STUDIES ON INTRAPULMONARY MIXTURE OF GASES. V. FORMS OF INADEQUATE VENTILATION IN NORMAL AND EMPHYSEMATOUS LUNGS, ANALYZED BY MEANS OF BREATHING PURE OXYGEN

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INTRODUCTION

Among the aspects of ventilatory function of the lungs, about which exact knowledge is lacking, is that of the effectiveness of aeration of pulmonary air spaces during quiet breathing. Among the questions to be answered are:

(*1*) Does the normal lung behave as a perfect mixing chamber, all portions sharing equally in each breath?

(*2*) In abnormal lungs, particularly in emphysema, how large and important is the factor of inadequate ventilation of portions of such lungs?

Regarding the second question, anatomical studies in pulmonary emphysema show that the bronchioles are narrow, in relation to the distended alveoli. Air aspirated from emphysematous bullae has relatively high carbon dioxide and low oxygen contents (1), indicating underventilation. Marked variations in the gas concentrations of the different parts of an expired alveolar specimen, in such subjects, have led to the same conclusion (2). The authors (3), in the course of analyzing the rebreathing method for measuring residual air, found that the usual alveolar samples represent an imperfect measure of average pulmonary gas concentration under the changing conditions of a rebreathing experiment. From these experiments, imperfect intrapulmonary gas mixture was recognized as a factor in pulmonary disability; but it could not be measured and compared with the other factors, namely, pulmonary overdistension, diminished vital capacity, and impaired gas diffusion, in these subjects.

Regarding the question of intrapulmonary mixture in the normal lung, opinions are far from uniform. Haldane (4) recognized that the apparent uniformity of the alveolar air obtained by his method of sampling signified only that the technique yielded a representative sample of the lung gases. Sonne (2) found differences in the different fractions of the alveolar air sample, which, he believed, indicated that the central, less elastic portions of the lung were less well aerated than the peripheral areas.

The fractionation of ordinary expired alveolar samples for this type of study has well-known limitations, namely: (*1*) that rarely more than one-third of the total alveolar air can be expired by any forced expiration, and (*2*) that the oxygen and carbon dioxide content of any fraction is related to the blood circulation of the alveoli from which it came, as well as to their aeration. For example, a high carbon dioxide content may indicate slow aeration or good perfusion, or both. To avoid these limitations, Siebeck (5, 6) and, more extensively, Roelson (7 to 9) used a foreign gas, hydrogen, in the breathing mixture. These experiments showed a greater degree of imperfect mixture than those using air, indicating either that hydrogen diffused into stagnant air spaces, not emptied by a forced expiration, or that reduced perfusion of the poorly ventilated spaces had masked the inadequate ventilation in the air-breathing experiments.

For the present study oxygen rather than hydrogen was chosen as the gas to be breathed since (*1*) it does not disturb normal lung function over short periods of time, and (*2*) its physical properties are more like those of air. Except for the fact that the arterial blood takes up some 7 per cent more oxygen, it behaves essentially as a foreign gas. In a previous paper (10), concerning the open circuit measurement of residual air, a

few curves were presented showing the speed of removal of nitrogen from normal and emphysematous lungs in the course of oxygen breathing. The gross differences were apparent, but these curves could not be analyzed quantitatively because periodic alveolar sampling modified the normal breathing pattern.

More recently Engelhardt (11) measured the expired nitrogen in successive breaths of pure oxygen. Assuming a constant dead space of 150 ml., he found less nitrogen expired than he predicted from the volumes concerned, and from this, he postulated an unventilated lung portion or "verweilluft" which amounted to 76 per cent in normal relatively shallow breathing and 23 per cent in very deep breathing. However, in our experience, the value for the upper pulmonary dead space is rarely as small as 150 ml., especially if the dead space of the mouthpiece is included. Recalculating his data, using a value of 175 or 200 ml. for the dead space, one finds that the "verweilluft" becomes 20 per cent or less on shallow breathing as well as on deep breathing. This demonstrates the importance of an accurate estimate of the dead space in this type of calculation when the tidal air is small.

In the present experimental program, we have studied the speed of nitrogen removal from the lungs by means of the inhalation of oxygen during regular quiet breathing. If the basic quantitative factors involved are accurately known, *i.e.*, the size of the pulmonary air space, the effective tidal air (tidal air minus pulmonary dead space), and the number of respirations per minute, and if perfect mixing of each tidal breath throughout the total pulmonary air space is assumed, then the amount of nitrogen remaining in this air space, at the end of any given number of breaths, can be calculated. Conversely, in actual experiments in which the subject breathes oxygen, the degree of *imperfectness* of mixture can be determined by the extent by which the nitrogen fails to reach the low value predicted by the theoretical calculation.

To derive the formula for the predicted rate of nitrogen removal, let us consider the situation following one normal breath of pure oxygen. The volume of gas in the lungs at the start of this breath is the functional residual air (R), which has a nitrogen concentration of approximately 80 per cent (a). It is assumed here and in later considerations that the normal breathing is deep enough to wash out the upper pulmonary dead space at each expiration so that, at the start, this dead space is filled with alveolar air of the previous breath. At the end of inspiration, the dead space is filled with oxygen and all the nitrogen is in the lungs in a volume equal to R plus the effective portion of the tidal air (T′).

Lung nitrogen concentration at 1st breath, $x_1 = a\frac{R}{R+T'}$.

