiting the inert-gas-exchange rate. Aside from the matter of differential solubility in blood, tissue and fatty tissue, the limiting factor of gas exchange is the blood-tissue perfusion rate of the body tissues. This implies merely that the diffusion rates of these dissolved gases are very rapid over such tissue and cell barriers as may exist compared to the rate of movement of blood through the capillaries.

The blood-tissue perfusion rate is the volume of blood/volume of tissue/min. It also is equal to the gas-exchange time constant K, within usual limits of experimental error. In any tissue component of the equation

$$A_t = A_0 e^{-kt} \text{ and } R_t = R_0 e^{-kt} \qquad (1)$$

the amount of blood flowing through that tissue $= R_0/\alpha B$, where αB = solubility of gas in the blood. Total volume of the gas A in the tissue at zero time by integration $= R_0/K$, and volume of the tissue $= R_0/\alpha_t k$, where α_t = solubility of the gas in the tissue. The blood perfusion rate then becomes

$$\frac{R_0/\alpha B}{R_0/\alpha_t k} = k\,\frac{\alpha_t}{\alpha B} \qquad (2)$$

In non-fatty tissues $\alpha_t = \alpha B$, and blood-perfusion vol/vol of tissue/min $= k$.

General Method of Gas-Exchange Calculations

The accumulated uptake or the accumulated elimination A is usually expressed as the quantity of gas at standard conditions absorbed or eliminated up to a

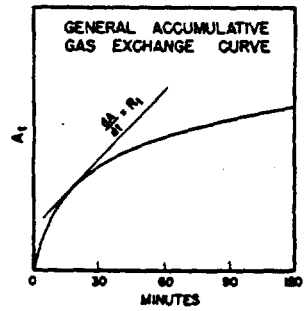

Fig. 1.

given time t. Examples of this treatment are calculations from compressed air uptake, radioactive gas measurements, foreign gas uptake. The general gas-exchange equation of the amount of exchangeable gas is

$$A_t = A_0'(1 - e^{-kt}) + A_0''(1 - e^{-k_2t}) + A_0'''(1 - e^{-k_3t}) + \ldots \qquad (3)$$

In the differential form the gas-exchange-rate equation becomes only slightly changed, and this form (equation (4)) of the equation is conveniently obtained when gas-exchange rates can be measured continuously, as with the radioactive-gas-exchange method. Experimental accumulative data are most readily differentiated by obtaining tangents to a smoothed curve through experimental points. My favorite method is to use transparent parallel rulers for this operation. One rule is held at a tangential point while the other reads the slope from 0 to 1, 0 to 10 or 0 to 100 min. For gas-exchange measurements, however, the tangent method of obtaining rates from the accumulative curves is relatively much less accurate on the asymptotic portion of the accumulation curve. Rate of gas exchange for the slowest components is better measured directly as rate of elimination (inert-gas elimination/Δt). In use of the tangent method of differentiation, caution must be used in differentiation and interpretation of published results where there is likelihood that the graphic data represent curves calculated on the basis of a particular theory and fitted to the experimental points or are perhaps shown without the experimental determinations. Such analysis will only extract a form of the original theory. The rate is usually given as rate/min

$$R = R_0'e^{-kt} + R_0''e^{-k_2t} + R_0'''e^{-k_3t} + \ldots \qquad (4)$$

The integral relationship of A and R is

$$A' = \frac{R_0'}{k_1};\ A'' = \frac{R_0''}{k_2};\ \text{etc.} \qquad (5)$$

A', etc., represents an amount of N_2 associated with a given tissue defined in terms of vascularity. A' particularly is not the N_2 from the blood as theorized by Smith and Morales[1] in a similar expression of gas exchange, but represents the most highly perfused tissues that can be detected by the methods used, and the tissues concerning A' include the contained blood. On the basis of gas solubility in body tissues for the non-fatty tissues, A', A'', etc., represent an amount of tissues. Similarly, R', R'', etc., represent amounts of blood perfusing the tissue per stated time interval. In equation (5), $A' = R_0'/k_1$, the time constant k_1 is the blood-tissue perfusion factor since $k_1 = R_0'/A'$ = $R' \times$ solubility factor = vol of blood/min. $A' \times$ solubility factor = vol of tissue + its blood pool.

Thus when the distribution ratio of the exchangeable gas is unity in the blood and tissues, the time constant k has both the meaning of fractional gas exchange/min and vol of blood/vol of tissue/min. k is calculated as the reciprocal of the time required to effect a change in rate of amount to $1/e$. Conveniently it is measured from the time to the half-value (half-time)

$$k = \frac{\log_e 2}{\text{half-time}}$$

Fig. 2 shows schematically the method of plotting gas-exchange rates as the log of the rate of exchange against time. Desaturation curves of tissues as determined by radioactive gases have a form similar to equation (4) since these data represent the unexchanged portion of tissue-dissolved gases A_t

$$A_t = A_0'e^{-kt} + A_0''e^{-k_2t} + A_0'''e^{-k_3t} + \ldots \qquad (6)$$

Such data can be treated as in Fig. 2; the differential form of equation (6) is the same as equation (4), and the integral relationship the same as equation (5). The

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semilogarithmic plot of either R_t or A_t vs t_1 may then be subtracted into component parts corresponding to the portions $R_0'e^{-kt}$, etc. The method depends on the obtaining of a complete curve for true accuracy; if the data are not carried out sufficiently long to expose each

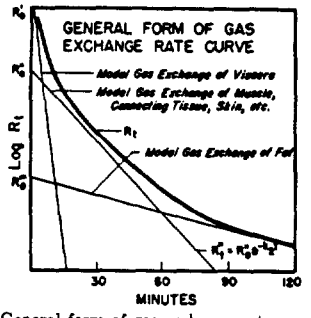

FIG. 2.—General form of gas-exchange-rate curve plotted as log of rate of exchange against time.

component, the last component is naturally left unresolved and no guess can be made as to its potential resolution. This fault lies not with the method but with the primary goodness of the data concerned, for they cannot be resolved better by any other method if they are truly of this indicated equation. The source of some of the difficulties in interpretation of N_2 exchange is that the gas-exchange measurements have seldom been good enough to make exact resolutions of this type. The accumulative N_2-elimination curves of Behnke's were fitted by him with a 2-component exponential equation:

$$A_t = 364\,(1 - e^{-0.098t}) + 500\,(1 - e^{-0.0038t})$$

Because of the difficulty of separating out a 3d component (body fat) in whole-body N_2 elimination, his

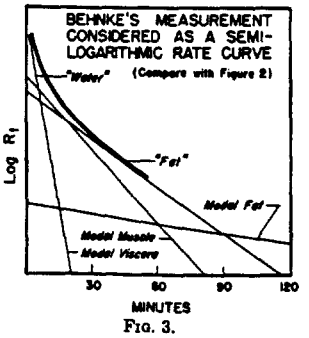

FIG. 3.

equation of N_2 exchange is essentially that of Fig. 3, which is the same as that in Fig. 2, but the data have been terminated at the point which permits establishment of only 2 component equations. The relative errors in interpretation are apparent, but they are not as serious as might be indicated here. The more rapidly exchanging component is little affected; the difficulty as regards the 2d and last component is that the tissues are unresolved and in this case represent neither muscle nor fat but a mixture of the 2 which is more nearly like muscle than fat. The time constant has limited meaning in terms of the blood-tissue perfusion factor.

The method of Stevens *et al.*[3] is applicable to the 1st 20 min of the gas-exchange curve. It comprises plotting log of rate against log of time. The straight line on the log × log plot appears to be due to coexistence of the main effects of 2 exponential components of the gas-exchange curve; beyond 20 min a plot of this type is not a straight line (Fig. 4). Although this method is exceedingly simple and has justifiable accuracy, it does not lend itself to the more general interpretations of the theory of gas exchange and vascularity of tissues.

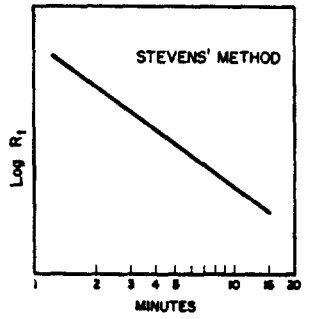

FIG. 4.—Stevens' gas-exchange-rate curve plotted as log of rate against log of time.

NITROGEN EXCHANGE OF THE BODY

The body tissues at sea level contain approximately 0.01 vol (STP) of dissolved N_2/vol of non-fatty tissue and approximately 0.05 vol/vol of fatty tissue (Bornstein;[4] Campbell and Hill;[5] Grollman;[6] Behnke[7]). After a change in barometric pressure, the amount of dissolved N_2 changes. And changes in barometric pressure are followed by re-equilibration of the dissolved N_2 to extents proportional to the N_2 partial pressure of the gas mixture inhaled. Associated with exposure to compressed air is a net movement of N_2 into the tissues and with decompression there is a net outward transfer (the mechanism was discussed earlier). Effective elimination of dissolved tissue N_2 can be brought about by replacement of air by other gas-O_2 mixtures. Helium is used to replace N_2 in diving; its presence in the body is more favorable during diving and decompression than that of N_2 on the basis of solubility. Inhalation of high concentrations of O_2 also induces N_2 elimination; such procedure for removal of dissolved body N_2 to protect against low-pressure decompression is known as *preoxygenation*. The rôle of N_2 in decompression sickness and the oxygenation principle of N_2 saturation were recognized in 1878 by Paul Bert.[8]

The vascular pattern of the body tissues primarily determines the characteristics of the N_2 exchange of the body. In a consideration of inert-gas concentration in the tissues it is desirable to have an understanding of the vascularization of the tissues, the proportion of

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arterial blood utilized/min/tissue or /organ and the estimated average rate of N_2 removal/min during denitrogenation. The fraction of N_2 removed/min, except for body fat, is the same as the blood-tissue perfusion factor. A factor of 0.3 means 30% removal of excess nitrogen/min. Gas-exchange rate closely approximates blood-tissue perfusion rate. The exception is fat. Body fat has about the same vascularity as resting muscle, but the relatively high solubility of inert gases in fat, as compared with blood, causes the gas-exchange rate for N_2 to be slower by a factor of 5 than the blood-tissue perfusion rate.

