THE VOLUME OF THE DEAD SPACE IN BREATHING AND THE MIXING OF GASES IN THE LUNGS OF MAN.

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The problem concerning the volume of the dead space in the air passages of man has been much debated of late years. Up to 1904 the measurements of Zuntz and Loewy(1) on the bronchial tree of a corpse were generally accepted as giving at least a good approximation to the volume, and by the Zuntz school of physiologists and many others the figure found (140 c.c.) was used for calculating the composition of the alveolar air from that of the mixed expired air. When Haldane and Priestley(2) had invented the direct method of taking samples of alveolar air they utilised this also for determining the volume of the dead space, comparing the CO_2 percentage of the alveolar air with that of the total expired air according to the formula[1]

$$EC_e = (E - D)\,C_a.$$

They measured and analysed the whole of the air expired in one deep expiration and determined the composition of the alveolar air in separate experiments. The results varied by about 30 % on either side of the mean, which was 142 c.c. for one subject and 189 for the other.

In 1911 Siebeck(3) introduced a new modification of the method invented by Haldane and Priestley which gave much more consistent results. He took an inspiration of between 500 and 1000 c.c. pure hydrogen and made an expiration of similar depth into a small spirometer. At the end of the expiration a sample of alveolar air was drawn, and the air in the spirometer as well as the alveolar sample were analysed for hydrogen. By a special series of experiments

[1] In the following E means the volume of the expiration, D the personal dead space, and d the additional instrumental dead space, C, O and H percentages of CO_2, O_2 and H_2 respectively, while the indices i, e and a mean inspired air, expired air and alveolar air respectively.

Siebeck showed that after the expiration of about 300 c.c.[1] the alveolar air after a single breath of hydrogen of constant volume had a H_2 percentage which was uniform enough for his purposes. The variations amounted to some 2 to 3 p.c., and the later portions did not contain appreciably less hydrogen than the earlier. Siebeck points out the advantages gained by employing a gas, which is not normally present in the inspired air, in that the differences in composition between the gas from the dead space and the alveolar air become much larger and the influences of the unavoidable errors therefore smaller.

Siebeck obtained very regular results in series of experiments on the same subject during rest and with natural respiration and concluded from his determinations on different subjects that there are individual differences which may amount to 50 c.c. He showed further that the depth of respiration has no measurable influence upon the dead space, which varies however with the volume of air in the lungs—the "Mittellage"—being for instance in one case 109 c.c. with a "niedere Mittellage," 135 c.c. after an inspiration of normal depth (500 to 600 c.c.), 152 c.c. after an inspiration of double the normal depth and 193 c.c. with as much air in the lungs as possible.

In 1912 Haldane and Douglas(4) published a series of determinations by means of CO_2 of the dead space of Douglas made during rest and during walking at varying rates. They obtained the (to us) startling result that the dead space became regularly increased with the increasing hyperpnœa and rose from 160 c.c. during rest in bed to the astonishing figure of 622 c.c. during work involving a ventilation of 61 l. per minute and a volume of each breath of 3150 c.c. They attributed the increase to active bronchial dilatation and assumed that the increases in diameter of the bronchioles were brought about by a physiological regulation and would diminish effectively their resistance to the flow of air.

The results of Haldane and Douglas were criticised by us(5) (1913), and we pointed out especially that during muscular work, when the gas exchange is much increased, the alveolar samples taken according to H.-P.'s method must show CO_2 percentages a good deal above those corresponding to the end of inspiration and of expiration respectively, because the sharp expiration from the end of which the

[1] Siebeck concluded from the fact that not even an expiration of much less than the volume of the dead space consists of pure inspired air that the conception of a dead space does not represent real conditions—"stimmt also mit den tatsächlichen Verhältnisse nicht überein." As will be seen below we think this particular conclusion unwarranted, but at the same time we can confirm the accuracy of Siebeck's experimental results on all points on which we have tested them.

sample is drawn takes a certain time during which a sufficient amount of CO_2 is produced to appreciably raise the CO_2 percentage of the sample.

In a later paper(6) we have attempted to measure the increase in CO_2 percentage occurring in the alveoli during a H.-P. expiration during a work hyperpnœa with respirations just exceeding 3 l. and found that it amounted to about 0·7 % which increase would raise the dead space as calculated from 100 to 500 c.c.

We examined further(5) the Siebeck method of determining the dead space and by taking two samples at different depths from the same expiration after an inspiration of hydrogen we were able to show, what Siebeck's experiments had not been delicate enough to discover, that the distribution of hydrogen in the alveolar air after a single breath of the gas is not completely uniform, but that the last portion of air expired will always contain less H_2 than any earlier[1]. This involves an unavoidable error in the determination of the dead space, in so far as the alveolar sample taken at the end of an expiration does not represent exactly the total alveolar air expired, but we were able to show that when pure hydrogen is inspired, and the expiration is not made too deep the influence of the error becomes unappreciable. We made, therefore, series of determinations of the dead space by means of hydrogen on different subjects both during rest and during muscular work, taking care to use expirations of less than 1 l. We found no evidence whatever of an active dilatation of the air passages during work. All our determinations were deliberately made with a practically constant volume of air in the lungs corresponding to the resting position of the chest before taking the inspiration of 500-800 c.c. hydrogen.

Later Lindhard(7) has shown that there is an approximate numerical relation between the length of the human trunk and the volume of the dead space as determined by our method, the volume being increased by about 7 c.c. per cm. length above a certain minimum.

The latest contributions to the dead space problem have been made by Haldane(8) and simultaneously by Yandell Henderson in collaboration with Chillingworth and Whitney(9). Haldane varied the frequency of his own breathing during rest between 60 and 3 per minute, by which consequently an inversely varying depth of the respiration was brought about. From analyses of the expired air,

[1] It is evident that when hydrogen does not instantly become evenly distributed in the alveolar air the same must *a fortiori* hold also for any other gas inspired into the lungs, since they will all diffuse more slowly than hydrogen.

collected over 3-minute periods, and samples of alveolar air he calculated the dead space in the same way as before, but for each of the gases CO_2 and O_2 separately. The results showed a great increase in the dead space with increasing depth of the respiration in spite of the absence of hyperpnœa. The dead spaces calculated from the CO_2 percentages agreed fairly well with those obtained by Douglas at corresponding depths, but the figures calculated from the O_2 percentages were considerably larger still. Haldane was led by these results to discard the idea of an active dilatation of the bronchi, and believing that the bronchi and bronchioles could not—on account of their relatively thick walls—be passively distended to the extent found (increases from 100 to 700 or even 900 c.c.), he found it necessary to seek the increase in dead space beyond the terminal bronchioles. Basing himself on the beautiful anatomical investigations of Miller(10) he claimed the "atria" as parts of the air passages contributing to the dead space. He says: "Miller's work seems to furnish the key to the interpretation of the increased dead space. Each terminal bronchus (see Fig. 7 and 8 of Miller's paper) ends in several openings or 'vestibula' each of which leads into an air-cavity or 'atrium,' lined by alveoli. From each atrium several openings lead onwards into 'air-sacs,' which are main cavities of which the walls are constituted by alveoli or air-cells. By far the greater number of the lung alveoli belong to the air-sac system, but a very appreciable number belong to the atria, and the latter act partly as air-passages to the air-sacs, and partly perform the same respiratory functions as the air-sacs themselves. The walls of the atria have the same general structure as those of the air-sacs, and must be just as free to expand when air enters the lungs.

It is evident that the atria must have a far greater supply of fresh air than the groups of air-sacs beyond them, since all the fresh air supplied to the air-sacs passes through the atria, and at the end of an inspiration they will be left full of relatively pure air. They will therefore contribute to the 'effective' or 'virtual' dead space due to the bronchi and upper respiratory passages; and as they will expand freely with a deep inspiration, and be washed out more thoroughly, the dead space will increase with a deep inspiration."

Henderson and his collaborators used in most of their experiments single inspirations and expirations, always beginning after an inspiration to the residual air. They took inspirations of air or of hydrogen, expired into a bag or a gasometer and analysed alveolar samples taken at the end of the expiration and the total expired air collected. Their

results are extremely irregular, but show on the whole an enormous increase in dead space with increasing depth of the inspiration [and expiration]. They find like Haldane a larger dead space for oxygen than for carbon dioxide. They accept Haldane's explanation of the atria as contributing the larger part of the dead space (in inflated lungs), but think that the inconstancy of their individual results are due to active variations (rhythmic and others) of the state of contraction of the bronchial muscles. We do not propose to enter upon a discussion of Henderson's results in so far as they differ from those of Haldane, concerning which we cannot avoid going considerably into details.