If the oxygen is not pure but contains a measurable nitrogen concentration (b), then

$$x_1 = \frac{aR}{R+T'} + \frac{bT'}{R+T'}, \quad \text{or} \quad x_1 = (a-b)\frac{R}{R+T'} + b$$

For simplicity let us consider the expression "$\frac{R}{R+T'}$" as a ratio (r) which represents the dilution rate per breath, in the sense that when r is small, lung nitrogen decreases rapidly on breathing oxygen. Then, following similar considerations:

Lung N_2 concentration at second breath = $x_2 = (a - b)r^2 + b$.

Lung N_2 concentration at third breath = $x_3 = (a - b)r^3 + b$.

Lung N_2 concentration at *nth* breath = $x_n = (a - b)r^n + b$.

For very short periods of only a few breaths, the nitrogen released from the blood (hereafter referred to as "nitrogen excretion") is small and may be disregarded. It must be estimated for experiments when the time is longer and when the gradient between blood and lung nitrogen tensions has been raised sufficiently. The total nitrogen excretion in 7 minutes has been found to average 220 ml. (12). Although Behnke *et al.* (13) have established an exponential type of curve for the rate of excretion over long periods of time, the rate may be considered nearly constant for the first few minutes $\left(i.e., \frac{220}{7} \text{ ml. per minute}\right)$. The figure desired for our calculation is the rise in lung nitrogen concentration caused by excretion in the time of one breath.

Designating this figure as "c,"

$$c = \frac{N_2 \text{ excretion per minute}}{(\text{Respiration rate per minute}) \times (R)}.$$

Introducing this value into the simpler formulae for predicting the lung nitrogen concentration, one obtains the following series of corrected formulae:

$$x_1 = (a - b)r + b + c,$$
$$x_2 = (a - b)r^2 + b + c(1 + r),$$
$$x_3 = (a - b)r^3 + b + c(1 + r + r^2),$$
$$x_n = (a - b)r^n + b + c\frac{(1 - r^n)}{1 - r}. \quad \text{Formula } (A)$$

The solid lines in Figure 2 illustrate the form of curve obtained from this formula, and thus describe quantitatively the progressive fall in intrapulmonary nitrogen, as the breathing of pure oxygen continues,—assuming that intrapulmonary mixing is perfect.

As "n" becomes very great, "x_n" approaches $b + c\frac{1}{1 - r}$, which is a mathematical expression for the lowest lung nitrogen concentration obtainable in the first few minutes. In actual experiments, it usually checks the measured value.

METHODS

The apparatus was similar to that used in the open circuit method of measuring residual air, described in a previous paper (10) (Figure 1). An addition to the previous apparatus was a moving drum (D) and a recording pen, attached to the Tissot counterweight. The distinctive feature is a special valve (V_1) adjacent to the mouthpiece. With this, the subject's breathing may be turned into either (*1*) a main circuit where a bag kept full of oxygen furnishes the inlet gas and the expired gases are collected in a Tissot gasometer (T) whose bell dead space has been determined; or (*2*) a side circuit for breathing room air before and after the period of the experiment and for alveolar sampling. For the latter, a second valve (V_2) closes the inspiratory side of this circuit.

As a preliminary to each experimental period, on each subject, the upper pulmonary dead space was estimated from measurements of tidal air volume, and of the expired and alveolar gas concentration during a 3-minute period, with the subject quietly breathing room air. The dead space was calculated from Bohr's formula (14) both in terms of carbon dioxide values as

$$\text{D.S.} = \text{tidal air} \times \frac{\text{alv. } CO_2\% - \text{exp. } CO_2\%}{\text{alv. } CO_2\% - 0.03}$$

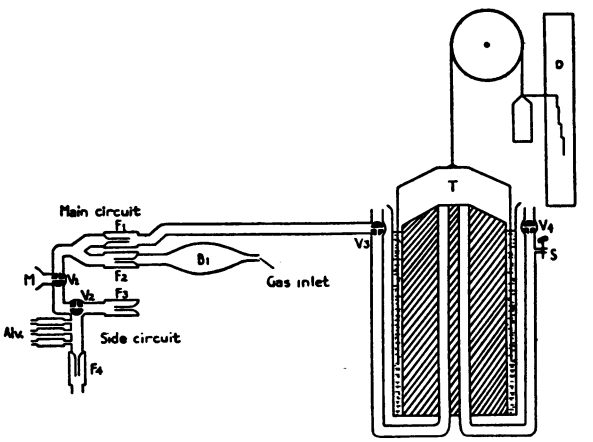

FIG. 1. DIAGRAM OF APPARATUS

M = mouthpiece; V_1 = valve for turning from one circuit to the other; V_2 = shut-off valve for alveolar sampling; V_3 and V_4 = gasometer control valves; "Alv." = alveolar sampling tubes; F_1, F_2, F_3, F_4 = flutter valves; B_1 = rubber bag for inlet gas; T = Tissot gasometer; s = sampling tube for gasometer; D = recording drum.

and in terms of oxygen as

$$\text{D.S.} = \text{tidal air} \times \frac{\text{exp. } O_2\% - \text{alv. } O_2\%}{20.93 - \text{alv. } O_2\%}.$$

We have used the latter (usually larger) value throughout, because it gives a slower predicted rate of mixing and is the value less liable to give a false conclusion of incomplete intrapulmonary mixing. For the same reason, we have neglected the small correction in the alveolar air analysis which might be made for the gas exchange during the time of sampling.

To determine a point on the *actual* mixing curve, the subject, previously breathing room air, was allowed to begin breathing oxygen, exactly at the end of a normal expiration. He was instructed to avoid sighing during the experiment. After the desired number of breaths of oxygen, the last normal expiration was allowed to go into the gasometer; then a forced expiration was made into the alveolar sampling arm, with its evacuated gas sampling tubes attached. (Before the experiment, the entire main circuit and gasometer had been thoroughly flushed out with oxygen.) Immediately after the alveolar sampling, the nitrogen still remaining in the tubing of the main circuit was washed into the bell, the total volume read, and a sample of the mixed gases taken from the gasometer. From these data, the total volume of expired nitrogen was directly calculated. The tracing of expirations was measured for rate and average depth of breathing. Experiments showing markedly irregular breathing were discarded.