If current values for the blood-perfusion rates of the body organs are accepted, it is apparent that almost $^3/_4$ of the cardiac output is distributed as follows (see also Table 4):

Thyroid	1.7% (Means[9])*
Kidney	23.0% (Smith[10])
Heart	2.6% (Bazett[11])
Small glands	1.8% (estimated)
Brain	13.0% (Kety and Schmidt[12])
Bone marrow	6.3% (Jones[13])
Hepatic portal	26.0% (Bradley;[14] Jones[13])
	74.4%

* 5.3% extrapolated to man from studies in the rat; according to Jones *et al.*[3]

This leaves about $^1/_4$ of the cardiac output to supply the remainder of the body. The vascularity of the carcass, i.e., the living body excluding viscera, should average about 25 ml of blood/l of tissue/min. This is in good agreement with values of blood perfusion of the carcass including extremities as calculated from radioactive-gas exchange (Tables 5–7).

Except for organs as vascular as the kidneys and thyroid, the measured N_2 exchange of the body acceptably describes cardiac output, body volume, percentage of body fat and vascularity of the body tissues. It is not possible to eliminate inert gases in the lung spaces rapidly enough to detect the small quantity of N_2 contained in the kidneys and thyroid. Since the rate of exchange of dissolved inert gas in these organs is about 500%/min, and since the amount of dissolved gas concerned is equal to approximately 3 ml, it is impossible to conduct such measurements at the time of washing out of lung gases. A short period of hyperventilation is necessary to remove lung gases sufficiently to pick up the inert gases being eliminated from the brain, red marrow and hepatic portal tissues. Indeed, even measurement of cerebral circulation by the N_2O method (which is the same gas-exchange mechanism) is difficult because lung mixing is occurring simultaneously with cerebral N_2O uptake (Kety and Schmidt[12]).

Nitrogen Elimination from Lung-Gas Mixing.—Inhalation of O_2 washes out N_2 from the lung's air. The rate of this exponential mixing of gas volumes is described by Darling *et al.*,[15] Bateman[16] and Jones.[13] In quiet normal breathing, equilibration of the lung gases with a newly inhaled gas composition does not approach completeness for 5–10 min. Table 3 gives averages of a small sample of data (Jones[13]). The usual normal subject has 2 major rates of ventilation of the lung-gas field. However, other subjects not included in this group have only 1 discernible mixing rate, 0.45 min half-time (column I, Table 3). Since this roughly coincides with a theoretical rate calculated for mixing on the assumption that there is uniformity in all parts of the lungs for mixing of the tidal and the lung-gas volume, perhaps

TABLE 3.—MIXING RATES OF PULMONARY GAS VOLUME DURING NORMAL QUIET BREATHING*

	RAPID RATE	SLOW RATE
Vol of respiratory gas	2.3 ± 0.81	0.71 ± 0.091
$^1/_2$-time of equilibration	0.45 ± 0.13 min	1.6 ± 0.4 min
Time constant, *k*, of equilibration	1.55 ± 0.49/min	0.44 ± 0.10/min

* Subjects were 7 males, weight 170 ± 20 lb, height 70 ± 1.8 in.

these subjects with a single rapid mixing have the true normal pattern of lung ventilation. In all subjects with histories of asthma there is great accentuation of the slow rate. With pulmonary emphysema the slow component is even slower and may approach 3–4 l. Occasionally there are observed additional slower rates of ventilation mixing in the "normal" group. Patients with polycythemia vera appear generally to have 1 or more additional slow mixing rates (this study is incomplete). In many normal subjects the pulmonary mixing rates are rapid enough so that they do not interfere with studies of elimination of dissolved N_2 from body tissues. Even after 5–10 min the usual subject will have some lung N_2 interfering with measurements of tissue N_2 unless precautionary hyperventilation is used to flush out the lung N_2.

Gas Exchange of the Brain.—The blood perfusion and gas-exchange rate of the brain are of relatively high intensity. The value for cerebral circulation in man obtained from the N_2O exchange rate is 0.76 l of blood through the brain/min (Kety[17]). In development of the N_2O method for cerebral circulation Kety and Schmidt[12] assumed that cerebral circulation is the same throughout the brain. The gas-exchange theory of cerebral blood flow and gas exchange is supported by the following evidence. (1) Different gases, radioactive Kr, radioactive Xe (Jones[13]) and N_2O (Kety and Schmidt[12]), give similar values for cerebral gas exchange. (2) The total amount of N_2O absorbed by the brain on the basis of solubility represents a tissue volume equivalent to the brain. (3) If a large portion of gas exchange to the brain were extremely slow (as suggested by the Campbell-Hill[18] data), it would be impossible to account for the tissue mass of the brain from the remaining rapid portion of the gas exchange, and such gas exchange as is observed would indicate much too large a blood-tissue perfusion factor; reasonable calibrations of gas exchange have, however, been obtained by Kety and Schmidt[12] with direct flow measurements.

The magnitude of cerebral circulation from N_2O measurements is 0.76 l/min (Kety[17]) or an average tissue perfusion of 0.54 vol of blood/vol of tissue/min. Another method, that of injecting Evans blue into the carotid artery and measuring the dilution in the jugular blood, has been used by Gibbs *et al.*[19] Their values roughly check those of Kety and Schmidt.[12] Average for 7 subjects by the injection technic was 0.62 l/min or 0.44 vol of blood/vol of tissue/min. Since both groups of investigators obtain precise calibration of their

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method with direct flow measurements, probably the difference between the 2 average values is due to the small samples concerned; the difference is approximately equal to the standard deviation of the measurements.

In view of other gas-exchange studies and some preliminary studies with N_2, radioactive Kr and radioactive Xe, it is likely that the circulation to the brain must be considered to include at least 2 differently vascularized tissues (Jones *et al.*[2]). This vascularity corresponds to blood-tissue perfusion rates of approximately 1.4 and 0.35 vol of blood/vol of tissue/min (Jones[2,12]). Application of the simplified situation of a single perfusion intensity for the brain leads to an impossible concept, that of a gas-exchange time constant changing with time (Kety and Schmidt[12]). The simplified condition of a single gas-exchange process is roughly sufficient under special procedures to give total or average cerebral circulation. However, consideration of N_2 concentration of cerebral tissue from the standpoint of decompression phenomena must at least assume gas-exchange rates of tissues as having 2 degrees of vascularization and thus represented by 2 different time constants. A significant factor in cerebral gas exchange is N_2 solubility in brain, measured by Campbell and Hill[16] and by Kety[17] and showing that brain lipids have the same N_2 solubility as non-fatty tissues.

Except for the work of Campbell and Hill,[16] specific information is not available on rate of total removal of N_2 from brain tissue during denitrogenation or decompression. There is reason to doubt the values of Campbell and Hill because their tissue-N_2 saturation levels are not consistent with the increased N_2 tension. Also, the concept of a slowly saturating brain is dependent on a single animal in their data. If this animal is neglected, the rest of the observations agree with the concept that the brain has a rapid gas exchange. A similar discrepancy is present in their report in regard to the rate of liver equilibration with increased N_2 tension. Again the same experimental animal with a lower than predicted saturation supports the conclusion that gas exchange in the liver is extremely slow. In view of the general discrepancy of these data with recent gas-exchange studies, further work on this approach to the problem is indicated. However, there is otherwise every reason to believe that gas exchange to most portions of the brain is as rapid as indicated, namely, 35% equilibration/min. Also, since there are no lipids in the brain that concentrate dissolved gases (Campbell and Hill;[6,16] Kety[17]), the indicated cerebral circulation would necessitate that the whole brain be equilibrated to a changing inert-gas concentration in the lungs to within 10% of the change in inert-gas concentration 6–7 min after the change in lung tension of the gas has been effected.

It should be expected that symptoms of aeroembolism of the brain should be seen only soon after decompression. Cerebral symptoms are, in fact, observed in low-pressure decompression (Engle *et al.*;[20] Lawrence and Lund;[21] Goggio and Houck;[22] Whitten[23]). They are associated with early severe symptoms, particularly "chokes." In some cases the cerebral symptoms occur, not during decompression, but after recompression and again only after severe chokes and bends. It is suggestive that the cerebral symptoms—scotomas, nausea, vertigo and headache—which occur after recompression are not due to emboli formed primarily within the brain but are circulatory aeroemboli which are lodged in the lungs and with recompression shrink sufficiently to pass through the lung capillaries and to be carried to the brain, where they block certain critical capillaries. It is difficult to predict the rate of resorption of an aeroembolus in the brain, since this certainly depends on the effective vascularity of the tissue immediately around the captive bubble, whether or not a thrombus is formed, on the attending degree of tissue reaction, etc. None of these factors will operate with the same rules that control the exchange of gaseous compounds dissolved in the tissues, which is determined by tissue vascularity. Behnke[24] suggested compression treatment of patients with such cerebral symptoms.

The brain, then, is relatively protected from supersaturation of dissolved gases on exposure to high-altitude decompression. On the other hand, if there is a tendency to bubble formation in the brain comparable to that in other body tissues, damage to the brain should be more likely in diving decompression when compression is great and decompression rapid even though exposure to compression is brief. I.e., the brain is vascular enough so that during 10 min of any exposure to compressed air it is 90% equilibrated with the N_2 tension. Other body tissues which have slow gas exchange, such as muscle or fat, may be less than 5–10% saturated. Rapid decompression from such a situation would result in an inert-gas supersaturation for the brain 9-fold greater than that for the tissues of the carcass.

Gas Exchange of Kidneys and Thyroid.—These 2 organs are probably too vascular (Table 4) to permit any great supersaturation of dissolved gases for more than a few seconds. Presumably they are never directly concerned with decompression sickness. The rapidity of kidney-gas exchange is apparent in measurements of urinary gaseous N_2 during compressed-air inhalation (Hill and Greenwood[25]). The 1st sample of urine taken 8 min after the start of denitrogenation is essentially equilibrated. Probably equilibration had taken place much sooner than 8 min (calculated 90% equilibration 20 sec after compression).

