A NOTE UPON THE TECHNIQUE AND ACCURACY OF THE METHOD OF DOUGLAS AND HALDANE FOR CALCULATING THE DEAD SPACE IN BREATHING.*

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PLATE 6.

The following notes are based upon the results obtained in a study of a group of cases of artificial pneumothorax, as employed in the treatment of pulmonary tuberculosis, of the application of the Haldane-Priestley[1] method of estimating the percentage of CO_2 in the alveolar air, and the calculation of the dead space by the method of Douglas and Haldane.[2]

No detailed report of these cases is undertaken at the present time, but in view of the recent critical analysis by Krogh and Lindhard[3,4] of the method employed, it has seemed to the writer that certain observations, which have arisen in the course of this study, bearing upon the technique and accuracy of this method of determining the dead space, particularly in clinical cases, might be of interest.

No attempt has been made to compare the applicability of any of the other various methods of estimating the percentage of CO_2 in the alveolar air, or for the calculation of the dead space, as by Siebeck's[5] method, or by that recently described in Krogh and Lindhard's[6] basic paper.

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[1] Haldane, J. S., and Priestley, J. G., *Jour. Physiol.*, 1905, xxxii, 240.

[2] Douglas, C. G., and Haldane, J. S., *idem*, 1912–13, xlv, 235.

[3] Krogh and Lindhard, *Jour. Physiol.*, 1913–14, xlvii, 30.

[4] Krogh and Lindhard, *ibid.*, p. 431.

[5] Siebeck, R., *Skand. Arch. f. Physiol.*, 1911, xxv, 87.

[6] Krogh and Lindhard, *loc. cit.*, p. 431.

Under the circumstances, any method involving a technique which must be carried out wholly in the laboratory was obviously impossible, as the cases studied were scattered about the village of Saranac Lake, many of them being confined to bed and only a small number being ambulatory. Fortunately the conditions under which it was necessary to carry on the observations fulfilled, in a large measure, the chief indication considered fundamental as affecting the accuracy of the Haldane-Priestley method of determining the percentage of CO_2 in the alveolar air, *i. e.,* the patients were at rest.

Krogh and Lindhard[7] have shown that the direct method of determining the composition of the alveolar air from samples taken by the Haldane-Priestley method becomes untrustworthy during muscular work, and in their later paper[8] they have emphasized this fact more fully. They also state:

> "During rest the increase in CO_2 percentage in the alveoli is not proportional to the time after the beginning of expiration, and the average of correct H.-P. inspiration and expiration samples is therefore *not* the true average tension. The difference can not be considerable, however, and we believe that in persons with a shallow respiration the H.-P. method may frequently be used with advantage as the variations in the composition of the alveolar air during the respiratory cycle must be small. There is a certain danger, however, that the respiration preceding the taking of a sample may be unconsciously but systematically altered (usually shortened) by the subject and that may vitiate the results to a great extent."

The technique of the method of procedure in this study was evolved in the endeavor to secure as great an accuracy as possible under the conditions imposed. It is self evident that the samples of alveolar air and of expired air must be secured under absolutely the same conditions, and it was soon found that the observations must be made, as far as possible, at the same hour of the day.

All the analyses have been made with Haldane's standard apparatus,[9] the samples being obtained by means of Haldane's gas sampling tubes.

[7] Krogh and Lindhard, *loc. cit.,* p. 30.
[8] Krogh and Lindhard, *loc. cit.,* p. 443.
[9] The apparatus was supplied by Baird and Tatlock, Ltd., London.

ALVEOLAR AIR.

The samples of alveolar air were obtained by the method of Haldane and Priestley, by the use of, in the earlier observations, the simple respiration tube, as originally described, with a single outlet for the alveolar air sampling tube two and a half inches from the mouth end. This tube was made from ordinary hose, and in order to overcome its tendency to curve it was reinforced by a thin brass rod wired to the outside, thus securing an absolutely straight egress and ingress for respiration.

After breathing quietly in and out through the tube, the nose being held, for a sufficient length of time to secure the normal respiratory rhythm for the individual under observation, the samples were secured at the end of a forced expiration following a normal inspiration (sample 1), and again at the end of a forced expiration following a normal expiration (sample 2). At the end of the sharp forced expiration the mouthpiece was closed by the tongue, the individual signaling by closing both eyes the instant the mouth piece was occluded, and the sample of alveolar air was taken.