On each experimental day, this procedure was repeated 4 to 12 times, the number of breaths (n value) being increased in each successive O_2 breathing period, so as to give significant points on the entire mixing curve. An interval of at least 15 minutes of rest between O_2 breathing periods

was allowed, so that at least the bulk of the nitrogen released from the blood could be reabsorbed. The last experiment of the day was used to determine the value of the functional residual air (R). In this case, the time of breathing pure oxygen continued beyond the washing-out period, usually to 7 minutes.

Data from the above procedures afford two separate estimates of the pulmonary nitrogen concentration after various numbers of breaths of oxygen: (*1*) The alveolar specimens represent direct attempts at such an estimate. (*2*) The values for expired nitrogen subtracted from the total lung nitrogen (measured in the determination of R) give an estimate which is independent of the subjects' ability to expire a uniform alveolar sample. The calculation for this second estimate, expressed mathematically, using the same symbols as in previous formulae, becomes:

$$x_nR = aR - (N_2 \text{ expired in n breaths}) + (N_2 \text{ excreted in n breaths}).$$

This measurement is accurate only in the first one-half or two-thirds of the mixing curve when the difference between the two volumes of nitrogen is relatively great and the factor of nitrogen excretion is minimal.

In experiments where both methods of calculation are possible, the comparison of the two values furnishes another test of the uniformity of the alveolar air. If they differ significantly, it may be assumed that the alveolar sample is not representative of the average gas concentration existing at the moment of sampling. Divergence might occur with the rapid changes of intrapulmonary gas contents during oxygen breathing, even though, during breathing of ordinary air, the alveolar samples are considered satisfactory, judging by the criterion that the CO_2 pressure approximates that of the arterial blood. Actually, all the subjects studied in these experiments could deliver good alveolar samples according to this criterion.

RESULTS

The subjects consisted of 18 normal adults (15 male and 3 female), and 5 patients with severe pulmonary emphysema. The normal subjects included physicians, medical students, and ambulant patients, suffering from non-respiratory disease. The entire group ranged in age from 21 to 65 years.

Figure 2 presents the results of two typical experiments, in which are plotted the lung nitrogen concentrations as ordinates against the number of breaths ("n") as abscissae. The "n" scale is presented logarithmically for convenience because the points are taken closer together in the beginning of the curve than in the end. In each experiment, the "r" value (r = dilution rate per breath) varied somewhat from one breathing period to another because of the unavoidable variations in average tidal air. The complete mathematical curves (cf. formula, above) are drawn for the largest and the smallest values of "r" as found in each experiment, to show the shape of the curves and the range of possible values for the experiment in question. From the data of each period of oxygen breathing, three points are presented on the chart at the "n" value of that breathing period:

(*1*) The open circles (○) represent the *theoretical* nitrogen concentrations existing after n breaths, assuming perfect mixing, *i.e.*, by the use of formula (*A*); (*2*) the solid circles (●) represent the actual *experimental* nitrogen concentrations after n breaths, using the measured concentration of nitrogen in alveolar air for this factor; (*3*) the solid triangles (▲) also represent actual experimental nitrogen concentrations, but obtained, in this case, by subtracting the total expired nitrogen from the initial total nitrogen in the pulmonary air space.

It will be seen that, on subject 4, the three points show only slight divergence, which may be attributed to experimental errors in the method. In other words, in this subject, the lungs appeared to behave as a perfect mixing chamber. Assuming the dead space from Bohr's calculation, each effective tidal air volume mixed uniformly with the total pulmonary (*i.e.*, functional residual) air volume. Also, the usual alveolar sampling method gave a value equal to the average concentration in the lungs at that moment.

In the case of the typical experiment on subject 6, a different result will be seen. This subject was a man of 65 whose heart and lungs were normal as far as could be determined. Yet as will be seen: (*a*) The "calculated" lung nitrogen values (definition (*3*) above) were regularly higher than the predicted value (definition (*1*) above). (*b*) The "alveolar" samples (definition (*2*) above), being lower than the "calculated" values and in three instances even lower than the "predicted" values, apparently gave an erroneous measure of average lung nitrogen concentration. The situation may be pictured as follows: each breath of oxygen mixed completely with only a portion of the alveolar air; in the remainder, the nitrogen was washed out only slowly. At the end of the breathing period, there were presumably various concentrations of nitro-