Gas Exchange of the Heart.—Blood flow to the heart has been variously estimated to be from 150 to 200 ml/min (Bazett[11]). This means a blood-tissue perfusion factor of at least 0.5 vol of blood/vol of tissue/min and a gas-exchange equilibration rate of at least 50% equilibration/min. The heart, then, is as imminent as the brain to supersaturation conditions. Exposure of the heart to the hypothetical bubble shower from the lungs on recompression is not as likely to occur as in the brain because the buoyant bubbles may tend to escape the openings of the coronary vessels, whereas they may easily pass up the carotid arteries.

Gas Exchange of the Small Glands.—The adrenals, pancreas, testes and prostate have not been measured with reference to their gas-exchange rate, but presumably they are well vascularized and their perfusion is of the order of or greater than a blood flow of 1 vol of blood/vol of tissue/min. It is not likely that any of these organs are involved in decompression sick-

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ness since their rate of clearance of dissolved N_2 would be at the rate of 100% equilibration/min.

The rapid disappearance of N_2 dissolved in saliva was measured during O_2 inhalation by Scholander.[26] If one uses these data as a basis for calculation and assumes the rate of N_2 disappearance from the saliva to be the same as that of salivary tissue, the salivary gland should be cleared of N_2 at the rate of 50%/min. The blood-tissue perfusion factor of the gland ought, therefore, to be 0.5 vol of blood/vol of tissue/min.

Gas Exchange of Bone Marrow.—Bone marrow is suggestively a site of decompression sickness. However, marrow aeroemboli are probably more frequent in fatty than in hemopoietic marrow. As determined by the uptake rate of a radioactive colloid that is highly selected by marrow cells, minimal circulation to the red marrow in the rabbit is 7% of the circulating blood vol/min (Jones[13]). These values, translated to man, would indicate approximately 300 ml of blood to the hemopoietic marrow/min and thus a gas-exchange rate of about 15% change/min. This intensity of circulation may be poor enough so that bubbles are formed in the hemopoietic marrow under conditions of decompression, but the vascularity and gas-exchange rate are still considerably greater than in the other tissues of the carcass.

In caisson disease, as mentioned for the brain, the red marrow may be subjected to a less favorable supersaturation than tissues greatly more vascular or greatly less vascular when decompression is rapid even though compression exposure is brief. Red marrow, like brain, can saturate rapidly. Ten-min exposure to any compression should result in 75–80% equilibration in the red marrow, but in desaturation this gas-exchange rate can easily be exceeded by rapid decompression. Fatty marrow in the same period is likely to be only 5% saturated (Table 7). Fatty marrow is presumably like body fat in terms of vascularity. No measurements of gas exchange for this tissue have been done since Campbell and Hill.[5] Although there may be reason to question the validity of this whole set of data, analysis of N_2 exchange in bone marrow (29–35% fat) from their 3 goats at 3 atm for 1.5 and 3 hrs gives an average time constant similar to that of body fat (Table 7). This means that the rate of gas exchange in fatty marrow is of the order of 0.5% change/min. With decompression, great supersaturation of dissolved gas can persist in fatty marrow for long periods and the fatty marrow

TABLE 4.—Regional Blood Perfusion Rates and Dissolved N_2 Exchange Rates

Tissue	Vol of Tissue, Ml[1]	Vol of N_2, Ml	Vol of Blood, L/Min	Fraction of N_2 Removed/Min
Lungs	1200	12.0	5.8[2]	4.8
Thyroid	30	0.2	(0.30)*[3]–0.10[4]	10–3.0
Kidneys	270	2.7	1.33[5]	5.0
Heart	300	3.0	(0.15)[6]	(0.5)
Adrenals, 7 ml; Testes, 50 ml; Prostate, 23 ml	78	0.8	(0.08)	(1.0)
Salivary glands	35	0.4	0.02	0.5[7]
Brain	1400	14.0	0.76[8]	0.5†
Marrow (hemopoietic)	1400[9]	30.0‡	0.30[10]	0.15
Hepatic portal				
Liver	1560	17.0‡	...	(0.27)
Spleen	150	1.5		
Pancreas	85	0.9	1.5[3,12,11]	0.5 (av.)
Intestines; Stomach; Colon	1350			(0.7)
Intestinal contents	(1500)	(100.0)	...	0.008[10]
			Prob.–Min.	Prob.–Min.
Muscle (40 l)	45 000–55 000	450–550	1.0–0.40[10]	0.025–0.01
Connective tissue (5 l)			0.1 –0.05[10]	0.02 –0.005?
Skin (5 l)			(0.35)–0.25[10]	0.07 –0.01
Fat (12 l)	15 000–5000	750 (600)–250 1182§	0.2 –0.15	0.005–0.003
70-kg man, 1.85 sq m	...	...	5.89 –5.09	Expected¶ (5.8[2])

* Figures in parentheses are approximated.
† 0.35—modal perfusion rates; 1.5—of cerebral tissues; from Jones.[13]
‡ Includes organ lipids.
§ Not including intestinal gas; at standard conditions.
¶ Calculated from average value of direct Fick measurements of resting cardiac output.
[1] From Wadsworth[24] and Rawling.[25]
[2] From Cournand *et al.*[27]
[3] From Jones *et al.*[2]
[4] From Means.[9]
[5] From Smith.[10]
[6] From Bazett.[11a]
[7] From Scholander.[26]
[8] From Kety.[17]
[9] From Bazett.[1 b]
[10] Jones.[13]
[11] From Bradley *et al.*[14] and Lipscomb and Crandall.[23]

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might be an ideal location for development and growth of aeroemboli as far as the factor of dissolved inert gases is concerned. In decompression following short compressed-air exposure, fatty marrow and fatty tissue may not develop a critical supersaturation because of slowness of gas exchange of these tissues.

Gas Exchange of Liver, Spleen and Intestines.—The amount of blood diverted to the hepatic circulation was measured by Bradley *et al.*[14] and Jones.[8,13] This volume of blood corresponds to 30% of cardiac output/min so that the tissues supplied must, from the standpoint of the body average, be considered fairly well vascularized. E.g., the liver receives 1 vol of blood/vol of tissue/min. Liver-gas exchange is complicated by the fact that most of this blood is portal blood from the spleen, pancreas, intestines, etc. During denitrogenation, portal blood would always be many times richer in dissolved N_2 than the arterial supply to the liver. Thus actual gas-exchange rate of the liver is considerably less than the blood-tissue perfusion rate, which would be 100%/min with this degree of blood flow if it were all arterial blood. It has been estimated that $^1/_{3}$-$^1/_4$ of the liver blood comes from the hepatic artery, but on the whole the liver can desaturate only slightly faster than the other tissues contributing to the portal stream. If the total hepatic portal blood flow and all the tissues concerned were lumped together, average blood flow would be 0.5 vol of arterial blood/vol of tissue/min. Perfusion to the spleen is known, from the rate of uptake of certain radioactive colloids (Jones[13]), to be approximately 1 vol of blood/vol of tissue/min. Thus the spleen should account for only 10% of the blood perfusing the liver. Another source of portal blood is the pancreas. Perfusion of the pancreas has not been measured by these technics, but even if it is as great as that of the thyroid, it could not account for a major part of the blood in the portal stream. Therefore the main portion of this blood comes from the gastrointestinal tract. Some also comes from the mesenteric fat pads, but in a lean individual blood flow through fat is so small as to be negligible for these pads (100 ml/min for 4 l of mesenteric fat). Approximately 15% of the cardiac output, then, can be guessed to move through the intestinal tissue each minute; thus average rate of nitrogen removal from the intestines is 50%/min.

In the case of the portal tissues, as indeed with all of the body tissues, gas exchange is not represented simply as an average of blood-tissue perfusion factors; instead, for each tissue, however homogeneous, there must be considered to be at least 2 degrees of relative perfusion vascularity. This presumably is due to the fact that the vascular bed in a tissue is not uniformly functioning; on the average, there is a characteristic vascularity, but here and there in each tissue is more or less than average blood perfusion because of random pattern of open capillaries. The sensitivity of gas-exchange measurements is such that small regions of coincidental excess of functioning capillaries are easily observed where these regions are present. In such regions of microscopic dimensions the blood-tissue perfusion factor may be 2–10 times that of surrounding tissues. Average saturation, neglecting the regions of high perfusion rate, is readily calculated from gas-exchange measurements and is given in Tables 5–7 as the modal value of the tissue circulation. The other statistical extreme of tissue vascularity is represented by regions that are momentarily poorly perfused by having relatively few open capillaries. In extent these amounts are possibly as much as the small fraction of a tissue that is more vascularized than the modal tissues, but the method of measurement of these tissues is very insensitive because so little blood perfuses them.

TABLE 5.—Blood-Tissue Perfusion in Resting Men Age 20–25
(Determined by Rate of Uptake of Radioactive Krypton; Room Temperature 20 C (Jones[8,13]))

Hand		Leg		Thigh	
Av.*	Mode, 80%†	Av.*	Mode, 95%†	Av.*	Mode, 95%†
0.118	0.043	0.017	0.013	0.029	0.017
0.080	0.018	0.027	0.016	0.037	0.019
0.104	0.029	0.016	0.010	0.015	0.011
0.058	0.026	0.013	0.011	...	...
0.073	0.024	0.020	0.018	0.037	0.028
0.063	0.026	0.018	0.014	0.020	0.018
0.054	0.023	...	...	0.040	0.028
0.053	0.023	...	...	0.012	0.010
0.081	0.029	...	...	0.032	0.021
0.045	0.019	0.016	0.014	0.026	0.026
0.040	0.013	0.027	0.020	0.016	0.011
0.070 Av.	0.025	0.019	0.014	0.026	0.019

* Average value is the perfusion rate as volume blood/volume tissue for the whole appendage.

† Mode values are for the main tissue mass of the appendage. I.e., in the hand, 80% of the tissues have 0.025 vol of blood/vol of tissue/min, whereas the whole hand is vascularized at 0.070 vol of blood/vol of tissue/min.