It was manifestly difficult to obtain always the intelligent coöperation of the individual at the first observation, but as the observations were repeated this difficulty was overcome and the incidental error largely, if not entirely eliminated.

After samples 1 and 2 were secured, as soon as the normal respiratory balance was recovered the sample of expired air was obtained, originally by the use of Zuntz's[10] apparatus and subsequently by the use of rubber bags.

The average of the percentage of CO_2 in samples 1 and 2 was taken as the mean percentage of CO_2 in the alveolar air. It soon became evident, from a number of observations, that not infrequently the percentage of CO_2 in the alveolar air, as determined in this way (the mean of samples 1 and 2), if taken again immediately after collecting the expired air varied slightly from the percentage obtained previously. This difference was not always marked, but the percentage of CO_2 in the alveolar air taken immediately after

[10] This apparatus, as used by the writer, was made under the supervision of Dr. J. J. R. Macleod, in the Physiological Laboratory of Western Reserve University.

securing the expired air was more often found to be lower rather than higher.

Two possible explanations for this difference appeared reasonable. Inasmuch as we were dealing with individuals in whom any unusual though slight effort tended to produce a certain degree of dyspnea, it was conceivable that following the collection of the expired air the CO_2 percentage in the alveolar air was actually lowered; or it may well be that the difference between the two samples is the result of an unavoidable error in technique due to a difference in the time of the expiratory phase at which the sample was secured.

Using a four-way mouthpiece (figure 1),[11] the writer found that, in a sharp forcible expiration, the percentage of CO_2 in the alveolar air increased gradually, from that period of time as nearly as possible coincident with the end of the normal expiratory phase, up to the extreme limit of forced expiration, as follows:

	I. Percentage of CO_2.	II. Percentage of CO_2.	III. Percentage of CO_2.	IV. Percentage of CO_2.
E. P. C.	4.84	4.87	5.29	5.62
E. P. C.	4.79	5.18	5.56	5.71
E. P. C.	4.31	4.71	5.41	5.59

I = approximately just after the limit of normal expiration.
IV = approximately the limit of forced expiration.

As a result of these observations the procedure was adopted of securing, in every instance, the two samples of alveolar air both before and after collecting the expired air. By means of the four-way mouthpiece samples 1 and 2 were secured, the expired air was then collected, and without any unnecessary delay the two additional samples (3 and 4) of alveolar air were obtained, and the mean percentage of CO_2 in all four samples was taken as the average percentage of CO_2 in the alveolar air at the time of the observation (table I).

[11] This mouthpiece has four outlets placed two and a half inches from the mouth end. The sampling tubes were opened and closed by colleagues in the order 1, 2, 3, and 4, at a given signal. Other similar records are not quoted. It is, of course, apparent that the figures 1, 2, 3, and 4 do not indicate with any accuracy the same period of time in the forced expiration in the different observations; they can be only approximately correct. (Krogh and Lindhard, *loc. cit.*, p. 431. This article was not published at the time the above observations were originally made.)

TABLE I.

Case No.	Date.	Tidal air in c.c.	Alveolar air CO_2% before taking expired air.	Alveolar air CO_2% after taking expired air.	Alveolar air CO_2, mean percentage.	Alveolar air CO_2 tension. In percentage of 1 atmosphere.	In mm. of mercury.
1	Jan. 15, 1914	294.3	5.73	5.51	5.62	5.61	40.1[12]
1	Jan. 19, 1914	174.6	6.02	5.98	6.00	5.65	40.4
1	Feb. 27, 1914	212.0	5.79	6.10	5.94	5.59	40.0
1	Feb. 28, 1914	281.0	6.16	5.63	5.89	5.57	39.8
1	Mar. 6, 1914	255.2	6.57	6.23	6.40	6.02	43.1
1	Mar. 7, 1914	261.0	6.55	6.26	6.40	6.02	43.1
3	Feb. 2, 1914	666.6	6.96	6.74	6.85	6.45	46.1
3	Feb. 3, 1914	728.7	7.02	6.65	6.83	6.43	46.0
3	Feb. 4, 1914	638.4	6.52	6.35	6.43	6.05	43.3
4	Feb. 18, 1914	534.2	6.16	5.82	5.99	5.64	40.3
4	Feb. 18, 1914	525.5	6.03	5.71	5.87	5.53	39.5
6	Mar. 11, 1914	569.0	5.39	5.52	5.45	5.13	36.7
6	Mar. 12, 1914	603.0	5.55	5.72	5.63	5.30	37.9

It is, of course, evident that such a four-way mouthpiece is not in any sense an essential necessity in securing the four samples. The writer adopted its use, however, as offering the greatest accuracy in standardizing his technique in the method of procedure, in avoiding any unnecessary delay after the observation was begun, and as a great convenience with bed patients. It has been used in all recorded observations since the end of January.