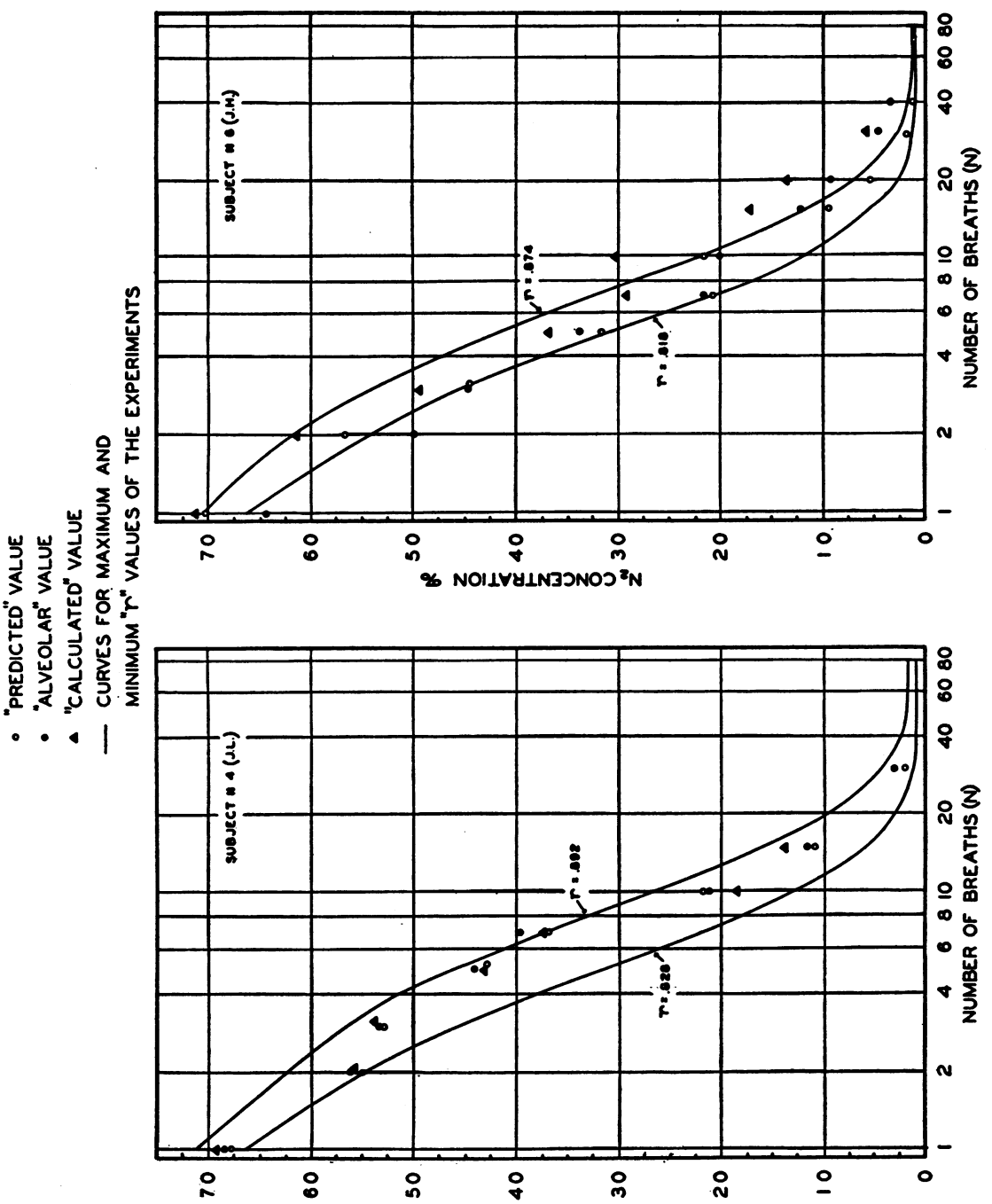

FIG. 2. SAMPLE EXPERIMENTS ON 2 SUBJECTS

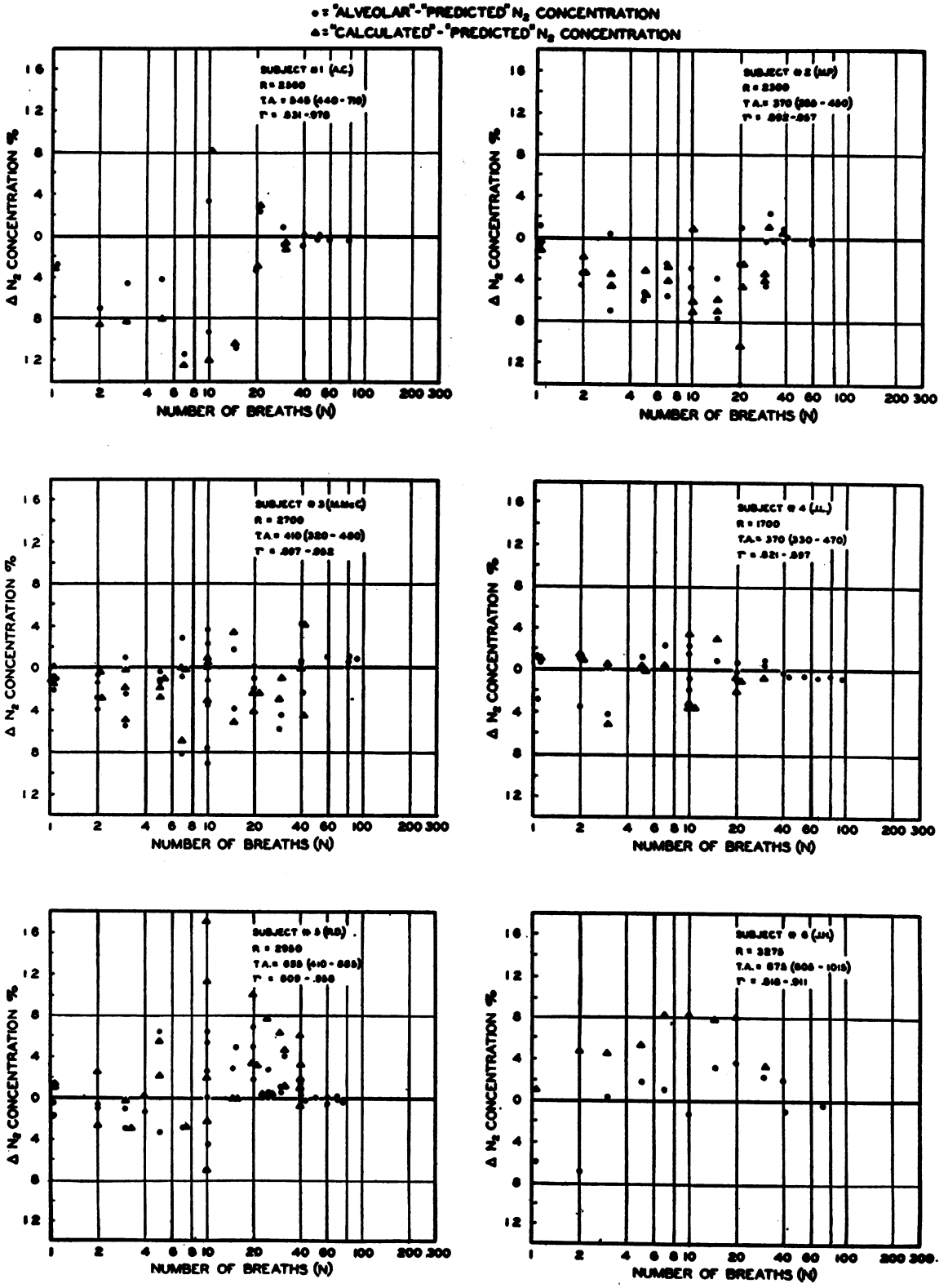

FIG. 3. SUMMARY OF DATA ON 6 NORMAL SUBJECTS

gen in different alveoli. The alveolar sample therefore came chiefly from the well-ventilated portions and so was below average in nitrogen concentration.

With these typical experiments as a background, we may now turn to a survey of all our data. Figure 3 presents the results on 6 normal subjects, which were those most thoroughly studied. Data on each of the other 12 normal subjects corresponded closely to those of one or another of the 6 presented in detail. Figure 4 presents, similarly, the results on 4 subjects with pulmonary emphysema.

The graphical scheme is as follows: the abscissae represent the number of breaths (n) on a logarithmic scale as in Figure 2. The ordinates, labelled "ΔN_2 Concentration," represent differences between the predicted (theoretical perfect mixing) values for each experiment (cf. derivation of formula in Introduction) and the values actually measured. The symbols remain the same as in Figure 2: the circles for alveolar samples directly analyzed, the triangles for the values for pulmonary concentration of nitrogen calculated from the expired nitrogen (cf. derivation under Methods).

This method of presentation offers several advantages over the more complete picture as in Figure 2: (*1*) It eliminates one of the points plotted in each experiment, *i.e.*, the predicted value, which may be considered to be set on the base-line. (*2*) The plotting of divergences from predicted values reduces the range of the vertical scale to a more convenient size. (*3*) The arithmetical divergences are themselves the figures of greatest interest since they directly indicate the adequacy or inadequacy of intrapulmonary mixing.

Looking at the charts on individual subjects, it will be seen on subjects 1 and 2 that the preponderance of points fall below the base-line of predicted values. No significant divergence between the circles and triangles can be noted. In other words, the nitrogen actually measured as remaining in the lungs after n breaths is less than the predicted (perfect mixing) value. Such a situation can be interpreted only as due to errors in one or more of the assumptions used in the formula for predicted values. It