It is rather difficult to predict the minimal values for tissue circulation in the hepatic portal circulation since we are dependent for values of circulation not on gas-exchange values but on other technics mentioned that give only average organ-perfusion rates. If one judges, however, from other tissues, the modal circulation of these tissues should be within 50% less than the average circulations to the tissues concerned. In absence of precise knowledge of the magnitude of the circulation to the portal tissues, there is no advantage in setting up an expression for gas exchange of the liver except that we have reason to believe the minimal circulation to the liver would account for an equilibration rate of

TABLE 6.—Nitrogen Elimination in Muscles

Condition	Vol Blood/Vol Tissue/Min; or Fraction Removed/Min	
	Av.	Mode
rest; reclining (thigh, Table 5)	0.026	0.019
anesthetized; rest	0.035	0.012
rest	0.023	0.011
heavy steady state; exercise	?	0.048
anesthetized; vigorous intermittent contraction	...	0.077

* From Rawling.[25]
† From Wadsworth.[24]

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dissolved inert gases of at least 10% change/min. Probably the liver-gas exchange rate is closer to 50% change/min. It is doubtful whether such slow equilibration rates of dissolved N_2 as 0.5% change/min or less

TABLE 7.—NITROGEN ELIMINATION IN FAT

	Condition	Fraction Removed/Min Av.	Fraction Removed/Min Mode	Vol Blood/Vol Fat/Min, Mode
Man*	rest	...	0.002	0.010
Man*	exercise; heavy steady state	...	0.0047	0.023
Cat†	anesthetized; contracting hindlegs	0.005	0.0042	0.021
Cat†	anesthetized; rest	0.010	0.0046	0.023
Goat (fatty marrow)‡	anesthetized	0.0045	0.007	0.035
			0.002	0.01

* From Jones.[13]
† From Whiteley and McElroy.[30]
‡ From Campbell and Hill.[18]

are acceptable, as would be indicated by literal interpretation of the data of Campbell and Hill.[18] Furthermore, this interpretation would necessitate that the circulation rate for nearly the whole liver would be something in the order of 3 ml/l of tissue/min, which is scarcely consistent with known values for the magnitude of hepatic circulation.

Gas Exchange of Skeletal Muscle.—The minimal blood supply to muscles, as calculated by rate of N_2 elimination or saturation or desaturation of radioactive argon or krypton in plethysmographic measurements of blood flow to the extremities, and the amount of blood perfusing the muscles are in keeping with a general picture of the distribution of the blood such that approximately 1/4 of the cardiac output is distributed, at rest, to the tissues of the carcass. Modal values for tissue circulation to the hand, leg and thigh—the latter 2 presumably referring mostly to the muscle mass—are, respectively, 25, 14 and 19 ml of blood/l of tissue/min at rest. These values are in good agreement with plethysmographic and calorimetric determinations of the hand's blood perfusion (Forster *et al.*[31]) and within the order of magnitude of the plethysmographically measured blood-perfusion rates given by Ferris and Abramson.[32] Similar but varying amounts of tissue in these extremities are better vascularized by a factor of 10 than these modal tissues; therefore, on the average, the tissues of the hand, leg and thigh receive, respectively, 70, 19 and 26 ml of blood/l of tissue/min (Table 5). These values are consistent with an analysis by Whiteley and McElroy[30] in which the N_2 content of blood draining muscle was measured. If these data are treated similarly, the time constants and amounts of N_2 concerned correspond in an anesthetized cat to muscle vascularity—between 20 and 35 ml of blood/l of tissue/min on the average and, for modal muscle circulation, between 11 and 12 ml of blood/l of tissue/min—values that are in general good agreement with the circulation factors derived from gas-exchange studies in man.

As in other tissues, measurements in muscle are indicative of 2 perfusion factors. This is apparent from all measurements of gas exchange. This bimodality is attributed to the slight difference in pattern of capillary circulation in the tissues concerned, so that there are small areas in which unit vascularity is very great because of effective overlap of open capillaries. There does not seem to be any quantitative rule, however, for the pattern of overlap of the capillaries; great variation is observed. Sometimes the amount of such tissues is as great as 10% of the total tissue concerned, and other times, less than a fraction of 1% (Jones[13]).

All measurements of gas exchange in muscles show an increase in gas exchange during exercise of the muscle. The data of Whiteley and McElroy[30] can be interpreted to show a 7-fold increase in muscle circulation during exercise over rest in the anesthetized cat. In man, from the rate of N_2 exchange during steady-state bicycle exercise (Jones *et al.*[2]) it is apparent that most of the body musculature becomes vascularized to the extent of 48 ml of blood/l of tissue/min whereas at rest most segments of muscle circulation may be as slow as 5 ml of blood/l of tissue/min. Some of the muscle mass,* such as leg muscles, which in this case are doing most of the exercising, presumably may be vascularized to the extent of 240 ml of blood/l of tissue/min. A few muscles or a few parts of these muscles may be vascularized as much as 900 ml, but it is difficult to make the deduction that this refers specifically to muscle or to certain muscles. In decompression sickness the degree of protection from symptoms afforded by N_2 elimination coincides with what we know about muscle circulation and N_2 removal rates from muscle. There is 1 ill-explained discrepancy: no specific set of data show exercise combined with preoxygenative denitrogenation to be beneficial in reducing N_2 tension and decompression intolerance. Particularly in the absence of such data we must assume that exercise does not confer additional protection when used with denitrogenative procedures, since combining exercise with denitrogenization has been shown to reduce strikingly the N_2 concentration in muscles so exercised (Whiteley and McElroy;[30] Jones *et al.*[2]). An alternative reasoning must be used to knit the theory together, namely, that the muscles themselves may not be the seat of decompression sickness, but rather that decompression sickness may be associated with tissues of about the same vascularity and gas exchange as resting muscles, as indeed are most of the carcass tissues at rest. These few tissues would comprise only a small portion of the body and might well be such connective tissues as the muscle sheathes, the tissues bordering the fascial planes, portions of tendons, joints, muscle insertions, etc. If this is true, exercise may have no effect on the efficiency of preoxygenative denitrogenation; in fact, conversely, there might be reason to guess that the circulation through these connective tissues might just as likely be less under the conditions of exercise than at rest.

Circulation to the carcass in man varies considerably with age; in youths of 18, rates of N_2 removal from the carcass of about 2.3%/min are observed, whereas in

* This tissue is defined not anatomically but from gas-exchange rates. In this instance little parts of tissue in terms of unit vascularity are summated from all the different parts of the tissue concerned into a single expression, which is different from average vascularity of the tissue.

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men of 25 the rates are 1.1%/min. These values are in good agreement with their susceptibility to decompression sickness and rates of protection against decompression sickness by preoxygenative denitrogenation. In all cases the data are consistent well within the experimental error. The 18-year-olds have twice the average carcass circulation and gas-exchange rate, half the incidence of decompression sickness and twice as much efficiency in preoxygenative denitrogenation as those over 25 (Jones[2,32]). The summated data in Fig. 9 and Figs. 6–8 express the relationship of age, carcass N_2 elimination and decompression tolerance. The change in circulation with age as indicated by these gas-exchange interpretations apparently concerns blood perfusion of the tissues of the resting carcass. Direct Fick measurements of cardiac output (Cournand *et al.*[27]) suggest an allowable inverse relationship of cardiac output with age. The magnitude of this effect is such that the decrease in cardiac output between 18 and 25 is expected to be approximately 0.3 l of blood/min/sq m of body surface, but this cannot be taken as confirming evidence. If this change in blood flow is confined to the body musculature, it just accounts for the effect noted with age in the gas-exchange data, amounting to approximately 0.4 l of blood/min/sq m. Measurements of O_2 and CO_2 exchange in working muscles give additional evidence that there is some change in blood-tissue perfusion of muscles correlated with age (Berg[34]). However, correlation of the amount of N_2 eliminated during the 1st 20 min of O_2 breathing with age in years has not been observed, although correlations of $r = 0.68$ were obtained with body weight (Stevens *et al.*[2]). Nevertheless, this is reasonable if the decrease in N_2 elimination with age is due to muscle circulation, for in 20 min only a minor part of the muscle N_2 would be eliminated whereas practically all of the N_2 from the viscera as well as possible lung N_2 is accounted for. Carbon-monoxide elimination has the same quantitative relationship to age (Pace[35]). Possibly the same mechanism is involved as in inert-gas exchange.

Gas Exchange of Body Fat.—Body fat has approximately the same blood-tissue perfusion rate as resting muscle. In terms of actual amount of cellular protoplasm, fat is richly perfused since it is composed largely of oil droplets. However, from the standpoint of gas exchange, a blood-tissue perfusion factor of 0.023 vol of blood/vol of tissue/min easily drops to a N_2 removal rate of 0.5% change/min ($k = 0.005$/min) if one considers the fact that N_2 is 5 times as soluble in fat (Campbell and Hill[14]) as in blood and other tissues (Lawrence *et al.*[16]). From comparative gas-exchange measurements of circulation in body fat it appears that there may be as little as 10 ml of blood/l of tissue/min in which the gas-exchange rate is correspondingly 0.2%/min.