Between Haldane and ourselves there is a clear and debatable issue. Haldane's conception is this: We can get pure alveolar air by making a deep expiration. This alveolar air is contained in the air-sacs (but not in the atria) of the lungs and is of constant composition throughout these at any given moment. The composition varies from moment to moment with the respiration. At the end of inspiration the alveolar air is comparatively rich in O_2 and poor in CO_2; at the end of expiration there is a minimum O_2 percentage and a maximum CO_2 percentage. The arithmetical average of samples taken just at the end of inspiration and expiration respectively is the "average alveolar air." This shows a constant CO_2 pressure independent of variations in frequency (provided the depth is allowed to regulate itself) and independent within certain limits of variations in the pressure and composition of the air breathed. The CO_2 pressure of the alveolar air as thus defined is equal to that of the arterial blood, and the constancy is maintained by the arterial blood acting on the respiratory centre.

Haldane maintains that the dead space is a physiological and not an anatomical conception; it can be determined separately for O_2 and for CO_2 by the relation between the percentages of the gases in the expired and alveolar air respectively, but it is wrong in principle to make determinations by means of other gases, and it is inadmissible to calculate the composition of the alveolar air from the dead space thus determined and the mixed expired air.

We hold: That the air in the air-sacs (as well as in the atria) is not at the end of inspiration of the same composition throughout, because the inspired air is incompletely mixed with the air previously contained. The mixing takes place chiefly by diffusion and requires a certain time.

That the alveolar air must include all the air with which the venous

blood coming to the lungs enters into gas exchange—in the atria as well as in the air-sacs.

That samples taken according to Haldane's method can, in certain circumstances only, represent *approximately* the average alveolar air of the moment.

That the average CO_2 tension of samples taken at the end of inspiration and at the end of expiration does not generally represent the average CO_2 tension of the alveolar air as a whole or of the arterial blood.

That the dead space can be defined anatomically as well as physiologically as the air passages down to and including the bronchioles, that it can be determined with considerable accuracy and that the composition of the average alveolar air, which determines the CO_2 tension of the arterial blood, can in most cases (exceptions to be detailed below) be most safely *calculated* from the composition of the expired air, the average depth of the respiration and the volume of the dead space.

The differences of opinion as here summarised will be considered in detail below, but before proceeding to do so we shall produce the additional experimental evidence on certain of the points at issue which we have thought it desirable to collect. The problems which we have endeavoured to elucidate by our experiments are mainly the following: Is there or is there not an anatomically defined dead space? To what extent does it vary with inflation of the lungs? Is the pulmonary air beyond the dead space at the end of inspiration uniform in composition or not[1]?

Methods. Our experiments for determining the dead space have been arranged practically as described in our first contribution to the subject with the addition of a spirometer for measuring the total inflation of the lungs. The tube (4) on the four-way tap, Fig. 1 (which is copied from our earlier paper), was connected like (3) with a recording spirometer (capacity 7 l.) containing atmospheric air. In the experiments the subject, after having closed the nose with a clip, began by expiring to the residual air. Thereupon he put the mouth to the tap (at 5) and inspired a certain quantity of atmospheric air from the 7 l. spirometer. The volume inspired was recorded graphically. Turning the tap the inspiration was continued from the bell-jar (1) containing a measured volume of the gas used for the determination (500 c.c.

[1] On all these points we think that the earlier experiments by Siebeck and by ourselves had given a definite answer, but as these experiments have been disregarded without comment it is necessary to extend and supplement them.

hydrogen in most cases). Having inspired this he turned the tap further and expired into the small (1·5 l.) recording spirometer (7). After an expiration of suitable volume the tap was closed and a sample of alveolar air drawn from it on the side of the subject. These samples we have always taken in evacuated vessels to get them instantaneous. Immediately afterwards the gases in the expiration spirometer and the tubing connecting it with the tap were thoroughly mixed and a sample drawn[1]. From the percentages of the gas used for the determination in the two samples and the recorded volume of the expiration the dead

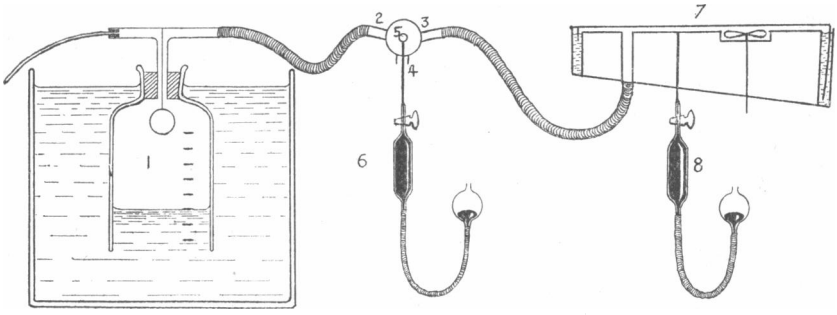

Fig. 1. Apparatus for determining dead space.

space is calculated. In experiments with hydrogen the calculation is made according to the formula

$$D = \frac{Eh_e - Eh_a}{h_i - h_a} - d.$$

We give an example of such an experiment.

Residual volume of expiration spirometer 173 c.c. Dead space of tubing from tap to spirometer 47 c.c. In all 220 c.c. Dead space in tap on the side of the subject d = 10 c.c.

Volume of inspiration 2·85 l. air + 0·5 l. hydrogen.

Volume of expiration E = 657 c.c.

Percentages[2]: h_i = 149·5; h_a = 17·47; h_{sp} = 34·8; $h_i - h_a$ = 132·0.

Eh_e = (657 + 220) 34·8 = 305·0

Eh_a = 657 + 17·47 = 114·7

190·3 D = 190·3 : 132·0 − 10 = **134.**

[1] Our spirometers are provided with a revolving fan, and we have found again and again that this fan must be worked at a high rate of speed for several seconds when complete uniformity is to be secured. Failing this the mixture may remain incomplete for many minutes.

Henderson, Chillingworth and Whitney do not seem to have taken any precautions to obtain a complete mixture of the gases in their expiration spirometer, and this is probably one of the reasons why their individual results are so extremely divergent.

[2] Instead of actual percentages of H_2 the contractions on combustion are given.

We began by making a series of "normal" experiments on J. L., varying the volume of air in the lungs within the widest possible limits, but keeping the inspirations of hydrogen and the expirations within the limits which we had formerly shown to be essential in view of the incomplete mixture of the alveolar gases: that is between about 500 and 1000 c.c. The results are tabulated in Table 1 and shown graphically in the curve Fig. 2. We have arranged the experiments according to the total volume of air in the lungs, taking as the starting

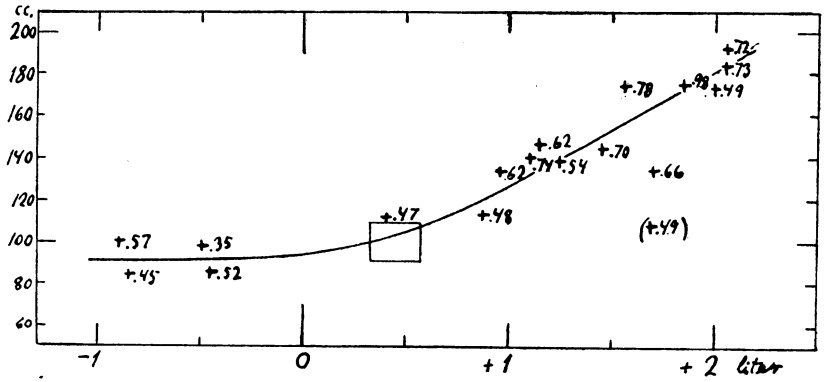

Fig. 2. Dead space of J. L. at varying inflation of lungs. Normal experiments.

TABLE 1. Normal determinations of dead space on J. L.