was mentioned that we used the larger value for upper pulmonary dead space, derived from oxygen values by Bohr's formula, and that we neglected alveolar corrections for gas exchange during the time of sampling. These assumptions were intentionally made to give the highest possible predicted values. Thus a deviation above the base-line is doubly significant; one slightly below the base-line, of little or no significance.

Charts on subjects 3 and 4 show a much closer approximation of the measured to the predicted values. This is representative of the majority of the normal subjects studied.

In the case of subject 5, there is a rather wide scatter of points but clearly there is a preponderance of points above the base-line, especially at $n = 10$ and $n = 20$. As discussed above, deviations in this direction are of real significance and probably indicate the effect of unequal ventilation of the different lung portions and thus imperfect mixture. The reason for variations in response in different normal subjects is one of the questions which will be discussed in a later section.

The sixth chart is taken from data on J. H., the eldest subject in the group (age 65). Aside from a mild chronic nephritis, without hypertension or heart disease, he was in good physical condition. It will be seen for the first time among the charts discussed that the values for "calculated" lung nitrogen (▲) lie regularly much higher than the "alveolar" values (●). In addition, the former values are well above the base-line. Thus, in this case, both of the criteria for incomplete alveolar mixing are satisfied. We may visualize that nitrogen persisted in some regions of the lung after it had been nearly washed out of other portions and that some of this nitrogen failed to be expired, even during the forced breath of alveolar sampling. Such a situation was demonstrated in 2 other normal subjects in the group, both over 50 years of age. The question may be raised whether the lungs of these middle-aged or elderly men were entirely normal. At present, we can only say that this picture forms a transition from the normal to that seen in clinically abnormal subjects.

The last 4 charts (Figure 4) on abnormal subjects are presented in order of increasing abnormality. In all, there is a wide divergence between alveolar (●) and calculated (▲) values.