Gas exchange of fat is so slow that practically it is separate from the other tissues of the body in consideration of any gas exchange except that of He. Simultaneously measured gases such as N_2 and Xe show fat N_2 to be a distinctly superslow component (Jones *et al.*[2]). Analysis of data of Whiteley and McElroy,[36] from measurement of blood N_2 from an adipose vein, shows bimodality of N_2 elimination rate from the tissue concerned and thus indicates 2 degrees of fat-perfusion rate. Evidence of non-uniformity of open capillaries in fat pads was demonstrated by Gersh and Still.[37] Average circulation for fat is some 30% higher than for the bulk of the fat noted in Table 7 as the mode value. In the case of He gas exchange, the fact that solubility of He in fat is approximately the same as its solubility in blood and other tissues should make the gas-exchange rate of fat as rapid as that of body muscle, since the

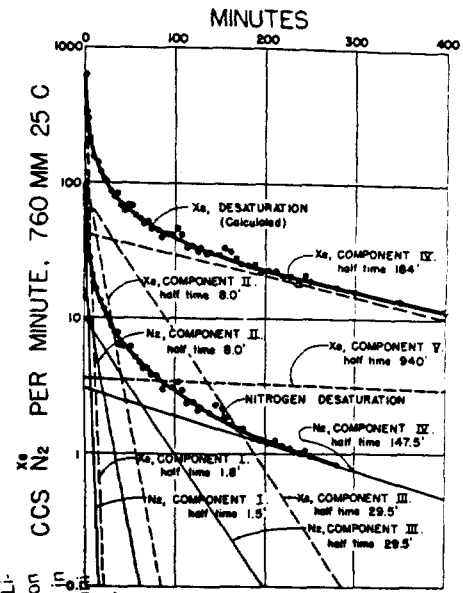

FIG. 5.

circulation to fat and muscle is approximately of the same order of magnitude in terms of the blood-tissue perfusion factor. The He effect was predicted by Behnke. However, neither the He-elimination data of Behnke and Willmon[38] nor the He data of Jones *et al.*[2] obtained by effecting N_2 elimination followed by He saturation are extended enough to determine this fact experimentally. Analysis of these data by N_2 and by He exchange indicates that the gases behave similarly and have identical time constants in a consideration of the non-fatty tissues. This is to be expected, since the data are not carried out for periods of time long enough to separate out fat N_2.

In low-pressure decompression the protection rates acquired by preoxygenation do not correspond to the N_2-elimination rate from fat. It may be concluded from this that the N_2 in body fat is little concerned in most of the cases studied in high-altitude decompression. In some, however, in which denitrogenation for long periods fails to protect against decompression symptoms, it is possible that the dissolved gases which give rise to decompression emboli are associated with fatty tissue or very poorly perfused tissues. There may be many small segments of tissue involved with slow N_2-elimination half-times of 3–8 hr and which would

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have blood-tissue perfusions of 0.0038–0.0014 vol of blood/vol of tissue/min. Gas-exchange values of this magnitude are apparent, but within the accuracy of the data this rate can be due to fatty tissue alone. Therefore, there is no evidence directly from gas-exchange data indicating normal blood-tissue perfusions of the magnitude of 0.0014 vol of blood/vol of tissue/min for non-fatty tissues, but it is possible that such tissue exists. Perhaps tendon, cartilage, etc., represent even poorer vascularization. However, some individuals require 3–4 hr of denitrogenation to experience only 50% reduction of decompression symptoms (Bateman[16]). In these cases fat N_2 may indeed play an important rôle in decompression sickness. Such behavior is not to be expected in subjects of military age who, for the most part, were studied by the various aeromedical laboratories. In these studies the established major rate of protection by denitrogenation had approximately a 30-min half-time for the 18–20 year group and one of 60 min for the group 25 years and older (Bateman;[16] Jones[22]). Both are in agreement with the gas exchange of the non-fatty portions of the carcass.

Gas Exchange of Skin.—The values shown in Table 4 represent an estimated breakdown of carcass N_2 exchange. No values for skin-gas exchange are directly available except for the hand and fingers, which are probably not representative of the rest of the body. Skin is assumed to have the same value as that estimated for the carcass. Diffusion of N_2 and He across the skin has been studied by Behnke and Willmon[38] and Eggleton *et al.*[39] Fortunately this effect does not come into the radioactive-gas-exchange methods, on which the critical concepts of this gas-exchange thesis are based. However, in 3- and 4-hr N_2-elimination studies I have made without an oxygen suit there does not seem to be a constant factor of N_2 elimination of the order of magnitude noted for skin diffusion of He noted by Behnke and Willmon or of N_2 in the Eggleton data, obtained with dogs. This lack of agreement may be due to a different degree of vascularity of the skin as a result of environmental conditions.

Relation of Gas Exchange and Circulation

Although all students of exchange of dissolved substances have considered the partial importance of the blood perfusion in exchange equilibration, none has pointed out that the exchange process for simple diffusible substances is limited by the circulation alone. Not only is this the situation with the dissolved inert gases, but it applies to iodide and probably to sodium. The thyroid can remove nearly all of the inorganic iodide in the perfusing blood and the thyroid circulation can be calculated (Jones *et al.*[2]). The rate of removal of iodide from the blood is the blood-perfusion rate of the thyroid where the volume of blood perfusing the gland = the time constant (k/min) × the iodide space (which is in equilibrium with the blood). Further evidence that blood-tissue exchange is limited by circulation is found in data obtained by Sheldon.[40] He demonstrated that the chloride ion transfer from perfusion fluid through the intestinal tissue to the washed lumen of an isolated, perfused frog gut was proportional to the hydrostatic perfusion pressure. He also showed that the volume of fluid flow in the intestinal loop is proportional to the hydrostatic pressure. It would appear that in such a case the exchange of potassium chloride into the gut lumen from the perfusion fluid is limited by the tissue-perfusion rate.

Differentiation and analysis of Behnke's[7] He curves give results in agreement with my N_2-He comparisons (see Table 1). The Behnke data reanalyzed consist not of 1 component rate but of 2. The 1st component is difficult to approximate from the limited published graph of the data, but the major portion of the exchange for N_2 and He, respectively, are time constants of 0.0083 and 0.0073; the slight difference is accountable on the basis of incomplete resolution of the gas-exchange rates and resulting inclusion of a greater fat-gas exchange effect in the case of N_2 than in the case of He.

Each inert gas, then, is exchanged at similar rates in the body tissues except as noted in fat, where the exchange rate differs from the blood-tissue perfusion rate by a factor of the ratio blood solubility/tissue solubility of the gas concerned. As noted by Haggard,[41] a gas of very great water solubility would depart from the general gas-exchange rule since lung clearance becomes a factor.

The similarity between the gas-exchange-time constants and the time constants of mixing of substances introduced intravascularly has been pointed out (Jones *et al.*[2]). Also, the dilution cycles of intravascularly injected substances such as sodium ion depend on the blood-tissue perfusion rates, and the time constants of equilibration dilution are similar to the blood-tissue perfusion rates obtained by the gas-exchange method. A literal interpretation of this concept requires more exact knowledge of the sodium spaces of blood and tissues. A sodium curve calculated from Gellhorn's[42] data gives the following equation for dilution in blood of radioactive Na following injection in dogs (Jones *et al.*[2])

$$C_p = 1987e^{-1.3M} + 580e^{-0.221t} + 641e^{-0.05M} + 90e^{-0.002M} + 960e^{-0.0000M} \text{ (amt of Na unexcreted)} \quad (7)$$

where C_p is concentration of Na in the plasma at any time. One of the most resolved N_2-exchange curves obtained in man, where N_{2t} is the amount of N_2 contained in the body at any time, is

$$N_{2t} = 111e^{-0.03M} + 193e^{-0.0071t} + 428e^{-0.02M} + 95e^{-0.0M} + 600e^{-0.001M} \quad (8)$$

The 1st 2 terms of equation (8) include some lung N_2.

From gas-exchange studies using gases of different solubilities and different oil/water solubility ratios, one can predict 90% of body fat to be concerned with 5th-component gas exchange in equation (8). The blood-fat perfusion rate of this subject would be 0.0024 × 5.24 (fat/water solubility ratio) = 0.013 l of blood/l of fat/min. Equation (9) was constructed from the data assembled in Tables 3 and 4

$$N_{2t} = 62e^{-0.0M} + 23e^{-1.0M} + 7e^{-1.M} + (2300e^{-1.5M}) + 18e^{-0.0M} + (710e^{-0.4M}) + 24e^{-0.2M} + 600e^{-0.0M} + 100e^{-0.00M} + 400e^{-0.00M} \quad (9)$$

It is the complete theoretical equation for elimination of N_2 from the body during inhalation of high concentrations of O_2. In equation (9) the parenthetical components are lung N_2. From comparison of equations

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(8) and (9) it is apparent that 85% of the N_2 of the 1st 2 components of equation (8) (obtained without lung hyperventilation) is due to lung gases. In equations (8) and (9), item $428e^{-0.02t}$ matches the theoretical item of modal muscle $500e^{-0.02t}$; items $95e^{-0.005t}$ and $100e^{-0.005t}$ are presumably representative of intestinal gaseous N_2; items $600e^{-0.0025t}$ and $400e^{-0.005t}$ are the component of body fat. Addition of all the items of equation (9) gives an amount of N_2 in excess of the expected amount in terms of body bulk and fat and the physical solubility of N_2 in each. In equation (8), approximately 250 ml of N_2 is from the lung gas spaces, and approximately 95 ml from the intestinal gases; skin transfer appears to be a negligible amount. Lung N_2 is difficult to eliminate, and vigorous hyperventilation with O_2 is the only method of removing its influence on the N_2-elimination curve (see Table 3). It is suggestive that the data of Behnke *et al.*[45] (see also Fig. 4) as analyzed into 2 components account for the total bulk of the body, despite disregard of body-fat nitrogen, by coincident inclusion of some lung N_2 with component I and inclusion of intestinal N_2 with component II. Thus Behnke's "fat" component appears to be in the correct order of magnitude by the summation of muscle N_2† and intestinal N_2, and the "water" phase of the body could appear reasonable by the inclusion of very small, but difficultly removed, amounts of lung air.

N_2 Elimination As Measure of Cardiac Output.—Short-term N_2-elimination measurements have been concerned with the minute volume of circulation (Marshall *et al.*[44]) and lung washing-out time and with measurement of the 1st elimination of body N_2 (Marshall *et al.*;[44] Darling *et al.*;[15,46] Cournand, *et al.*;[46] Stevens *et al.*[3]). They establish the rapidity of the washing-out of N_2 from the normal lung, the normal rapid and almost complete clearance of the arterial blood and the general correlation of body size with the quantity of N_2 eliminated in the 1st few minutes. Precise use of N_2 to obtain the minute volume is disallowed in my opinion. The best value that can be obtained is cardiac output minus blood perfusing the heart, thyroid and kidneys and portions of other tissues such as brain, liver, etc.—an amount at times as great as 40% of the true cardiac output. Nevertheless Marshall has obtained "reasonable" results from the Bornstein[4] technic, probably owing to incorporation of enough slow-mixing lung-air N_2 to make up for inability to measure the very vascular tissues. Similar errors are possible with all foreign-gas methods.