Inflation of lungs c.c.	Inspiration from residual position c.c.	Expiration c.c.	Dead space c.c.
− 900	0 + 750 H_2	571	99·5
− 850	0 + 800	445	83·5
− 500	650 + 500	345	98·5
− 450	700 + 500	520	85·5
+ 400	1550 + 500	470	111
+ 870	1720 + 800	475	112
+ 950	1800 + 800	615	134
+ 1100	1900 + 850	740	140
+ 1150	2050 + 750	621	148
+ 1230	2130 + 750	538	139
+ 1450	2600 + 500	700	144
+ 1550	2400 + 800	780	175
(+ 1680	2530 + 800	490	107·5)
+ 1700	2850 + 500	657	134
+ 1850	2700 + 800	982	175
+ 2000	2900 + 750	494	173
+ 2050	2850 + 850	723	193
+ 2050	2900 + 800	727	185

point the normal resting position of the chest: that in which no inspiratory or expiratory muscles are active and the elastic forces of the chest wall and lungs balance each other. Volumes of the lungs below this position of physiological equilibrium are designated as negative in column 1 of the table and on the abscissa of the curve. All the volumes given in this and the following tables are measured moist at room temperature. In the figure the rectangle at a positive inflation of 500 c.c. represents the older series of determinations made on J. L.(5). All the results obtained, with one exception put in parenthesis in the table and Fig. 2, can be represented by the curve drawn, which shows that at inflations at or below the equilibrium the dead space has a constant volume, whereas it is very regularly increased with inflations above the equilibrium. Our results confirm and amplify those of Siebeck(3) and we have no doubt that they are due, as Henderson and his colleagues suggest, to a passive stretching of the air passages. There is the difference, however, that while these authors find the dead space varying between 33 and 1200 c.c. we find a maximum increase of just 100 c.c. in the case examined.

A corresponding series of determinations have been made on the female subject M. K. with almost identical results. Up to the equilibrium position of the lungs the dead space is practically constant and

TABLE 2. Normal determinations of dead space on M. K.

Inflation of lungs c.c.	Inspiration from residual position c.c.	Expiration c.c.	Dead space c.c.
− 750	0 + 500 H_2	310	98·5
− 750	0 + 500	354	98
− 750*	0 + 500	483	114
− 750	0 + 500	493	89
− 750	0 + 500	573	88
− 250	520 + 500	500	96·5
− 250	520 + 500	588	110·5
0	750 + 500	668	108·5
+ 250	1000 + 500	488	113
+ 450	1200 + 500	310	102
+ 450	1200 + 500	460	121
+ 550	1310 + 500	570	121
+ 700	1450 + 500	713	131
+ 1350	2100 + 500	520	147
+ 1600	2350 + 500	587	140
+ 1650	2400 + 500	735	173
+ 1850	2760 + ca. 350	464	171

* Previous expiration perhaps not quite down to the residual air.

with greater inflation it is regularly increased. The increases corresponding to identical inflations are slightly smaller than in J. L.

In the two series of experiments so far mentioned we have varied the inspiration of hydrogen between 500 and 800 c.c. with no detectable influence upon the results. We have further varied the volume of the expiration between 300 and 1000 c.c. also without any visible influence. In order to make this clear we have noted the expiration volumes on the curves and an inspection of the figures will bear out our statement. Now it seems clear that if our results did not correspond to an anatomical reality—the volume of the air passages—it would be impossible to obtain such constant results with such widely varying conditions. If the real dead space at an inflation of say + 2000 c.c. was 800 c.c. instead of 180, an expiration of 1000 c.c. ought to give a much higher value than

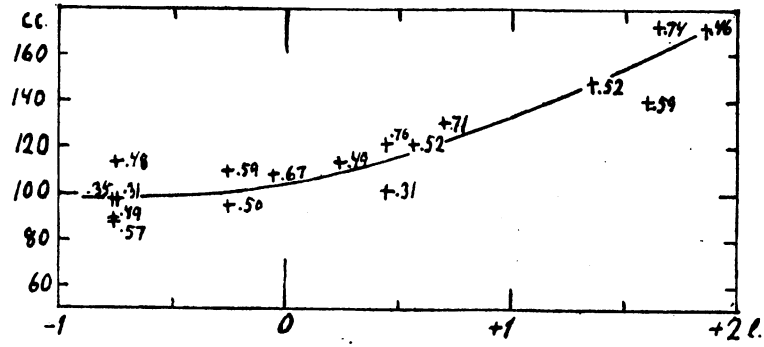

Fig. 3. Dead space of M. K. at varying inflation of lungs. Normal experiments.

one of 500 c.c. In order to make this point clear we have made further series of tests in which we have reduced (1) the volume of the hydrogen inspiration and (2) the volume of the expiration, and finally we have made some tests with a pause of 2–3 seconds after the hydrogen inspiration.

A reduction of the hydrogen inspiration so as to make it insufficient to wash out the dead space should of course reduce the volume found and there should be a distinct relation between the size of the inspiration and the result. The same holds good also for a reduction of the expiration, because the sample of alveolar air will contain an admixture of gas from the dead space—that is too much hydrogen.

The introduction of a pause must reduce the value found for the dead space, because hydrogen will diffuse during the pause from the bronchioles to the alveoli. During a short pause (a couple of seconds)

the diffusion can have influence only over short distances in the bronchial tree (probably not beyond the bronchioles of the last order) and the

TABLE 3. Determinations of dead space on J. L. with diminished H_2 inspiration.

Inflation of lungs c.c.	Inspiration from residual position c.c.	Expiration c.c.	Dead space c.c.
+ 150	Equilibr. + *150* H_2	395	95
+ 150	„ + *150*	700	108
+ 1270	2770 + *150*	757	133
+ 1670	3170 + *150*	665	139·5
+ 1800	3250 + *200*	465	166
+ 1800	3250 + *200*	695	151

TABLE 4. Determinations of dead space on J. L. with reduced expiration.

+ 500	Equilibr. + 500	*147*	96
+ 500	„ + 500	*162*	105
+ 500	„ + 500	*273*	109
+ 1650	2550 + 750	*168*	83
+ 1900	2800 + 750	*210*	150
+ 2150	3000 + 800	*284*	189

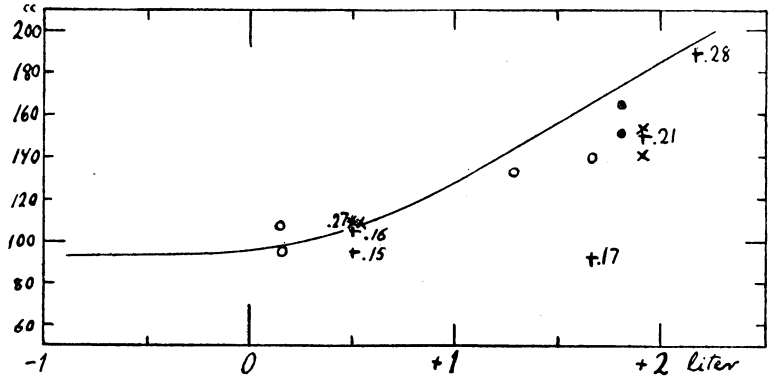

Fig. 4. Dead space determinations on J. L. with small inspirations and expirations of hydrogen. o Inspiration of 150 c.c. • Inspiration of 200 c.c. + Normal inspiration, small expiration. × A pause between inspiration and expiration.

TABLE 5. Determinations of dead space on J. L. with a pause after the inspiration.

Inflation of lungs c.c.	Inspiration from residual position c.c.	Expiration c.c.	Pause sec.	Dead space c.c.
+ 500	Equilibr. + 500	572	*3·8*	110
+ 500	„ + 500	610	*3·5*	109
+ 1910	3060 + 500	538	*2·5*	154
+ 1910	3060 + 500	703	*2·5*	141

reduction of the dead space found may therefore give some indication of the part played by the bronchioles in making up the total dead space.

The results have been summarised in Tables 3–5 and Fig. 4 in

which the curve obtained in the normal experiments on J. L. has been drawn for comparison purposes. Inspirations down to 150 c.c. hydrogen do not diminish the results at pulmonary inflations up to the equilibrium position. With greater inflation and the correspondingly larger dead space a slight diminishing influence upon the result is noticeable, when inspirations of 150 or 200 c.c. hydrogen are taken instead of the normal 500 to 800 c.c. The same holds also for small expirations, though the influence of the volume expired is more marked and it is distinctly seen that the smaller the expiration the smaller is the resulting dead space. It follows we think from these results that the inspirations and expirations normally employed by us cannot have been too small, and it appears further that a hydrogen inspiration of one and a half times the true volume of the dead space is sufficient to wash it out practically completely. This could not be done with gases of approximately the same specific gravity as the air, as we have noticed repeatedly and as Henderson and his collaborators have shown in their experiments on the axial flow of columns of smoke in glass tubes, but we are not surprised to learn that hydrogen introduced from above in an essentially vertical tube will move up and down nearly as a piston on account of its very small specific gravity as compared with the normal content of the air passages. Siebeck found in his experiments with hydrogen inspirations that he got pure alveolar air after the expiration of 300 c.c. with a total dead space of 160 c.c.