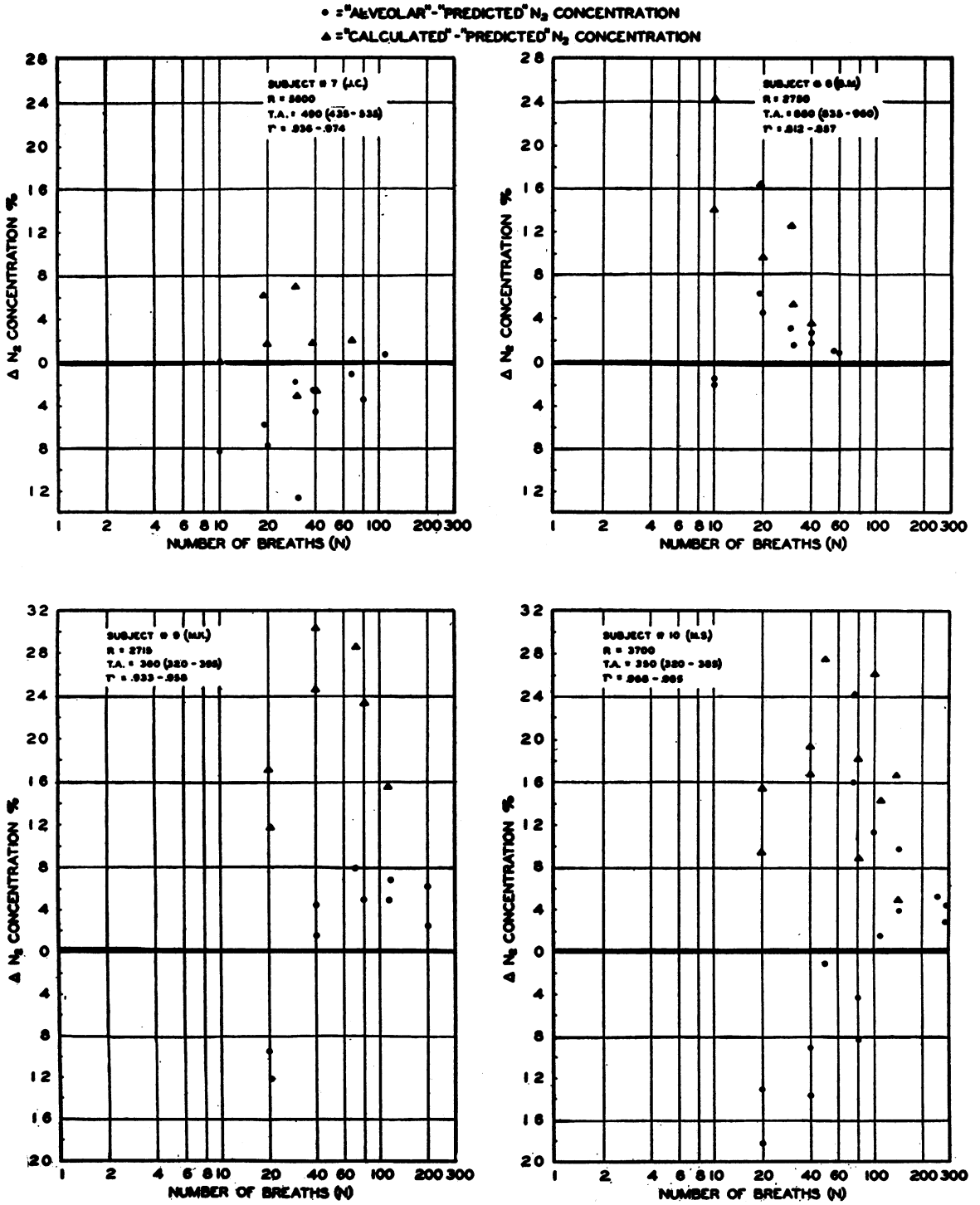

FIG. 4. SUMMARY OF DATA ON 4 SUBJECTS WITH SEVERE PULMONARY EMPHYSEMA

during the first part of the mixing curve. In the last 3 subjects, the calculated values lie high above the predicted values, higher by far than any points in the normal subjects. In other words, much more nitrogen still remains in the lungs of these subjects after n breaths of oxygen, than that which would have remained if intrapulmonary mixing had been perfect.

In subject 7, the calculated values lie above the line but somewhat less so than the last normal subject (Number 6). Since subject 7 was suffering from severe respiratory disability, it is of interest to discover possible differences between him and the other 3 on Figure 4.

Unlike the others, he did not show significant arterial oxygen unsaturation, although he suffered from severe dyspnea on the slightest exertion. However, his functional residual air volume was by far the largest of the 4—over 5,000 ml. as compared with 2,500, 2,700, and 3,700 in the other 3. These facts, together with the data on the speed of mixing, almost surely distinguish two important types of pulmonary disability, about which we have previously had no distinguishing test. In fact, principal emphasis has been placed on the increase in residual air, together with the fall in vital capacity, to explain the disability in pulmonary emphysema. From a critical analysis of usual residual air measurements in a previous paper (3), it was concluded that frequently, in such cases, the measurements gave falsely high residual air values due to the factor of imperfect intrapulmonary mixture. At that time, the latter factor could not be accurately measured.

Now we may conclude that subject 7 suffered his chief disability from the disturbances in lung size and gross mechanics, and that the other 3 subjects, with less of this type of disability, had in addition a marked degree of retarded and inadequate intrapulmonary mixing. Presumably the latter defect is due to narrowing or distortion of the bronchiolar structure.

DISCUSSION

In the data presented above, certain qualitative facts stand out: (*1*) Some normal subjects appear to have nearly perfect mixing of each inhaled breath through the alveolar spaces. (*2*) Other apparently normal subjects have small to moderate degrees of imperfect mixing. (*3*) Three of 4 cases of emphysema showed a striking inadequacy of mixing of inhaled air evenly through the lungs. One emphysematous subject, with a very large functional residual air, had defective pulmonary emptying on this account, but the distribution of inhaled air throughout this large lung volume was relatively good.