Attempts at measuring cardiac output have for the most part been unsuccessful (Jones[13]) when care has been taken to eliminate lung N_2 as much as possible and to begin measurements after 5 min of O_2 inhalation. The method consists in extrapolating the resolved components of the gas-exchange-rate curve and summating the rates at zero time for the indicated components. This method is quite reproducible but it gives "cardiac output" consistently in the range of 2.5–4.0 l, which can be approximated by subtracting from the value of the cardiac output, as obtained by other methods, the values known of the blood supply of the thyroid, kidneys and heart. Possibly the method can be made more inclusive of the minute volume by intensifying the hyperventilation period to rinse the lung out thoroughly. There is, however, a definite limit imposed by the kidneys and thyroid (Table 4), for which tissues there is only 3 ml of N_2, which is half eliminated every 6 sec following O_2 inhalation.

Applications of Gas-Exchange Studies

Use of He in Decompression Sickness.—Sayers *et al.*[47] suggested use of He-O_2 mixtures to mitigate the severity of caisson disease.‡ The suggestion was based on the physicochemical properties of He, namely, that it exhibits much lower solubility in tissues than N_2 and that it should diffuse more rapidly into the body tissues because of its greater diffusion rate. Use of He-O_2 mixtures permits divers to work at greater depths and to be decompressed more rapidly (Behnke[7]). Part of the effect of He seems to be elimination of N_2 narcosis. The other beneficial results in the light of gas-exchange measurements are not so easy to analyze since the gas-exchange rate of He in the body is not influenced by the great diffusion rate of He. Helium exchange is the same as N_2 exchange except as regards body fat. Possibly the fat effect accounts for relative safety of rapid decompression rates of divers using He although, on a theoretical basis, as in the case of the brain and bone marrow discussed earlier, in exposure to He the fatty tissue is saturated more rapidly than with N_2. This may make this tissue somewhat more prone to a critical state of supersaturation in certain conditions of compression exposures and decompression rates.

Representation of Intestinal-Gas N_2 in Gas-Exchange Measurements.—Intestinal gases include a portion of exchangeable N_2 which is eliminated through the lungs during O_2 inhalation. The O_2 concentration in such gas pockets of the intestines should be rather constant and low because of the O_2 tension buffering of the blood and the rather high metabolism of the intestinal cells and bacteria. The N_2 of the gut diffuses out progressively during O_2 inhalation and is not exchanged for O_2 molecules. This leads to reduction of total gas volume, and with sufficient O_2 inhalation the incidence and severity of decompression abdominal pain can be decreased (Henry *et al.*[48]). The benefit is a function of the length of preoxygenation. From the data of Henry *et al.*, a simple calculation has been made starting from the assumption that the degree of symptoms of gas pain is proportional to the amount of expandable intestinal gas in decompression. The calculation shows a rate of acquired protection of 0.008 fractional change/min or a gaseous N_2 elimination from the gut of 0.8%/min during O_2 breathing. This time constant of exchange is slower than that for muscle and slightly more rapid than that for fat and indicates that intestinal gases can be a source of considerable error in the general use of this portion of the gas-exchange curve. This may account for many shifts in magnitude of the slower components of the curve; for the most part, however, such shifts do not account for more than ±50 ml of N_2. By coincidence, the gas-exchange time constant k is 0.008; this is almost identical with the 2d time constant described by Behnke[7] ($k = 0.0085$).

† A portion of fat N_2 is still included in Behnke's 2d unresolved component.

‡ See also Behnke, Decompression Sickness.

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Similarity of Preoxygenation Protection Rates and N_2 Elimination Rates.—Three experimental groups are considered in comparison of rate of N_2 elimination to rate of protection to decompression sickness by preoxygenation.§ Both the gas-exchange data and the preoxygenation-decompression data have been subjected to the same type of semilogarithmic graphic analysis. The times of N_2 measurements were short (60–90 min), and thus it is improbable that greater resolution of the N_2 curve could be effected than into the 2 approximate components. The 2d component, which will be the 1 considered in detail, is an approximate measure of the average change of N_2 content of the carcass and its value in these subjects probably chiefly determined by the muscle mass of the body.

Ideally, all gas-exchange measurements should have been followed for several hours to permit accurate reconstruction of the component parts of the total elimination curve. By theory, these components represent tissues classified chiefly by the rate of blood flow/volume of tissues and also by the dissolved-gas distribution ratio between blood and tissues (equations (1) and (2)). The last component resolved is subject to some bias, depending on the magnitude of the components of slower rate of time change that are left unresolved. The "components" themselves are an average of tissues having approximately the same gas exchange. Theoretically, it would be expected that there might be a complete continuum of degrees of vascularization in the body tissues. If the tissue volumes were evenly distributed in this continuum, semilogarithmic analysis of this data would have failed, and the data would have been resolvable only as a series of tangents to a continuously curving total semilogarithmic plot. However, the tissues actually cluster at several points on the total scale of vascularization and these distribution centers correspond to the gas-exchange components (note Tables 4–7).

1. The data reported by Stevens[46] have been reviewed by the methods used here for analyzing elimination. The N_2-elimination data and the preoxygenation-decompression (altitude, 35 000 ft) data of this group were reanalyzed semilogarithmically. Subjects breathed O_2 while resting for various periods before decompression. This gave an apparent single semilogarithmic component for the log of preoxygenation-decompression data plotted against time and 2 components for the N_2-elimination data. Fig. 6 gives the combined plot of this semilogarithmic data. The percentage of descents due to decompression sickness of the group are plotted on a logarithmic scale against the length of the preoxygenation period. This susceptible group has nearly 100% descents in the initial flight without preoxygenation. Superimposed on the percentage of descents of various periods of preoxygenation is the average semilogarithmic curve of the 2d component of N_2 elimination, which is adjusted so that 100% normal N_2 concentration corresponds to the control of zero preoxygenation for these tissues. Tissues that have more rapid N_2 elimination and which should be sufficiently cleared to keep the dissolved gas concentration in balance with the decompression level are disregarded. Theoretically, the visceral tissues should be too rapid in gas equilibration to contribute to decompression effects, and, practically, there seems to be no suggestion of their having a limiting rôle in decompression sickness. It can be seen from Fig. 6 and comparison

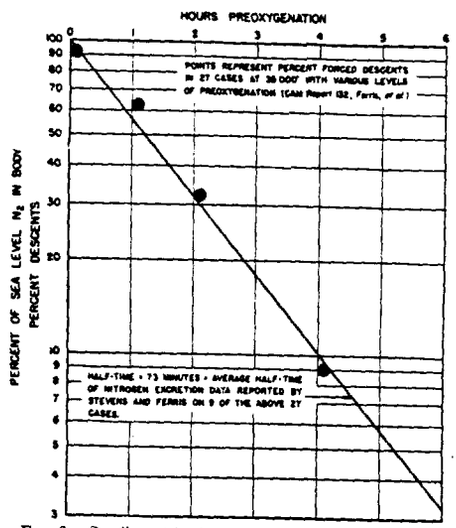

FIG. 6.—Semilogarithmic curve of combined N_2-elimination data and preoxygenation-decompression (altitude 35 000 ft) in 27 subjects (Stevens *et al.*[46]).

with Tables 4–7 that there is a rather exact coincidence between the average rate of N_2 removal from the carcass and the rate of protection against decompression sickness by O_2 inhalation.

2. A 2d group consisted of 12 members of the staff of the Aeromedical Unit, University of California, in 2 flights with 2 N_2 measurements (90 min) (Jones[32]). Subjects breathed O_2 while resting for various periods before decompression. The data were treated as for the 1st group. The main slow component was obtained from analysis of the N_2-elimination data. Because of the smallness of the group, decompression scores are given in terms of percentage of average score of the control group, which was without preoxygenation. One, 2, 3 and 4 hr of preoxygenation were obtained before the decompression-exercise test (five 9-in. step-ups every 10 min) at 35 000 ft equivalent. In this group again there is remarkable agreement between the gas-exchange rate of the 2d component tissues and the preoxygenation-protection rate for decompression sickness (Fig. 7).

The data from both foregoing groups (Figs. 6 and 7) are in agreement with a bubble and gas-exchange theory as applied to decompression physiology. The subjects in these groups were, however, generally more susceptible to decompression sickness than the usually encountered subjects aged 18–21. The altitude of both groups was 35 000 ft. Nitrogen-elimination rate and rate of decrease in expected symptoms had a half-time of 73 min for the Stevens group and of 68 min for the California group.

§ See also Gagge and Shaw—Aviation Medicine.

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3. Analysis of preoxygenation protection in younger groups at 38 000 ft is possible in 2 instances. Data on 1 group, compiled by Gray[50,51] at Randolph Field, are

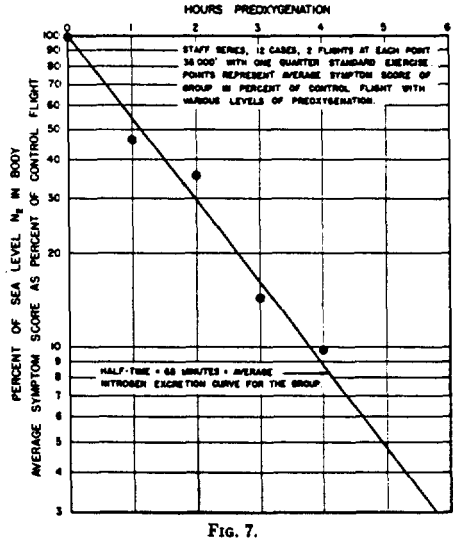

FIG. 7.

for young subjects with intervals of preoxygenation from 0 to 60 min before a standard resting flight to 38 000 ft equivalent. Percentage of descents plotted

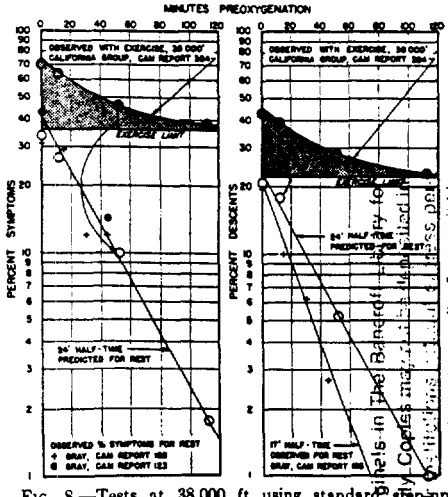

FIG. 8.—Tests at 38 000 ft using standard step-up exercises, showing little increase in protection by additional hour of preoxygenation (Gray;[50,51] Henry *et al.*[52])

on a logarithmic scale against time of preoxygenation (Fig. 8) gives a good indication that the protection half-time of these subjects under resting conditions at 38 000 ft is approximately 20 min. This is strikingly different from the older groups previously discussed, in which average preoxygenation protection half-time was approximately 70 min. Furthermore, there is still a discrepancy, discussed later, in that the protection half-time of 20 min is even faster than the average of the 2d component of N_2 elimination for this group, 33 min half-time.