A pause of 2–4 seconds has apparently no influence on the dead space determination at or near the equilibrium position of the lungs but with greater inflation (+ 1900 c.c.) the results are diminished by something like 30 c.c. This means according to the above that when the chest is not inflated the bronchioles form only an insignificant part of the total dead space, but that a large part of the dilation of the air passages, taking place when the chest becomes inflated, affects the smallest bronchioles.

In order to meet Haldane's objection, that it "seems wrong in principle" to determine the dead space by means of other gases than oxygen and carbon dioxide, we have made a number of determinations by means of these two gases using exactly the same arrangement as with hydrogen but filling the bell-jar either with atmospheric air or with pure oxygen. The calculations for CO_2 and O_2 were made according to the formulas:

$$D = E - E\frac{C_e}{C_a} - d, \qquad D = E - E\frac{O_i - O_e}{O_i - O_a} - d.$$

The samples have always been analysed for both gases and we give as an example of the calculation.

Vol. of inspiration 1·43 + 0·75 l.
Vol. of expiration 487 c.c.
Percentages: $O_i = 20{\cdot}9$, $C_i = 0$, $O_{sp} = 18{\cdot}95$, $C_{sp} = 1{\cdot}92$, $O_a = 16{\cdot}01$, $C_a = 4{\cdot}33$.

	Vol. c.c.	O_2 c.c.	CO_2 c.c.
In spirometer after expiration	770	146·0	14·8
In spirometer before expiration	283	59·2	0·3
In expiration	487	86·8	14·5
„ „ %		$O_e = 17{\cdot}82$	$C_e = 2{\cdot}98$

Hence $D_o = 487 - 487\dfrac{20{\cdot}9 - 17{\cdot}82}{20{\cdot}9 - 16{\cdot}61} - 10 = 125$, $D_c = 487 - 487\dfrac{2{\cdot}98}{4{\cdot}33} - 10 = 141$.

If our view is correct that the dead space is an anatomical as well as a physiological reality it must be possible to measure it at least approximately by any gas, though it is obvious that gases which diffuse more slowly are less adapted for the purpose than hydrogen, and the systematic difference found by Haldane and also by Henderson between the dead spaces for O_2 and CO_2 should disappear when the real dead space is measured.

TABLE 6. Determinations of dead space on J. L. Atmospheric air.

Inflation of lungs c.c.	Inspiration from residual position c.c.	Expiration c.c.	Dead space c.c.
− 1150	0 + 500 atm. air	325	77 CO_2 95 O_2
+ 530	1430 + 750	487	141 CO_2 125 O_2
+ 980	2130 + 500	712	202 CO_2 204 O_2
+ 1820	2970 + 500	576	159 CO_2 150 O_2
+ 1870	3020 + 500	578	160 CO_2 150 O_2

TABLE 7. Determinations of dead space on J. L. Oxygen.

− 1150	0 + 500 O_2	400	63 CO_2 96 O_2
+ 250	1400 + 500	550	122 CO_2 128 O_2
+ 400	1550 + 500	835	168 CO_2 161 O_2
+ 1950	3100 + 500	435	189 CO_2 174 O_2
+ 1950	3100 + 500	741	202 CO_2 202 O_2

Our results, which are summarised in Tables 6 and 7 and compared with the normal curve in Fig. 5, conform very well to these *a priori* conclusions. The deviations of the single results from the curve are distinctly larger than with hydrogen, but except in the middle (inflations from 0–1000 c.c.) where they lie on an average about 30 c.c. above the curve, they do not give higher results and the oxygen determinations certainly do not give larger values than those calculated for the CO_2.

The experiments so far detailed show, conclusively as far as we can see, that whatever gas is used for the experiments and whatever quantity inspired or expired between the limits indicated, the same values for the dead space will be obtained at identical inflations of the lungs, and though it cannot be proved that the increases measured with increasing

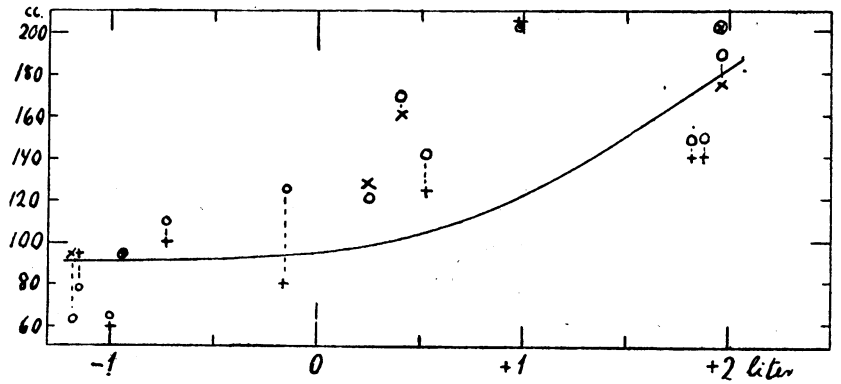

Fig. 5. Dead space determinations on J. L. by means of O_2 and CO_2.

× O_2 } o CO_2 } Inspiration of pure oxygen. + O_2 } o CO_2 } Inspiration of atmospheric air.

inflations are due to passive distension of the bronchioles (and bronchia) it is certainly a very probable assumption.

We have finally made two series of determinations with a constant inflation of the lungs (+ 1850 c.c.), a very large inspiration from the residual air and expirations varying from 800 up to 3300 c.c. These experiments are in a sense crucial, because their results can be predicted both from the standpoint of Haldane and from our own. From Haldane's standpoint all the preceding experiments with large inflations could possibly be doubted on the ground that both the inspirations and the expirations were too shallow to wash out the dead space, but when the inspiration is deep and the expiration is sufficient to bring up a sample of "undiluted alveolar air" from the air-sacs (1·5 l. should

be enough according to Haldane) the results ought to become constant and independent of any further increase in the depth of the expiration because, according to Haldane, the air in the air-sacs is uniform.

From our own standpoint we must maintain that the inspired gas will not become completely mixed with the alveolar air either in the air-sacs or in the atria and that, therefore, the figures found for the dead space will increase regularly with the volume of air expired when this is raised above 1 litre. The results bear out our contention and there is moreover a curious systematic difference between the results obtained with different concentrations of the same gas—oxygen. In one series the subject expired to the residual air and then took in 3·5 l. atmospheric air. The results are given in Table 8 and show a dead space increasing fairly regularly with increasing depth of the expiration up to values which are not very different from those obtained by Haldane and some of Henderson's. As in their experiments the dead spaces for oxygen are larger than for carbon dioxide.

TABLE 8. Experiments on "dead space" of J. L. Inflation of lungs + 1850 c.c. Inspiration 3500 c.c. atmospheric air in all the experiments.

Expiration c.c. ...	1900	2150	2340	2820	3140	3210
"Dead space" for CO_2	342	439	313	520	512	615
" " O_2	403	485	379	547	564	748

In another series the subject took a corresponding inspiration of approximately pure oxygen. The results given in Table 9 show the same general trend as in the former series, but here the oxygen results are decidedly lower than those for CO_2 which are, as would be expected, practically the same in both series.

TABLE 9. Inspiration of 3500 c.c. oxygen in all the experiments.

Expiration c.c.	810	1490	1820	1980	2360	2730	3070	3310
"Dead space" for CO_2	267	278	411	452	340	480	502	672
" " O_2	162	125	181	232	301	144	369	370

These experiments demonstrate that the large dead spaces found by Haldane and Henderson are not due, as they thought, simply to the inflation of the lungs and the air passages but are brought about chiefly by the deep expirations employed by them. They are consequently unreal and due mainly to the incomplete mixture of the gases in the atria and air-sacs of the lungs[1]; in part also they are due to

[1] Haldane(8) has made experiments to show that the air in the air-sacs is of uniform composition throughout by comparing samples taken by means of expirations of varying depths. The differences existing during ordinary quiet breathing are, however, too small to be detected in this way except by averaging very large numbers of determinations.

the gas exchange taking place during the expiration. It can easily be explained why the incomplete mixture *must* make the results for oxygen higher than for carbon dioxide when atmospheric air is breathed and inversely with pure oxygen, but as the explanation is superfluous for the carrying on of our argument we leave it out.