Discussion of errors

One limitation on accuracy in these and previously published experiments is the difficulty in accurately estimating the upper pulmonary dead space. Some workers, especially Haldane (15 to 18), found that the dead space increased markedly with deeper breaths; others, chiefly Krogh and Lindhard (19 to 21), found a constant dead space. Schoedel (22) would seem to have reconciled the differences by more careful consideration of the changes in concentration during sampling, thereby establishing that the dead space is nearly constant, except in pathologically shallow breathing.

A few direct experiments on this subject are presented in Table I. Here, the tidal air was

TABLE I

Values of the dead space of the upper respiratory spaces, determined at different depths of quiet breathing

Subject	Tidal air	Dead space	
		From CO_2 values	From O_2 values
	ml.	*ml.*	*ml.*
J. H.	670	293	351
	815	274	286
	900	304	372
	980	308	358
M. McC.	345	176	194
	355	172	173
	390	180	203
	395	193	216
	425	193	213
M. P.	315	167	180
	385	174	168
	460	184	183
	475	173	177
	480	171	211
J. L.	285	147	146
	305	124	132
	345	147	158
	380	151	164
	385	150	190
	600	161	179

varied at rest, keeping the total ventilation constant by reducing the respiratory rate. Because of the difficulties of such voluntary regulation, the results embody more errors than would be ideal, yet it is definite that the dead space increases only slightly, if at all, with increased depth of breathing.

With this evidence as justification, we have assumed a constant dead space in our "predicted values" when the tidal air differed from the volume used in Bohr's formula. However, in actual experiments, the tidal air varied both up and down from the standard value, so that the mean error from such an assumption should not be great. This may explain in part the scatter of points found in some normal subjects.

Another cause of scatter is undoubtedly due to slight variations in the functional residual air from one breathing period to another. This value was determined each day as the last measurement. It could have been determined for each breathing period by prolonging the oxygen breathing and collecting the remainder of the expired nitrogen in a separate gasometer. However, in such a procedure, no alveolar sample could have been obtained.

Small variations in tidal air from breath to breath introduce another source of error, which, however, is smaller than might be expected. Actual calculation shows that on experiments using more than 10 breaths of oxygen, a variation of 50 per cent about the mean tidal air leads to an absolute error of less than 2 per cent in the value of the predicted nitrogen concentration. When the number of breaths was less than 10, the tidal air was usually quite constant, provided sighs were suppressed.

Possible simplification for a practical test

In order to reduce unnecessary labor in any practical test it is important to know at what number of breaths (n), the deviation from the predicted value is maximum. With this information available, only 1 or 2 determinations would be necessary to evaluate intrapulmonary mixing.

An approximate mathematical relationship can be derived for this and then tested on some of the experiments. In its simplest form, the "prediction formula" is

$$x_n = Kr^n.$$

The actual mixing curve may be considered to follow a similar formula with a slightly larger dilution ratio (r'),

$$i.e., \quad x_n = K(r')n.$$

The difference between them can be expressed, $y = x' - x = K[(r')^n - r^n]$. Differentiating, setting $\frac{dy}{dn} = 0$ for a maximum and solving,

$$n = \frac{\log \log r - \log \log r'}{\log r' - \log r}.$$

Solving this for the various values of r commonly found, substituting a slightly larger value for r' (actually r' taken = r + 0.001), it was found that the value of "n" best for the purpose of showing divergence varies, as in the accompanying Table II.

TABLE II

Values for the best choice of number of breaths (n) calculated to show the greatest divergence from predicted curves

r	Optimum n
0.75	4
0.80	5
0.85	6
0.90	10
0.93	13
0.95	20
0.96	25
0.97	34
0.98	51
0.99	105

Let us apply this table to 2 of the abnormal subjects. In subject 8, r averaged about 0.85 and the maximum of the curve is obviously at 10 or less. In subject 10, r equals about 0.98; the maximum is at 40 or higher. Thus, as a rough approximation, the formula holds true. Since the usual value for r is 0.90 ± 0.05 for almost all subjects, it seems wise to pick the point of n = 10 as the most likely to show the effect of slow mixing, in any single test, which may be advised. If more points are possible, n = 20 and 40 could be used.

If constant underventilation of significant portions of the lungs occurs in normal individuals, one must imagine some mechanism whereby the blood circulation of these portions is simul-

taneously reduced. Otherwise, an oxygen unsaturation of the mixed arterial blood would result. It seems likely, however, that serious underventilation of normally perfused areas does exist in patients with severe pulmonary disease and is undoubtedly one of the causes of arterial anoxemia in such subjects. Thus, in a given patient with arterial anoxemia, tests such as we have presented will help to explain the cause of the disability. A positive test for poor mixing would point to such a mechanism as the cause of the anoxemia and would logically indicate the therapeutic use of bronchodilator drugs. A negative test would point to poor diffusion between alveoli and blood, to central depression of ventilation, or to some other cause of anoxemia. Appropriate tests might decide among these and other logical treatment might be indicated.

Possible mechanisms of poor mixing

At least two theories to explain incomplete intrapulmonary mixing in normal lungs have been proposed: (*1*) That of Sonne based on anatomical differences in elasticity, and (*2*) that of Engelhardt who suggests a physiological alternation of function of the various lung units. It is doubtful whether the proponents' experiments or the data here presented can adequately prove either theory. Possibly a more fruitful experiment would be to compare the mixing during voluntary hyperpnea with that during the increased ventilation of exercise. A difference between the two would favor some form of physiological adjustment over a purely anatomical cause.