Age range of a 2d group, studied by the Aeromedical Unit, University of California (Henry *et al.*[52]), was approximately the same as Gray's. This group was tested at 38 000 ft with a standard step-up exercise (ten 9-in. step-ups every 5 min). The points of time are approximately 0, 12, 51 and 111 min of preoxygenation, respectively, at rest before decompression. Data are given in percentage of descent due to decompression sickness and plotted on a logarithmic scale against time of preoxygenation. This method of plotting is comparable to the plotting of the N_2-elimination curve and to the plotting in the 3 previously cited groups. However, in this instance, a straight-line relationship is not achieved with this semilogarithmic plot; i.e., the change of the log of percentage of descents against time is not compatible at once with our ideas of N_2 elimination from the body. On the same graph (Fig. 8) are shown the data obtained by Gray[50,51] for a group of approximately the same age over the same period of preoxygenation. The difference here is that Gray's data were obtained on *resting* subjects, whereas the data from the California group were obtained during the standard step-up exercise at altitude. In the case of percentage of descents under resting conditions, there is a straight-line relationship of the log of the percentage of descents plotted against preoxygenation time. This would be compatible with a N_2-elimination half-time of approximately 24 min and is considerably faster than that of the 2 groups reported previously. Still, as will be shown later, this can be in good accord with current knowledge of N_2 elimination.

It appears in the data of tests at 38 000 ft equivalent by the California group using the standard step-up exercise that the curve is approaching some kind of horizontal asymptotic limit; i.e., after 1 hr of preoxygenation there is little improvement in protection by an additional hour of preoxygenation. Thus a condition is approached wherein, no matter how much preoxygenation is applied, there will be no additional protection beyond this limit. (However, if CO_2 is involved in this exercise limit, it may be possible that it will be effective only within certain levels of tissue-N_2 concentration.) It is assumed that a specific effect of exercise was producing symptoms in excess of those which would have occurred even under sitting-resting conditions and furthermore, that this effect was not related to time of preoxygenation. Accordingly, the data have been analyzed to separate these 2 effects. If this limit is drawn (Fig. 8), the difference between the amount of symptoms due to the exercise effect, which is approximately 22% descents for any period of preoxygenation, and the observed percentage of descents should, according to the above assumption, give the percentage of descents that would have been observed under these conditions had this group rested at altitude instead of exercising. Plotting of these differences (shaded area,

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Fig. 8) shows that the data predict those obtained by Gray. Approximately the same incidence of symptoms or descents as is observed in Gray's data is predicted in the California data, and the protection half-times are similar.

In every fractionation of these data the same quantity of exercise limit is seen. It does not matter (Fig. 8) whether percentage of symptoms or percentage of descents is used; the results are similar, and the exercise limit in relative magnitude to the whole data is approximately 49% in either instance. It has also been possible to obtain the same effect using time to onset of symptoms as a criterion of measurement (Jones[33]).

A 3d analysis of data from this group is possible, namely, incidence of chest symptoms. Fig. 8 gives data for combined descents from both joint and chest pain. However, the extremely low incidence of descent from chest pain in this group effectively resolves these data into joint symptoms alone. Bridge *et al.*[53] compiled the incidence of chest symptoms of the same study, and analysis of their tabulation of the incidence of chest symptoms by plotting the log of the percentage of incidence against the time of preoxygenation indicates only a single component of 35 min half-time protection. From this analysis the definite statement can be made that there is no exercise limit to the chest symptoms even though the exercise limit is apparent in 2 analyses of the joint symptoms in this same group of subjects. It is logical that the symptoms associated with the exercise limit should have occurred as joint pain. This would be in agreement with the hypothesis of Lund and Lawrence[54] that decompression joint pain is produced in the extrafascicular spaces of the muscles. It is also possible that the exercise-limit effect has its origin in an increased local concentration of CO_2. Such a concentration might attain local concentrations many times greater than the dissolved nitrogen concentration.

The data of Clark *et al.*[55] are again suggestive of the general relationship noted between age, circulation and gas exchange, taken collectively, and protection rates of preoxygenation. Decompression-protection rate follows the expected N_2-elimination rate as shown in individual and group decompression scores (Fig. 9). Older individuals are more likely to be slower in rate of protection. Similar plotting of individual response to preoxygenation (Bateman[16]) also compares protection rate to possible N_2-elimination rate (Fig. 9). In the older subjects there is this progressive tendency toward slow protection rates (Bateman;[16] Jones;[33] Clark *et al.*[55]). Slow rates are not seen in the younger population and are sometimes slow enough to correspond to a gas-exchange rate of body fat. This does not by any means relate the phenomenon specifically to body fatty tissue. It is equally possible that it represents a general lessening of the degree of vascularity of some critical tissues of the body.

Besides an exercise limit, there is evidence for a still greater complexity of the factors increasing or diminishing the severity of decompression sickness. There is a large diurnal shift in decompression tolerance. Morning runs tend to be more severe than the afternoon runs even though the flights themselves are carefully standardized (Henry *et al.*[56]). Coincident with this, the metabolic rate in the morning is lower than in the afternoon in these same test subjects and the gas-exchange rate is slower in the morning than in the afternoon. These variations would account for a large

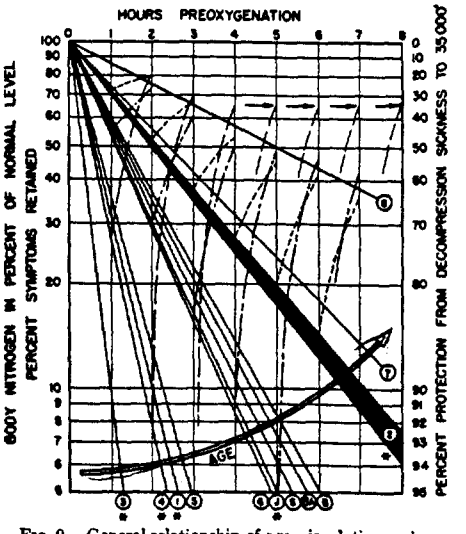

FIG. 9.—General relationship of age, circulation and gas-exchange and protection rates of preoxygenation shown in individual and group decompression scores. *BA*, average individual protection rate (Bateman[16]). Average N_2-elimination curves for age groups under 24—*B*, Behnke; *S*, Stevens and Ferris; *J*, Jones (*1*, fastest curve; *2*, slowest curve; *3*, fastest curve and *4*, average curve of 18-yr-old group); *5*, percentage of symptoms retained, 17-yr-old group (Clark *et al.*[55]); *6*, percentage of symptoms retained, 27-yr-old group; *7*, percentage of symptoms retained, 35-yr-old group; *8*, slowest individual protection rate. Broken lines indicate loss of protection during 1 hr of air breathing.

difference in the dissolved-gas concentration for the same period of N_2 elimination and decompression exposure depending on the time of day in the same group of subjects. Stevens *et al.*[3] showed the diurnal shift in metabolism as evidenced by O_2 consumption but reported no such shift in gas exchange from morning to afternoon as was noted by Henry *et al.*[56] This discrepancy is puzzling.

Gray[57] reported a linear progression of symptoms in groups tested from 28 000 to 38 000 ft under either resting or exercise conditions. Although his data are reasonable, similar data compiled by Cook *et al.*[58] disagree with Gray's findings. In Fig. 10, these data have been analyzed for uniform decompression flights by plotting atmospheric pressure (in mm Hg) of the test altitude against percentage of descents. The data are separately divided into A.M. and P.M. groups. The morning and afternoon differences are striking, and the greatest time-of-day difference both relatively and absolutely is present at 38 000 ft. In the morning, when the metabolic tissue perfusion by blood and gas-exchange rates are lowest, data are closest to a linear progression of descents with barometric pressure reduction (Jones;[34]

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Henry *et al.*[56]). In the afternoon, when metabolic and gas-exchange rates are greater, data for descents are so curvilinear that there is practically no gain in the number of descents at 38 000 ft. These 2 separate groups appear to give no support to the bubble theory of the origin of decompression sickness.

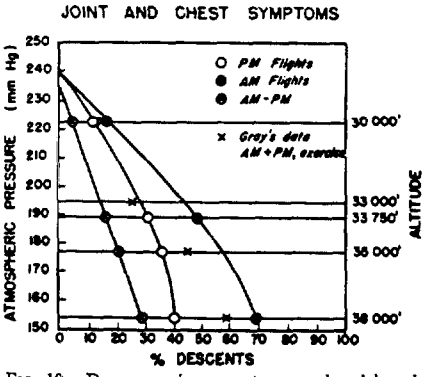

FIG. 10.—Decompression symptoms analyzed by plotting atmospheric pressure (mm Hg) of test altitude against percentage of descents, showing differences in morning and afternoon.

If the experimental conditions were only different by the indicated barometric pressures, there should have been a linear progression, as Gray's data had formerly indicated. The differences between morning and afternoon flight descents do give a linear plot of barometric pressure against descents. This may indicate that whatever effect has caused the general decrease in expected descents with increasing altitude has been a change in concentration of dissolved gases in the body, or, at least, the difference is in accord with the gas laws.