TABLE II.

Case No.	Date.	Tidal air.	I. Alveolar air CO_2%.	II. Alveolar air CO_2%.	III. Alveolar air CO_2%.	IV. Alveolar air CO_2%.	Alveolar air, mean CO_2%.	Alveolar air CO_2 tension. In percentage of 1 atmosphere.	In mm. of mercury.
9	Mar. 31, 1914	520.7	5.40	5.51	5.09	5.34	5.33	5.02	35.9
9	Apr. 1, 1914	542.0	5.39	5.59	5.09	5.41	5.37	5.06	36.2
9	Apr. 2, 1914	602.0	5.59	5.76	5.30	5.72	5.59	5.26	37.6
Mean		554.9	5.46	5.62	5.16	5.49	5.43	5.11	36.5

I = alveolar air sample following inspiration before collecting the expired air.
II = alveolar air sample following expiration before collecting the expired air.
III = alveolar air sample following inspiration after collecting the expired air.
IV = alveolar air sample following expiration after collecting the expired air.

[12] Saranac Lake is 503 meters above sea level. In all calculations the mean barometric pressure,—based upon actual barometric observations extending over three months,—is taken at 716 mm. of mercury.

As illustrating in greater detail the point emphasized, a single example will suffice (table II), being the results of three observations on successive days before the establishment of an artificial pneumothorax.

THE EXPIRED AIR.

The collection of the sample of the expired air was at first attempted by means of the Zuntz apparatus, in the hope that it would be possible to collect data regarding the respiratory quotient, which would be more reliable than when the bag is used, but this method was given up in favor of the rubber bag, as used by Douglas and Haldane[13] and their associates, for the following reasons. In a number of individuals the sense of air-hunger induced by the Zuntz apparatus was so great that the observation had to be abandoned in a very short time. It was also found that with the Zuntz apparatus the length of time necessary to secure an accurate sample of the expired air was longer than any of the cases studied could submit to; and finally there remained the difficulty of transporting the apparatus and meter from house to house, and its inapplicability for patients in bed.

With the rubber bag it is only necessary to collect the expired air for a definite length of time, counting accurately the number of respirations during the period of observation, and then to pass the amount collected through the wet gas meter, collecting the samples into previously exhausted sampling tubes. In this way one can collect any number of samples desired. Four minutes were taken as the standard length of time for the collection of the expired air. In a number of observations this was lengthened to five minutes, and in a few instances it was found necessary to shorten the time to three minutes, but in no case did the time fall below this latter figure. In individuals with a large tidal air the duration of any such observation depends in a measure upon the capacity of the bag employed. The two bags used had a capacity of fifty-two and fifty-seven cubic liters respectively.

The bag is used with an inlet tube of wide caliber about two meters long. By constructing a valve, on the principle of the in-

[13] Douglas, C. G., Haldane, J. S., Henderson, Y., and Schneider, E. C., *Phil. Tr. Roy. Soc. London,* 1913, cciii, series B, 185–318.

take valve of the Zuntz apparatus, and using dogs' intestine as the valve proper, it was possible to provide a valve which offers the least resistance to expiration and yet effectually prevents any unconscious rebreathing or escape of the air from the bag before it is clamped off at the conclusion of the observation. The allowance for dead space when measuring the expired air is ninety cubic centimeters.

Before starting the observation the patient breathes quietly into the bag for one to two minutes, without the valve in place, and this expired air is then forced out of the bag, thus assuring that the slight amount of residual air in the bag at the commencement of the observation was the individual's own expired air.

The method of procedure was as follows: At a given signal the patient starts breathing directly into the bag through the mouthpiece of the valve described above, inspiring through the nostrils and expiring through the mouth, the nostrils being held closed during expiration; the patients were also taught to occlude the opening in the mouthpiece with the tongue during inspiration, thus automatically reinforcing the valve.

In cases 3, 4, and 9 of this series, from which a few observations reported herewith are taken, it was found impossible to occlude the nostrils during expiration, because of the sense of discomfort produced, and the failure to do this leaves the method as employed in these cases open to a certain just criticism. A number of control observations, however, with different individuals, gave a difference of less than fifteen cubic centimeters in the tidal air figure when the expired air is collected in this way, at the same respiratory rate and for the same length of time, and no difference in its analysis.