We have now brought together the data by which it is possible to account for the sequence of events in the air passages, atria and air-sacs during the respiratory movements. At the end of expiration air of fairly uniform composition is found throughout the whole system, though there is in the air passages slightly more oxygen and slightly less CO_2 than in the alveoli. During inspiration atmospheric air will begin to enter the atria from the bronchioles after inspiration of about one-third the volume of the anatomical dead space, and after the inspiration of three times the volume of the dead space the air passages are completely washed out with pure air. In the atria and air-sacs as well as through the openings between atria and air-sacs the atmospheric air inspired is mixed with the alveolar air partly by gas diffusion (independent movements of single molecules) and partly by mass movements (currents and eddies) set up by the dilatation of the lungs and by the jet of air entering each atrium from its bronchiole[1]. The part played by diffusion and mass movement respectively cannot at present be made out, but it seems logical to assume that with a rapid inspiration the mass movements can be considerably augmented and the mixing of the air therefore become more complete. Reasons will be given below indicating that such is indeed the case. So long as pure atmospheric air is entering (that is, throughout the inspiration) the mixture in the alveoli can never become absolutely complete, but the atria will contain more oxygen and less carbon dioxide than the air-sacs and in each compartment the O_2 percentage is highest (the CO_2 lowest) near the opening through which the air is entering. That the atrium air as a whole cannot be of very different composition from the air-sac air follows from the fact that the opening between atria and air-sacs are rather large and the walls in which those openings are found extremely thin. The rate of diffusion through them must therefore be very rapid. That the composition of the air in the lungs at the end of inspiration does not show a distinct difference between atrium air and air-sac air has been demonstrated experimentally above by the regular increase

[1] We are well aware that the limit between the air passages and the respiratory portions of the lungs is not absolute, since a few small alveoli are found also on the last branches of the bronchioles.

in "dead space" observed with a regularly increasing volume of the expiration.

In point of fact the difference between Haldane's view and our own concerns the difference in composition between the air in the atria and in the air-sacs at the end of inspiration. Haldane believes that this difference is considerable while the air in the air-sacs is uniform throughout.

In point of theory there is the further difference that Haldane takes the air from the air-sacs alone as alveolar air, while we will include the air from the atria as well. The term alveolar air has reference to the blood gases. The alveolar air is the air with which the blood coming from the right heart enters into gas exchange, and the physiological significance of the CO_2 and O_2 pressures of the alveolar air lies in the two facts that the blood leaving the lungs is in practical CO_2 tension equilibrium with the alveolar air, as shown experimentally by A. and M. Krogh, while the O_2 pressure of the alveolar air constitutes the limit to which the arterial blood can attain by diffusion. Now it is distinctly stated by Miller(10, p. 177) that each atrium, as well as each air-sac, possesses its own pulmonary arteriole, and that the blood from each atrium, as well as from each air-sac, is in the main collected by a single small vein. The blood does *not* flow from the walls of the atria into the walls of the air-sacs. The blood going to the left heart is therefore a mixture of blood coming from atria with that from air-sacs, and the air in the atria with which part of the blood has exchanged gases is alveolar air just as well as the air in the air-sacs. In our opinion it follows necessarily from these facts and considerations that the best approximation to the true average composition of the alveolar air must be obtained by calculation from the composition of the expired air, the volume of the expiration and the dead space in the air passages.

We wish to point out, however, one important restriction to this general rule, viz. that with a shallow and frequent respiration the influence of the volume of the dead space as used in the calculation becomes very large, and that in view of the unavoidable errors on the determination of this volume it may be safer to determine the alveolar air by direct sampling, the more so as in these circumstances the alveolar air must be of a practically uniform composition throughout and also from moment to moment. When good determinations of the dead space are available we should prefer calculation of the alveolar air at all depths of respiration beyond about five times the volume of the dead space, expect the two methods to give about equal and equally reliable results at depths from about 5 to 2–3 times the volume of the dead space, and use direct sampling according to Haldane and Priestley at lower depths. That the two methods do agree at medium depths has been shown repeatedly and follows also from the dead space found by Haldane at such depths being of nearly the same size as our own.

It should always be kept in mind, however, that any determination of the average composition of the alveolar air, however made, can be only an approximation to that which it is desired to know, and this approximation may sometimes be very imperfect. In order to make this clear let us suppose the CO_2 to diffuse so rapidly through the alveolar wall that each particle of blood is in absolute CO_2 tension equilibrium with the alveolar air at the moment of leaving the alveolar wall. Now, if the alveolar air is supposed to have a constant CO_2 tension from moment to moment as well as from point to point the current of blood may obviously vary in intensity and the distribution of the blood between the alveoli may be very unequal without the equilibrium between the CO_2 tension of the total blood and of the alveolar air becoming affected. If, however, the CO_2 tension of the alveolar air varies with time the blood current must remain constant if the equilibrium shall remain perfect. Suppose the blood current to have a much increased velocity just when the alveolar CO_2 tension is at its lowest: the total blood will get a CO_2 tension below the average alveolar air. If, further, different alveoli do not possess the same CO_2 tension the distribution of blood between them must be even to secure perfect equilibrium between the total blood and the average air. Suppose the atria with the lowest CO_2 tension to get more blood in proportion to their volume than the air-sacs, the CO_2 tension of the total blood will again be lower than of the average alveolar air. Now, the current of blood through the lungs is known to vary with the respiratory movements, and the more the deeper they are, while the other factors are totally unknown, and it follows that with increasing depth of the respiration it becomes more and more unsafe to assume that the CO_2 tension of the mixed arterial blood is the same as that of the average alveolar air, even when this be determined with absolute accuracy. The relations are further complicated by the two facts, that a mixture of, say, equal parts of blood with different CO_2 tensions will not generally possess just the average tension, and that the distribution of blood between different alveoli may probably be the same per unit surface, but is not likely to be proportional to the gas volumes.

Haldane's chief reasons for assuming, in spite of the anatomical structure of the atria and the nature of their blood supply, that true alveolar air can be obtained only from the air-sacs are (*a*) the general constancy of the alveolar air, as thus defined, in varying conditions of pressure, etc., and (*b*) especially the observation, recently made by him(8), that when he varies his own respiration frequency without

taking any notice of the depth, which is supposed to be regulated automatically by the CO_2 tension of the arterial blood, he finds at all frequencies between 3 and 36 per minute the same constant composition of the average alveolar (air-sac) air, as determined according to his method.

(*a*) As we have found repeatedly and pointed out above, sampling according to Haldane during rest and with natural respiration gives practically the same results as calculation from the anatomical dead space. The constancy of the alveolar air, as determined by Haldane, is therefore no proof either for or against excluding the atria, since the calculated alveolar air would be equally constant.

(*b*) It must be admitted that the constancy of the CO_2 percentage in the air-sac air, observed by Haldane with widely varying frequencies, *appears* to be a strong argument in favour of the view, that it is the air-sac air which determines the CO_2 tension of the arterial blood, while the arterial blood regulates the ventilation. If in this case the alveolar CO_2 percentage had been calculated on the basis of a constant (or nearly constant) dead space it would have been found far from constant. We must point out, however, that in Haldane's experiments the breathing with each regulated frequency was maintained for a period (2 minutes before and 3 minutes during the sampling) which was much too short to adapt the composition of the pulmonary air to the changed conditions. This is clearly shown by the experiments themselves. The production of CO_2 or consumption of O_2 in the body should not, certainly, become affected by the frequency of breathing, but if the gas exchange per minute is calculated from the figures given in Haldane's table and reproduced below, very variable results are obtained with the artificial frequencies, while the natural ones give quite consistent values, showing that with the frequencies 6 and 24

TABLE 10. From Haldane, with the respiratory exchange calculated by us.

Frequency of resp. per min.	Depth of expir. 37°, saturated	Expired air CO_2 percentage	R. Q.	Effective "dead space." Calculated from CO_2	Effective "dead space." Calculated from O_2	Gas exchange per min. 0°, 760 mm., dry CO_2	Gas exchange per min. 0°, 760 mm., dry O_2
3	2984	4·29	0·848	683	920	312	367
4	2438	4·56	·875	467*	619	361	411
6	1413	4·24	·905	272	392	294	325
18·5	683	3·31	·871	224	—	336	386
17·0	650	3·59	·887	171	223	321	362
17·7	643	3·58	·888	161	231	329	371
24	410	3·22	·780	111	136	254	327
60	357	1·89	·820	185	199	323	394

* By recalculation we find 407.

CO_2 has been held back in the body and lungs, while with 4 it has been washed out. When this is so the CO_2 tension in the arterial blood cannot have been constant, whatever may have been the case with the CO_2 percentage in the alveoli.