A tentative theory may be advanced: that approaching altitude as high as 38 000 ft, O_2 tension is becoming so low that some anoxia is probably present even on breathing of pure O_2. If a mild stimulus to anoxia is present at 38 000 ft or below, it is likely that circulation might be increased in certain critical areas of the body. This would necessarily increase N_2 transfer from these same areas, so decompression sickness would be lessened. The fact that there are proportionally many more decompression symptoms and descents in the morning at 38 000 than at 35 000 ft, whereas in the afternoon the incidences are the same, seems to be the main support of the argument. If anoxia is the causative agent, its effect is likely to be greatest when the metabolic rate is the greatest. This is the observed case.

The stimulating effect of mild anoxia on the cardiac output is known (Grollman[6]). McMichael and Snyder[59] demonstrated increases in arm circulation as great as 100% on breathing of air at 16 000–18 000 ft equivalent and proportional reduction on breathing of pure O_2. Whitehorn and Edelmann[60] stated that there is even a decrease in resting cardiac output at sea level when pure O_2 is inhaled. In a small group with a probably significant effect ($N = 22$, $C.R. = 2.6$), Smith[61] reported that symptoms were decreased at 35 000 ft if the subjects were mildly anoxic owing to restricted O_2 supply during the test flight (incidence 27% with mild anoxia, 45% with full O_2). Measured arterial saturation for these subjects averaged 85%. The explanation of this effect is either that the anoxic stimulus to circulation increases N_2 exchange or that the severity of symptoms is lessened by cerebral depression, or both.

To study this hypothesis, several subjects were selected whose N_2-elimination curve could be followed for 2–3 hr on a fairly exact 2-component curve. Thus, the main body component of N_2 elimination offers a straight reference line on the semilog plot from which changes in gas exchange may be referred during a period of 1–2 hr. A typical data sheet is shown in Fig. 11. The solid

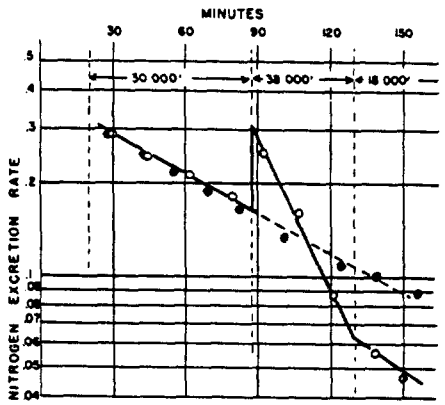

FIG. 11.—Changes in N_2 elimination at altitude. Solid dots, N_2 excretion at sea level; circles, N_2 excretion at 30 000 ft. Rate and rate of change of N_2 elimination increased when altitude increased to 38 000 ft.

dots are measurements made at sea level the day preceding. Open dots represent measurements made at 30 000 ft and agree well with the sea-level measurements. However, on decompression to the equivalent of 38 000 ft the rate of N_2 elimination and the rate of change of the rate increase. Thus, when the subject drops back to 18 000 ft after 40 min at 38 000 ft, the rate of N_2 elimination at 18 000 ft is almost 50% slower than it would have been with the same elapse of time of denitrogenation had the 40-min flight at 38 000 ft not been included. It is inferred that the concentration of dissolved N_2 associated with this tissue was reduced the amount of the difference by the 38 000-ft simulated flight. Of 8 subjects tested for changes in N_2 elimination at altitude, all showed 25–100% increase in rate of change of N_2-elimination rate at 38 000 ft. No change was seen at 30 000 or 33 750 ft. Of 4 subjects measured at 35 000 ft before measurement at 38 000 ft, 1 showed what may have been a 10% increase, which is not regarded as significant.

Apparently the change of N_2 elimination at altitude occurs rather abruptly near 38 000 ft, which would substantiate the hypothesis that it is associated with a stimulus of decreased O_2 tension or mild anoxia. There seems to be no evidence that this effect might be associated with a change in pressure *per se*, since no change in N_2-elimination rate is observed up to 35 000 ft; this

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is in agreement with the observation that there is no detectable change in N_2-excretion rate up to 30 000 ft (Shaw *et al.*[62]). A decrease in rate at altitudes in individuals having decompression sickness has been predicted from the fact that some of the body's dissolved gases become transformed into gaseous pockets that are more difficult to eliminate than dissolved gases. From estimation of collections of gas pockets in roentgenograms of body appendages at altitude, it is probable that less than 1% of body N_2 is so trapped under the conditions of decompression sickness ordinarily seen at altitude. It would be extremely difficult to show such a minor effect by the N_2-elimination method.

All measurements of N_2 elimination in direct comparison to decompression testing have been made with resting subjects. It might be expected that if mild anoxic effects could be detected at rest at 38 000 ft, the effect would be greater under the conditions of exercise used in most altitude decompression tests.

It appears that the longer a group preoxygenates the longer it can stay at altitude before onset of symptoms in the subjects in whom symptoms are destined to appear (Jones;[34] Henry *et al.*[52]). An increase of about 15 min in average time for onset of symptoms is noted with 1 hr of preoxygenation. Thus, with 1 hr of preoxygenation, the true N_2-elimination time might really be equivalent to nearly 75 min of preoxygenation instead of 60. Furthermore, the additional gain in N_2-elimination time is spent at 38 000-ft altitude, where we expect the N_2-elimination rate to be increased. In consideration of these 2 effects it is apparent that the time scale of preoxygenation used in Fig. 8 cannot be strictly equivalent to the real time scale of denitrogenation.

However, some data of Gray[63] indicate that O_2-inhalation time spent at "prebends" altitudes (20 000–28 000 ft) does not strictly add to the general preoxygenation time. (Extrapolation of descent curves of Fig. 10 shows that 28 000 ft is about a critical altitude below which descents due to aeroembolisms should be exceedingly rare.) In the region of 20 000–35 000 ft this time is only $^1/_4$–$^1/_2$ as effective as sea-level preoxygenation. This suggests that the physical events responsible for decompression sickness occur at about this barometric pressure, although they are not manifest until there is further decompression. This is commonly referred to as the "silent stage" of decompression sickness. Extrapolating to 35 000 and 38 000 ft, we would expect that additional time at these altitudes spent without symptoms might be even less additive to the total of sea-level preoxygenation. Thus instead of a maximal time distortion of 15 min/hr of preoxygenation by delay of onset of symptoms, the time distortion at 35 000 ft is probably no more than 10 min/hr when the gas-exchange rate is that of the young group under discussion. Then at 38 000 ft, with the specific additional effect of increased (doubled) N_2-elimination rate from the slow tissues, the time distortion might be expected to be about 20 min/hr. This is then equivalent to 80 min of sea-level preoxygenation. Since observed N_2 elimination at sea level for such a group is about 33 min half-time and preoxygenation protection half-time for a 38 000-ft flight is 24 min, the estimate of 8 min shrinkage of the half-time of decompression sickness protection by preoxygenation is reasonable.

Prediction of individual susceptibility to decompression sickness or individual protection time of preoxygenation has been rather discouraging. Correlation of N_2-elimination rate and decompression sickness has been observed repeatedly, but the values have not been high (Stevens *et al.*;[49,64] Henry *et al.*[56]). Some attempts have been made to increase the accuracy of this prediction by measuring the N_2-elimination rate for 1 hr before flight. Protection levels of tissue N_2 have been roughly estimated to be 10% of the equilibration level as calculated from the time necessary to acquire protection and the rate of the individual's main "carcass" N_2 elimination (Jones[34]). The method is not very accurate because, for an individual, there is only a probability that the "critical tissue" matches the modal value for the "carcass." The interpretations from curves of individual protection rates with preoxygenation by Clark *et al.*[15] and Bateman[16] are better guides to the characteristics of the "critical tissue" in individuals; direct comparison with N_2 elimination has sufficient accuracy only with group measurements.

The discrepancy of individual protection rates is perhaps comprehensible: there may be individual variations in actual formation of bubbles; body fat may occasionally play a rôle in decompression sickness, and it is not taken into full account in the theorized protection level of N_2; last, the curves of N_2 elimination presented here are a sort of average for a certain group of tissues. Many tissues, as classified by gas exchange and vascularity, must exist that have a faster or a slower gas-exchange rate than the component of gas exchange that represents the bulk of such tissues; when such tissues exist in small amounts, they are masked by the relative mass of differently vascularized tissues. Thus in prediction of an individual's protection rate or protection level, there is fair probability that the "limiting tissue" of his body will lie within his "average" gas-exchange component. However, it may not. In fact, the limiting or critical tissue might in any instance differ radically from the average or the modal value. In group data these deviations tend to cancel themselves, and the large group should and does give reasonable agreement with comparison of decompression phenomena to gas-exchange predictions, despite the fact that prediction of individual protection is fraught with great variation.

The stability of the probability of group performance can be seen repeatedly in the data analyzed here. In Figs. 6–8 there is a remarkable smoothness in recession or progression of group averages along the curves of the graphic analyses. The coincident reliability of group prediction of N_2 elimination and decompression sickness of groups is made use of in Fig. 9.

Fig. 9 is used as a basis for selecting required preoxygenation times. Loss of protection by 1 hr of air-breathing is also shown.‖ The N_2 scale refers to the total

‖ There is experimental proof that resaturation of the tissues with air N_2 occurs in the reverse process of N_2 elimination (Jones[34]). The similarity of saturation and desaturation is not apparent until the gas-exchange measurement is separated into its component parts. When analysed by rate, the time constants of saturation and desaturation are readily shown to be identical, but in the usual experiment, if the desaturation curve starts from saturated tissue, the saturation curve begins with partially saturated tissues, and the converse is also true. It is necessary to make a very accurate resolution of such comparative measurements to avoid the error of incompletely resolved data that have different magnitudes of exchange occurring at the same rate.

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amount of N_2 associated with component II tissues. The construction is similar to the other schemes presented with preoxygenation-decompression data here in which the protection or protection rate was always proportional to the observed or predicted tissue-N_2 concentration. Thus with any percentage of N_2 removal from the tissues there would be expected a proportional reduction in symptoms of decompression sickness from what would have been observed had there been no preoxygenation. Percentage of body N_2 retained and percentage of symptoms retained are synonymous.

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