While we can say very little about the exact mechanism of poor mixing, it is useful to inquire what the deviations from the curves in our data represent in terms of percentage failure of ventilation. It should be realized that the term "percentage failure of ventilation" is an arbitrary one. Actually, all degrees of relative under- and overventilation probably exist in the many lung units. Yet, for an arbitrary measure, we may calculate it as though at each breath a proportion of all units is completely shut off and the remaining units share equally in the new breath.

Considering the situation for a single breath of oxygen and using the same symbol and formulae (*A*) as in the introduction,

I. $(a - b)r' + b =$ actual lung nitrogen concentration.

In this case, r' is the value representing the actual dilution rate per breath and so may not equal the theoretical dilution rate $r = \frac{R}{R + T'}$. However, we may consider $r' = \frac{R}{R + T''}$. T'' in this case is a value obtained arbitrarily to fit the measurement. It has no real meaning but in case of imperfect mixing it will be smaller than T', the effective tidal air measured by Bohr's formula.

If α portion of the lung is ventilated, then

II. N_2 concentration of that portion $= \frac{\alpha R}{\alpha R + T'}(a - b) + b$ (using formula (*A*) of introduction).

III. N_2 concentration of unventilated portion $= a$ (by definition of "a").

IV. Total N_2 content of lungs $= \left[\frac{\alpha R}{\alpha R + T'}(a-b)+b\right]\alpha R + a(1-\alpha)R.$

V. Dividing by R, average lung nitrogen concentration $= \left[\frac{\alpha R}{\alpha R + T'}(a - b) + b\right]\alpha + a(1 - \alpha) = (a - b)\frac{R}{R + T''} + b$ (from equation I).

VI. Dividing by $(a - b)$,

$$\frac{\alpha R}{\alpha R + T'} + 1 - \alpha = \frac{R}{R + T''}.$$

VII. Solving for α, $\alpha = \frac{T'T''}{R(T' - T'') + T'T''}$.

It will be seen from the final formula that a small difference in T' and T'' will have much greater significance, the smaller the tidal air, and, conversely, the effect of imperfect mixing will be much more easily measured, the larger the tidal air.

Although this formula involves several additional assumptions when applied to experiments of more than one breath, these are probably preferable to the extreme complexities of any other mathematical treatment. Actually, the chief assumptions are that the portion ventilated is

constant at each breath and that the ventilated units occur by chance throughout the lung from both the previously ventilated and unventilated portions. Since these assumptions are more nearly those of the theory of alternation of function than the anatomical theory based on differences in elasticity, it follows that a constant α value would be a bit of evidence toward the theory of alternation of function, whereas a decreasing α value would favor the presence of constantly underventilated areas.

The following brief table gives the calculated α values in subject 10.

n	
20	4.1 per cent
40	3.4 per cent
80	3.0 per cent
120	2.9 per cent

The striking feature is the very low value for the ventilated portion (α) as calculated in this manner and the tendency for α to decrease with increase in the number of breaths in the experiment. This latter point fits with the known pathology of emphysema in which there are constantly underventilated lung regions.

Likewise, in subject 6 among the normal subjects, the following table shows similar trends, to a less striking degree. Possibly the decreasing values of α indicate some undiagnosed emphysema.

n	
1	54.7 per cent
2	36.1 per cent
3	50.8 per cent
5	48.0 per cent
7	37.6 per cent
10	30.0 per cent
15	27.2 per cent
20	20.9 per cent

The sensitivity of the methods in detecting incomplete mixing

It is striking that the ventilated lung portion (α), less than 60 per cent in subject 6, is calculated from a difference between T′ and T″ of only 50 cc. Unfortunately, the method as presented here cannot detect small or moderate degrees of unequal ventilation, especially when the tidal air is small. Let us take a hypothetical case (approximating subject 3) where the tidal air is 300 ml. and the functional residual air 2500 ml. Here a difference of only 10 cc. between T′ and T″ would lead to an α value of 50 per cent.

It is now obvious that, to measure accurately the degree of poor mixing, the tidal air must be large. In those cases in which it is naturally large, the effect may be evident from natural breathing. In other cases, it will be necessary to study the measurements on voluntarily deepened breathing. Such a study is being undertaken.

SUMMARY AND CONCLUSIONS

1. The effectiveness of the process of mixture of inhaled tidal air with the air already present in pulmonary spaces has been studied by means of the analysis of the respiratory gases during the breathing of pure oxygen, in normal subjects and in patients with pulmonary emphysema.

2. If intrapulmonary mixing of air is perfect, then the concentration of nitrogen in the lungs at the end of any given number of breaths of pure oxygen can be calculated when (*a*) the effective tidal air volume, (*b*) functional residual air volume, (*c*) initial "alveolar" (intrapulmonary) nitrogen concentration, and (*d*) rate of washing out the dissolved nitrogen in the body, are known. The formula describing this phenomenon has been derived.

3. Values for pulmonary concentration of nitrogen after breathing oxygen have been measured on 18 normal subjects and 5 patients with severe pulmonary emphysema.

4. For normal subjects, the divergence between predicted and measured values was small in the majority, but moderately great in a few. Difficulties in accurate measurement of the upper pulmonary dead space make further clarification difficult, but imperfect intrapulmonary mixture in some normal subjects is probable.

5. Four out of 5 emphysema subjects showed markedly higher nitrogen concentrations in the lung than predicted, indicating a marked degree of unequal lung mixture. It was possible to demonstrate, in actual clinical cases, the distinction between inadequate ventilation of pulmonary spaces due to greatly increased residual air, and that due to unequal mixture of tidal air through these spaces.

6. An estimation of the extent of underventilation of pulmonary spaces, in successive samples of alveolar air from normal and diseased subjects, provided some evidence against the existence of

any systematic alternation of function of discrete groups of alveoli.

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