In every instance the expired air was measured within half an hour after its collection.

In using the rubber bag two precautions are necessary and of fundamental importance as affecting the accuracy of the results obtained. Before measuring the expired air the bag must be thoroughly shaken to ensure a complete mixture of its contents, otherwise the resulting analyses of the CO_2 and O_2 may be wholly inaccurate. Finally, but by no means the least important procedure in the technique of the rubber bag method, the bag should be thor-

TABLE III.

Case No.	Date.	Respirations per minute.	Tidal air in c.c.	Alveolar air CO_2%.	Alveolar air CO_2 tension.		Expired air CO_2%.	Alveolar air in c.c.	Calculated dead space in c.c.	Remarks.
					In percentage of 1 atmosphere.	In mm. of mercury.				
3	Feb. 3, 1914	17.6	729	6.83	6.43	46.0	4.24	465	264	Ambulatory, all observations sitting.
3	Feb. 4, 1914	17.5	638	6.43	6.05	43.3	4.32	428	210	
3	Mar. 20, 1914	15.0	508	6.78	6.37	45.6	4.29	327	187	
4	Feb. 4, 1914	14.0	500	6.09	5.72	40.9	4.18	343	157	Ambulatory, all observations sitting.
4	Feb. 4, 1914	15.0	551	6.19	5.83	41.6	4.27	380	171[14]	
4	Feb. 18, 1914	13.5	534	5.99	5.64	40.3	4.12	367	167	
4	Feb. 18, 1914	13.0	525	5.87	5.53	39.5	4.37	390	135[14]	
6	Feb. 11, 1914	15.4	423	5.87	5.53	39.5	4.08	327	96	Ambulatory, all observations sitting.
6	Feb. 11, 1914	18.7	413	5.21	4.90	35.0	4.12	332	81[14]	
6	Feb. 21, 1914	17.0	211	5.47	5.15	36.8	4.07	157	54	
6	Feb. 21, 1914	18.3	251	5.55	5.22	37.3	4.06	183	68[14]	
6	Mar. 3, 1914	18.3	396	5.34	5.03	36.0	4.04	301	95	
6	Mar. 3, 1914	18.3	328	5.60	5.27	37.7	4.14	242	86[14]	
9	Mar. 31, 1914	12.2	521	5.33	5.02	35.9	3.98	388	133	In bed.
9	Apr. 1, 1914	12.0	542	5.37	5.06	36.2	3.94	399	143	In bed.
9	Apr. 2, 1914	12.2	602	5.59	5.26	37.6	3.91	421	181	In bed.
9	Apr. 3, 1914	13.5	277	5.68	5.35	38.2	4.42	212	65	24 hrs. after first artificial pneumothorax.
10	Apr. 6, 1914	19.7	355	6.18	5.82	41.6	3.81	220	135	In bed.
10	Apr. 7, 1914	24.2	299	6.10	5.74	41.0	3.77	184	115	24 hrs. after first artificial pneumothorax.

[14] One hour after paracentesis for reëstablishment of artificial pneumothorax.

oughly washed out after each observation by ordinary atmospheric air, in order to prevent any accumulation of organic exhalations or the collection of pockets of CO_2 which may also give rise to inaccurate readings. This has been done by filling the bags from an ordinary laboratory bellows blower twice and then emptying completely. The writer found that unless this procedure was carried out the CO_2 percentages were not as accurate as when controlled by a control bag.

The figures in table III are taken from five of the cases studied in this series, and are chosen as being typically characteristic of the results obtained in an attempt to apply the method of Douglas and Haldane for determining the dead space in breathing in a group of individuals who fulfill to an unusual degree the requirement of bodily inactivity.

No detailed analysis of these cases is attempted at the present time; they are cited merely to add force to the points noted above in the technique of the method employed, and serve to emphasize the truth of Krogh and Lindhard's contention that:

> "When however the alveolar CO_2 percentage is used together with the corresponding percentage in the expired air for calculating the dead space of the subject, even small deviations from the true composition of the air expired from the alveoli may have a very considerable effect upon the reliability of the result."

It must be borne in mind that all the individuals in this series are the subjects of a more or less advanced pulmonary tuberculosis, E. P. C. alone being entirely free from the disease. This fact explains the high percentage of CO_2 in the expired air.[15]

TABLE IV.