Large numbers of experiments with artificially varied frequencies of 6, 15 and 30 per minute have been made by Liljestrand and Wollin(11). In these experiments the CO_2 output was *found* to be practically independent of the frequency and remarkably constant. From the data given by the authors it is easy to calculate the CO_2 percentage of the expired air and the depth of the respiration, and when the alveolar CO_2 percentage is known the dead space can be figured out. If the calculation is made on the basis of a constant alveolar CO_2 percentage it is possible to check Haldane's result and to see whether the dead space increases considerably with increasing depth of the respiration or not. We give as an example the results obtained by us for the dead space of G. L. whose alveolar CO_2 percentage is known to be very nearly 6 %(12).

TABLE 11. "Dead space" of G. L. with varying frequency and assumed constancy of alveolar $CO_2 = 6$ %.

	Frequency of resp. per min.	Depth of expir. 37°, saturated	Expired air CO_2 percentage	Effective "dead space." Calculated from CO_2	Gas exchange CO_2 per min. 0°, 760 mm.
Lying on back	6	976	4·87	183	233
„	15	537	3·42	230	228
„	30	378	2·39	227	221
Sitting	6	1025	4·55	247	230
„	15	561	3·32	251	231
„	30	427	2·23	268	234

It is seen at a glance that the dead space comes out practically constant[1] or, if anything, very slightly increasing with *decreasing* depth of the respiration. Similar results have been obtained by computing the dead space of G. W. from several series of experiments on this subject, but in his case an arbitrary constant level for the alveolar CO_2 percentage had to be assumed. Trying different levels within the possible limits 5 to 6·5 % no increase in dead space with increasing depth of the breathing could be made out.

[1] In this case the calculated dead space includes the mouthpiece and tubing between it and the respiration valves. The absolute figures for the dead space are of course not very reliable, since we have no guarantee that the alveolar CO_2 percentage was just 6, nor that it did remain constant with the varying frequency.

The dead space and the alveolar air during muscular work. Agreement has been reached that muscular work does not produce any increase in the dead space, except in so far as the air passages are stretched mechanically by the deep inspirations. During muscular work of increasing severity the inspiratory (and expiratory) movements become more and more rapid, and it is possible, nay probable, that a rapid current of air entering the atria from the bronchioles may improve the mechanical mixing of the alveolar gases. The time available for diffusion is shortened, however, and it is not possible to tell beforehand, whether the final result will be a more uniform composition of the alveolar air at the end of inspiration or not. A comparison between the dead space determinations of Haldane and Douglas(4) and the recent ones of Haldane(8) will furnish valuable information on this point. The respective tables show that at great depths of respiration the results are in practical agreement (Rest, depth of respiration 2·98 l., dead space 683 c.c.; Work, 2·81 l., 609 c.c.—Rest, 2·44 l., 407 c.c.; Work, 2·52 l., 549 c.c.). Now, nobody has attempted to dispute the validity of our criticism that during muscular work the samples of alveolar air are taken too late and for that reason show percentages of CO_2 which are a great deal too high. As mentioned above we have in one case with a depth of respiration of 3·25 l. found this error to be sufficient to raise the dead space as calculated from 100 to 500 c.c.(6). Since, therefore, this error is nearly sufficient to explain quantitatively the high results obtained by Douglas and Haldane, it follows that the error which we have pointed out as present in Haldane's dead space determinations during rest cannot have had any serious influence in the work experiments, that is: The alveolar air must have been much more uniform at the end of inspiration during the work hyperpnœa with rapid breathing, than during the very slow deep respirations employed by Haldane in his recent experiments.

The possibility of unequal ventilation of different lobes of the lungs. According to our interpretation the combined result of Haldane's and our own experiments is, that the mixture of gases present in the alveoli at the end of inspiration is not complete, but the composition varies with the distance from the bronchioles. With ordinary respirations the differences are certainly not large, but they become considerable with deep and slow breathing. When the breathing is deep and rapid, as in muscular work, the differences are again, apparently, comparatively small.

So far we have tacitly assumed—as all other physiologists have done

—that alveoli from different bronchi contain the same gas mixture, that is that different lobes of the lungs are ventilated to the same extent. That this is so has never been proved—so far as we are aware—and it is in our opinion worth while to investigate the assumption a little more closely. If the different lobes of the lungs are not equally dilated during inspiration the air in them must obtain a different composition and this must be true both with regard to O_2 and CO_2 during normal breathing[1] and with regard to other gases during special mixing respirations. During expiration the air from the different lobes becomes mixed. If the expiration is of the same depth as the inspiration just that quantity of air which had entered each lobe must leave it again, and the composition of the expired air must become just the same as if all lobes had been equally dilated. If, on the other hand, the expiration differs in depth from the inspiration the relation between the volumes of the different lobes may become altered and in that case, but only in that case, the composition of different portions of the expired air may become different. It is logically conceivable that differences of this kind might effect samples of alveolar air obtained after deep expirations and give rise to errors and it will be useful to construct an example of this in order to see to what magnitude the differences may possibly attain.

We assume that the apical parts of the lungs contain 1 l. air and the basal 2 l. We assume further that a series of inspirations (and expirations) of 1·4 l. each be made from a spirometer containing 20 % H_2 and that these inspirations are distributed with 0·4 l. to the apical and 1·0 l. to the basal lobes. A calculation shows that after one inspiration the percentages of H_2 will be: apical 5·7 %, basal 6·67 %, after two, 7·2 % and 8·9 % respectively and after three respirations, 8·3 % and 9·6 % respectively. An expiration of 1·4 l. after the third inspiration will contain 0·4 l. air with 8·3 % H_2 and 1 l. with 9·6 % H_2, that is in the mixed air 9·23 % H_2. If now an expiration be made to the residual air, and if we assume that during this the ratio of ventilations is reversed, the apical parts of 1 l. capacity expiring 0·6 l. air and the basal of 2 l. capacity expiring 1 l. air, the percentage of H_2 in the expired volume of 1·6 l. air will be 9·10 or only 0·13 % lower than in the first portion.

This calculation shows the improbability of differences of this kind causing any serious errors on samples of alveolar air and makes it clear, that if such differences are to be detected at all, they can be sought for only in cases in which the air in the single alveolus is practically

[1] Unless, indeed, the circulation through each lobe should be in proportion to its ventilation.

completely mixed. Otherwise they must become obscured. We possess two series of experiments in which this condition is fulfilled.

(*a*) When five years ago we worked out our method of determining the circulation rate(14) we made a series of experiments with hydrogen. This gas diffuses so rapidly that it can be safely assumed to be practically evenly distributed inside each alveolus at the end of the introductory period. On the other hand differences in H_2 percentage between different lobes of the lungs cannot be affected by diffusion during the few seconds of a circulation rate experiment, and when therefore the hydrogen percentage is found to be the same (with the necessary corrections for H_2 absorption by the blood and contraction of the enclosed air, as pointed out in our paper) before and after the respiration pause constituting the circulation experiment, this shows the expired air to be of the same composition throughout. We have found:

TABLE 12. Circulation experiments with hydrogen.

Subject and method	Sample I % H_2	Sample II % H_2	Sample I corr.	Difference %
J. L. Equil.	11·36	11·49	11·71	0·22
„ „	13·07	13·05	13·40	0·35
			Sample II corr.	
„ Resid.	13·03	12·94	12·65	0·38
„ „	12·71	12·79	12·59	0·12
A. K. „	15·57	15·49	15·30	0·27
			Average	0·27

There is in all cases very nearly the same hydrogen percentage in the second sample as in the first. When the correction for contraction of the air in the lungs is introduced we find small positive differences (column 5). When these are utilised for circulation rate determinations we find values which are certainly on the whole too high (minute volumes of 3 to 20 l.), but if the average difference is diminished by 0·09 % the rest corresponds to a normal circulation rate. A difference of 0·09 % may therefore *possibly* be due either to incomplete mixture of H_2 within each alveolus or to differences between the lobes of the kind considered, but part of it must be caused by diffusion of hydrogen into the pulmonary tissues and probably about one-third of it (0·03 %) can be accounted for by an error detected in the calculated contraction.