Four Control Observations Made on E. P. C. at Weekly Intervals.[16]

Respirations per minute.	Tidal air in c.c.	Alveolar CO_2%.	Alveolar air CO_2 tension.		Expired air CO_2%.	Alveolar air in c.c.	Calculated dead space in c.c.
			In percentage of 1 atmosphere.	In mm. of mercury.			
17	783	5.62	5.29	38.0	3.55	496	287
16	934	5.59	5.26	37.6	3.22	538	396
17	753	5.68	5.35	38.3	3.29	429	324
17	751	5.54	5.21	37.3	3.27	443	308

[15] The actual analyses were all carefully checked by duplicates.

[16] The writer has a large tidal air capacity, and a very constant respiratory rate. It is perhaps unnecessary to add that all the observations have been made on adults.

Turning to the figures given in tables III and IV, it is evident that in those instances in which the tidal air exceeds 423 cubic centimeters the calculated dead space is out of all true proportion to the alveolar air. In only one instance, observation 4, case 4, in which the tidal air is above this figure, does the calculated dead space for the individual approach what is probably the normal or true dead space for the individual at rest, and here the CO_2 percentage in the expired air rose abruptly following the paracentesis for the reëstablishment of the pneumothorax.

I wish, in concluding, to express my great indebtedness to Dr. Edward R. Baldwin, without whose interest and aid these observations would have been impossible, as they have been made almost entirely upon his private cases. To Dr. J. J. R. Macleod, of Western Reserve University, to whom I owe my introduction into the method of the physiological technique, my appreciative thanks are due. The study from which these brief notes are taken has been carried out entirely under Dr. Macleod's guidance. I am under deep obligations to him for many valuable suggestions and his friendly interest in the problems encountered.

CONCLUSIONS.

The determination of the percentage of CO_2 in the alveolar air, by the method of Haldane and Priestley, is sufficiently accurate for clinical purposes when the individual is at rest.

It is evident, however, that an error may arise in the determination of the percentage of CO_2 in the alveolar air, due to the time during the forced expiration, short of the extreme limit, at which the sample may be unconsciously taken. This error can only be overcome by taking several samples.

In individuals at rest having a tidal air below 425 cubic centimeters, the method of Douglas and Haldane for the calculation of the dead space gives approximately accurate results; with a tidal air above 425 cubic centimeters the results obtained may be wholly inaccurate.

In patients with marked pulmonary tuberculosis so slight an effort as that involved in collecting the expired air tends to lower the percentage of CO_2 in the alveolar air.

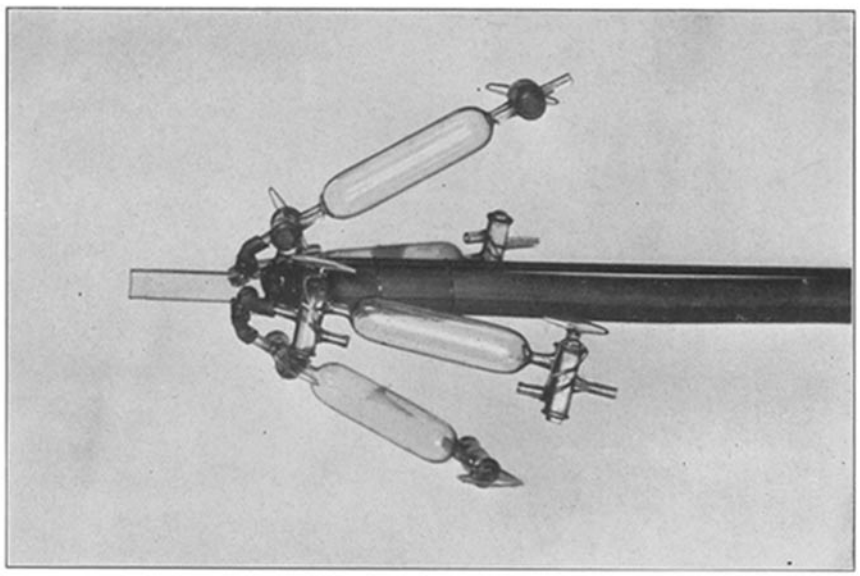

FIG. 1.

(Carter: Calculation of Dead Space in Breathing.)

In collecting the expired air by the rubber bag method, it is absolutely essential that the bag be washed out with ordinary atmospheric air after every observation.

EXPLANATION OF PLATE 6.

FIG. 1. The four-way mouthpiece used in the experiments. For further details, see footnote 11, page 84.