(*b*) If ventilation differences between the lobes existed they must —as pointed out—lead to a different composition of the air in different lobes during ordinary breathing, and such differences might influence the composition of samples taken at the end of deep expirations—

Haldane samples of alveolar air. Nothing of the kind has ever been noticed, but to make sure we have in a series of experiments compared Haldane samples taken in the ordinary way with the total alveolar expired air as calculated from the total expired air collected in a recording spirometer and the dead spaces of tubings and air passages. The unavoidable uncertainties in such calculations, arising out of the various dead spaces, which are not known with absolute certainty, and out of the gas analytical errors make the oxygen results unreliable beyond 0·1 % and with comparatively small expirations the influence may become even greater. To the calculated composition of the alveolar air a correction must further be applied corresponding to the gas exchange during half of the expiration time. The expiration time has in our experiments been about 0·024 minute, and as the average volume of air in the lungs during the expiration has been about 2 l. we have assumed a correction of 0·15 % for the CO_2 and 0·2 % for the oxygen, corresponding to a gas exchange of about 250 c.c. CO_2 and 330 c.c. O_2 per minute. We have obtained the results given in Table 13.

TABLE 13. The composition of the alveolar air during approximately normal breathing.

		CO_2 %			O_2 %		
Subject	No.	calculated	corr. for gas exch.	found	calculated	corr. for gas exch.	found
A. K.	1	4·58	4·73	4·77	15·9	15·7	15·69
	2	5·03	5·18	5·15	14·9	14·7	14·75
	3	5·15	5·30	5·30	14·05	13·85	14·19
	4	4·77	4·92	4·90	15·65	15·45	15·48
	5	4·49	4·64	4·64	15·7	15·5	15·50
	6	4·80	4·95	4·89	15·35	15·15	15·19
	Average		4·95	4·94		15·06	15·13
J. L.	7	4·95	5·10	5·16	15·0	14·8	14·77
	8	5·40	5·55	5·38	13·65	13·45	13·80
	9	5·10	5·25	5·19	14·75	14·55	14·60
	10	4·97	5·12	5·11	14·5	14·3	14·23
	11	5·05	5·20	5·31	14·5	14·3	14·00
	12	4·40	4·55	4·70	15·25	15·05	15·00
	Average		5·13	5·14		14·41	14·40

In two out of the 12 experiments (Nos. 3 and 8) the differences are a little larger than desirable though not outside the limits of error. In the rest the agreement is as good as might be desired, and it must be legitimate to conclude that in *normal lungs* such differences between the ventilation of different lobes as might influence the composition of

different portions of the expired air do not exist. Stress should be laïd on the point, however, that this result is probably valid for normal lungs only. It is quite possible that it may be otherwise in cases of bronchial catarrh and bronchial spasms or in lungs which are more or less adherent, cavernous, emphysematous or œdematous.

Deductions from the results.

1. We must maintain our former result, that the composition of the alveolar air should preferably be determined by calculation from the expired air except in cases where the respiration is very shallow. With deep breathing the increase in dead space resulting from the inflation of the lungs ought to be taken into account, but the error arising from not doing so is usually extremely slight. With deep breathing during rest and during the hyperpnœa caused by muscular work the direct sampling of the alveolar air will lead to very fallacious results showing the alveolar air to be considerably richer in CO_2 and poorer in O_2 than it actually is. This apparently trivial difference is one of the chief sources of the differences of opinion still existing regarding the mechanism of the gas exchange between the blood and the air in the lungs. If Haldane were right it might be impossible to explain some of the results obtained in mountain experiments on the basis of gas diffusion through the pulmonary epithelium and a secretion hypothesis might have to be adopted. If we are right regarding the volume of the physiological dead space all the experiments from which reliable data are available can be explained by simple diffusion of oxygen.

2. In our investigation of the alveolar air by means of several consecutive samples from the same expiration (13) we have *not* taken the incomplete mixture into account. This must have caused systematic errors, but in most of the experiments there is no reason to think that they have been anything but very small, as the alveolar mixture must have been so nearly complete that the differences for CO_2 and O_2 have been in the second decimal place of the percentages. The errors are in the direction of making the gas exchange, both of CO_2 and O_2, measured during expirations larger than it has really been and smaller during inspiration. A correction would on the whole accentuate the variations in gas exchange measured. In one experiment (13, p. 276, Table X, fig. 5) a deep and rather slow inspiration was taken just before the expiration examined. In this case the error is probably rather

considerable, and the large increase in gas exchange found during the first part of the expiration is perhaps unreal and at all events exaggerated.

3. We have found it necessary to make a rather extended investigation to see whether the incomplete mixture might influence the circulation rate determinations, as worked out by us (14, 15)[1]. We must remind the reader that we have described two forms of technique. In the "residual method" one very deep inspiration of an N_2O mixture is taken after an expiration to the residual air and the breath held for some seconds before the expiration to obtain the initial sample of alveolar air. In the "equilibrium method" the air in the lungs is mixed with the air in the N_2O spirometer by three fairly deep (1–2 l.) and fairly rapid respirations immediately preceding the expiration from which the initial sample is obtained. It is evident from the foregoing that when the residual method is employed the alveolar gases will have ample time to become completely mixed by diffusion, but in the equilibrium method it is conceivable that the mixture may still be incomplete at the end of the third expiration. When that is the case the initial sample will contain a percentage of N_2O which will be higher than that of the total alveolar air and the results for the minute volume will become too high[2]. Our recent tests have included (*a*) series of comparisons between the total alveolar air expired after a normal period of mixing, and (*b*) series of circulation rate determinations in which we have varied the number of mixing respirations in the introductory period.

(*a*) The subject made the mixing respirations into a recording spirometer through a three-way tap. At the end of the introductory period the tap was turned and a deep expiration made into a second

[1] The outward occasion for this investigation was the report by an author who had endeavoured to modify the circulation rate method for clinical purposes (Sonne, *Pfl. Arch.* **163**, 1915, *Hosp. tid.* No. 43, 1915, and No. 9, 1916) that he had found the gas mixture in the lungs to be extremely incomplete both during natural breathing and after the mixing respirations incidental to circulation rate determinations. We do not propose to discuss Sonne's results which we consider as the outcome of lack of familiarity with the technique and theory of the problems involved. They are absolutely at variance with our own and with those of other respiration physiologists.

[2] We must be allowed to point out that we did investigate the possibility of incomplete mixture in our original paper, but with negative results, and that we found that determinations according to the two methods gave the same results. Later the circulation rate determinations have been checked by Fridericia(16) and by Boothby and Sandiford(17) who calculated the circulation rate from the saturation of the venous and arterial blood with oxygen and found figures which agreed well with those determined on the same subjects according to our method.

recording spirometer. At the end of this expiration an alveolar sample was taken and the gases in the expiration spirometer carefully mixed, sampled and analysed. From the analysis, the volume of the expiration, the initial volume of air in the expiration spirometer and the dead spaces in the air passages[1], the tap and the tubing the composition of the alveolar expired air was calculated. As mentioned above there is a correction to be applied for the gas exchange during the expiration, amounting to about 0·15 % CO_2 and 0·2 % O_2[2]. The corresponding correction for N_2O cannot be accurately determined but is on the whole rather larger than that for O_2.

We have made a series of experiments with O_2 mixtures and obtained the results given in Table 14. As a control on this series we have made the experiments 7–10 with a gas mixture containing very nearly the alveolar O_2 percentage. In this case it is obviously indifferent if the mixing in the alveoli is more or less complete, since the O_2 percentage is nearly the same everywhere beforehand, and the differences observed between the calculated and observed O_2 percentages of the alveolar air are a measure of the influence of the gas exchange and of the probable

TABLE 14. Mixing of alveolar air with oxygen.

Subject and Method	No.	Composition of alveolar air CO_2 % calculated	CO_2 % found	O_2 % calculated	O_2 % found
A. K. 3 small resp.	1	4·65	4·76	22·4	21·62
J. L. residual	2	4·33	4·13	19·1	19·03
,, ,,	3	4·39	4·28	19·7	19·64
,, 3 resp.	4	4·23	4·56	21·7	21·63
,, ,,	5	3·68	4·15	20·0	19·63
,, ,,	6	3·87	4·01	24·9	24·53
,, ,,	7	4·30	4·52	14·5	14·25
A. K. residual	8	3·36	3·73	15·2	15·09
,, 3 resp.	9	3·83	4·00	14·95	14·80
J. L. residual	10	3·72	4·03	14·85	14·48

errors on the determination as a whole. The experiments show on the whole the same differences with low as with high O_2 percentages and

[1] At the beginning of the expiration the dead space of the air passages and the tap is filled with air from the inspiration spirometer. A sample of this was taken just after the three mixing respirations and analysed. The contents of this spirometer were mixed vigorously throughout each experiment.

[2] Just after the somewhat forced mixing respirations the circulation rate through the lungs is altered and probably inconstant. The correction for gas exchange during the expiration is therefore not nearly so constant or reliable as in Table 13 after normal breathing.

give no indication of anything but practically complete mixture. One single experiment (No. 1, A. K.) shows a difference which is distinctly outside the normal limits of accidental errors. We do not venture to affirm that some serious error cannot have been committed, but on the other hand we have just in this case used the smallest amount of mixing allowed by us on the basis of our first experiments: three rather slow respirations of 1 l.. It is just possible that we have to do in this case with incomplete mixture, but since such respiration is in practice never used for mixing purposes we have not investigated the matter further.

We have further made experiments with N_2O mixtures on three different subjects employing those N_2O quantities which are used also in regular circulation rate determinations. It is clear that in these cases the difficulties are greater, because the influence of N_2O absorption in the blood during the expiration cannot be accurately estimated and also because the analyses are less accurate. For this reason we have been exceptionally careful and in most cases made double analyses of all the samples. In four of the experiments the double analyses did not agree so well as we could wish, and we have been obliged to classify these analyses as not completely reliable. The error from this source may amount to $\pm$ 0·1 %. The results for the first two subjects are not so fine as we might desire owing no doubt to accidental errors, but the series on M. K., who mixed by means of three respirations of about 1·5 l. is extremely regular and shows for the CO_2 and O_2 differences

TABLE 15. Mixing of alveolar air with nitrous oxide.

Subject and Method		Composition of alveolar air CO_2 % calculated	CO_2 % found	O_2 % calculated	O_2 % found	N_2O % calculated	N_2O % found	Remarks
A. K.	3 resp.	4·48	4·28	14·2	14·21	10·25	11·37	Analyses less accurate
,,	residual	5·28	5·24	13·0	12·90	13·95	14·05	
,,	3 resp.	4·65	4·89	13·3	13·05	14·5	14·03	
	Averages	4·80	4·80	13·5	13·39	13·13	13·15	
J. L.	residual	5·89	5·70	12·1	12·20	11·85	11·80	Analyses less accurate
,,	3 resp.	4·00	4·19	13·6	13·39	13·6	13·33	
	Averages	4·95	4·95	12·85	12·80	12·72	12·56	
M. K.	3 resp.	3·82	3·97	14·22	14·06	14·00	13·55	
,,	,,	3·79	4·00	14·20	14·05	13·33	12·95	
,,	,,	4·24	4·39	13·64	13·44	12·51	12·15	
,,	,,	3·66	3·70	14·62	14·53	11·70	11·42	
	Averages	3·88	4·02	14·17	14·02	12·88	12·52	
M. K.	3 resp.	3·82	3·89	13·80	13·80	13·15	13·12	Pause before expiration
,,	,,	3·95	3·89	14·08	14·05	12·90	12·82	

which correspond to the gas exchange during the expiration. The difference for N_2O is on an average 0·36 % which is probably slightly (about 0·1 %) more than would correspond to the N_2O absorption during the expiration. The mixture is therefore, *probably*, not quite complete, but the error is too small to have any appreciable influence on a circulation rate determination. In the two last experiments of the series the subject made a pause of about one second before expiring into the spirometer. This seems to have practically obviated the difference, which confirms the view that part of the N_2O difference in the preceding experiment is really caused by incomplete mixing.

(*b*) If the gases in the lungs are incompletely mixed by three respirations we must expect that by using more mixing respirations of equal depth and rate in the introductory period we should obtain a lower figure for the minute volume or, what amounts to the same, a higher figure for the oxygen taken up per litre blood. If the mixing can be considerably improved we should expect the figure to rise rapidly at first and gradually approach a constant level.

On the subject M. K., on whom we found above some slight evidence of incomplete mixing with three respirations, we have made the experiments given in Table 16.

TABLE 16. Utilisation of oxygen, c.c. per litre blood.

	Number of mixing respirations			
Subject	3	4	5	6
M. K.	40	44	50·5	46
	48	40·5	41	59
	42	—	39	—
	54·5	—	43	—
	—	—	45	—
Averages	46	42	43·5	52·5

These show that the number of respirations in the introductory period is without influence at least up to five, but with six respirations the O_2 per litre perhaps rises a little. This is of course not due to any incomplete mixing with fewer respirations but, if it is real, simply to the fact that a prolonged deep respiration will affect the circulation itself. The number of respirations in the introductory period which a subject will stand before this effect will make its appearance is not constant. On A. K. we found in two experiments the same O_2 absorption per litre blood with three and five respirations. On J. L. the circulation was practically unaffected by four respirations but a large increase (40 %) in the O_2 absorption per litre blood was observed with five. On R. E.

we found also that five respirations increased (by about 20 %) the apparent O_2 absorption per litre blood during rest.

In order to avoid psychic influences and to have a regular circulation we have finally made a number of determinations on J. L. and R. E. during light and constant muscular work on the ergometer[1]. We have compared experiments with one inspiration from the spirometer and a pause of 3–5 seconds with others with two, three and in a few cases four mixing respirations of approximately the same depth but a slightly more rapid rate than those made in the rest experiments. The natural respiration during the work was further not very different from that employed for the mixing. The results are on the whole

TABLE 17. Utilisation of oxygen, c.c. per litre blood.

Subject	Number of mixing respirations 1	2	3	4
J. L.	82	73	94	120
	73	86	81	120
	80	85	89	100·5
	114	88·5	79	98
	—	88·5	—	94·5
	—	94·5	—	—
	—	81	—	—
	—	88	—	—
Averages	87	85·5	86	106·5
R. E.	83·5	90	88	—
	93·5	—	—	—
	94	—	—	—

very regular and very striking. On J. L. the number of mixing respirations up to and including three is evidently without any influence upon the result, but four respirations take too much time, when the circulation is increased to about 13 l. per minute, and the resulting circulation rate becomes too low. On R. E. experiments with one, two and three respirations have been compared and give exactly similar results. The mixing has therefore been complete in all cases.

While the control experiments made by Fridericia, Boothby and Sandiford and ourselves have demonstrated that there are no inherent errors of a technical nature in our method for the determination of the circulation rate, when it is carried out in accordance with the rules, laid down especially by Lindhard(15), we desire to emphasize

[1] Lindhard(15) has formerly in a number of experiments involving muscular work of varying severity compared circulation rate determinations with two and three introductory respirations respectively and observed no difference.

a point to which Lindhard has also drawn attention, namely the great difficulty inherent in determining the *normal* resting circulation of any individual. The circulation during muscular rest is evidently an extremely labile function, which can be easily and greatly influenced psychically by the experiments themselves and all sorts of extraneous factors[1]. We cannot give any definite rules the observance of which will secure normal results, but it will always be necessary to watch the subjects closely and to repeat the determinations several times. The first values obtained on a subject not trained to respiration experiments are almost always misleading. For these reasons we think it our duty to warn against the clinical use of the method, the more so as abnormal conditions of the lungs of patients may also, possibly, give rise to incomplete mixing of the alveolar gases and thereby to grave errors.

SUMMARY.

1. Just after inspiration the gas mixture in the lungs beyond the dead space (the alveoli taken in the widest sense of the term) is not uniform throughout. The differences are usually slight but with deep and slow breathing they become considerable. With deep and rapid breathing, as in muscular work, the mixing seems to be again improved.

2. In attempts to determine the dead space of the air passages these facts must be taken into account if reliable results are to be obtained. The very large dead spaces determined by Haldane and by Henderson and his collaborators are unreal.

3. The real dead space of a human subject is constant at pulmonary inflations below the resting position of the chest. At larger inflations it increases gradually. With a maximum inflation of the lungs the increase may amount to 100 c.c.

4. No evidence has been obtained of any unequal ventilation of different lobes of the lungs.

5. The composition of the alveolar air should in most circumstances be determined preferably by calculation from the expired air, the volume of the expiration and the dead space. When the breathing is deep the resulting increase in dead space should be taken into account, but during muscular work very slight errors only will usually result from not doing so, because the increase is small compared with the depth of

[1] During muscular work it is, as we have noted repeatedly, much easier to avoid the disturbing influences and to obtain reliable results.

respiration. The direct sampling according to Haldane and Priestley has in certain cases given rise to fallacious results.

6. Our method of examining the composition of the alveolar air by a series of consecutive samples from the same breath is open to objections. The errors are probably not large except in one case specified above.

7. The errors caused by incomplete mixing of the pulmonary gases in our circulation rate determination are much too small to be perceptible in experiments on normal lungs.

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