THE RESPIRATORY RESPONSE TO CARBON DIOXIDE.

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(Received for publication, October 21, 1924.)

I.

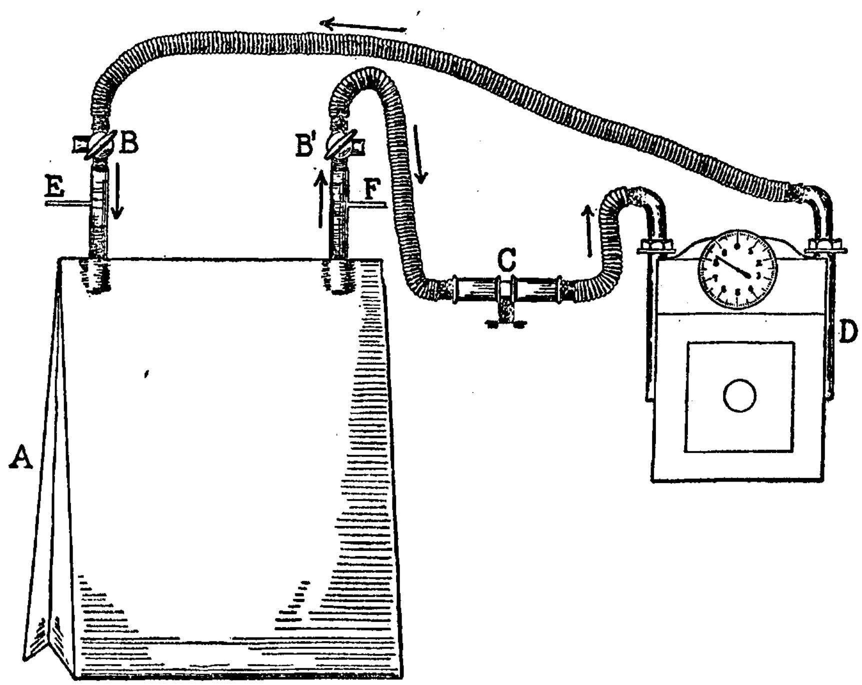
INTRODUCTORY.

The present paper deals with an attempt to determine whether the respiratory response to carbon dioxide stimulus obeys a simple law, and, if so, to what modifications this law is subject. Scott (1) has studied this response in cases of pulmonary emphysema, and Peabody (2) in cases of cardiac disease. Scott studied the normal response of two individuals while Peabody determined the limits of variation in nine normal individuals. These authors were concerned mainly with the variations occurring in pathological conditions, and therefore did not make any detailed critical study of their normal data. We had intended to make a study of the variations in response in a number of individuals, but the findings in a single one appeared sufficiently interesting to warrant separate and detailed consideration.

II.

Methods.

The effect of gradually increasing percentages of carbon dioxide was studied by means of rebreathing in a closed circuit consisting of a modified Douglas bag with inflow and outflow tubes, a dry meter, and a rubber mouthpiece fitted with inspiratory and expiratory valves. The general arrangement of the apparatus is shown semidiagrammatically in Text-fig. 1. The direction of air flow is indicated by means of arrows. *A* is the modified Douglas bag of 100 liters capacity. *B*, *B'* are wide bored three-way taps. *C* is the mouthpiece. *D* is a twenty-light capacity "B type" dry meter manufactured by D. McDonald and Company of Albany. The resistance of this meter is almost negligible even at the maximal rates of pulmonary ventilation produced by high percentages of carbon dioxide in the inspired air. *E* is a small bore side tube connected with an oxygen tank fitted with reducing valve and a flow meter calibrated to register with approximate accuracy rates of flow of less than 1 liter per minute. A similar side tube, *F*, is used to obtain samples of inspired air, either into exhausted sampling tubes or directly into the burette of the Haldane gas analysis apparatus. By means of the three-way stop-cocks *B*, *B'* the subject may be made to inhale from and exhale into the room air through the meter, and his normal respiratory rate and minute volume may be determined. When the stop-cocks are turned the apparatus becomes a closed circuit, inspiration and expiration being from and to the Douglas bag *A*. In addition, the side limb of the stop-cock *B'* can be attached to the three-



TEXT-FIG 1. Rebreathing apparatus. *A*, modified Douglas bag; *B*, wide bore three-way tap; *B'* wide bore three-way tap; *C*, rubber mouthpiece; *D*, dry gas meter; *E* and *F*, small bore side tubes.

way outlet of a Tissot spirometer so that the subject could be made to inspire either room air from the free limb of the Tissot outlet, or pure oxygen, or any other required gas mixture from the spirometer, exhaling it through the meter and out into the room air through the opened stop-cock *B*. By means of the meter, graduated in liters and tenths of a liter and capable of being read with approximate accuracy to 0.05 liter, the respiratory rate, minute volume, and average tidal air could be readily determined with the aid of a stop-watch and tally hand register. These were determined as a rule over a 3 minute period every 5 minutes throughout the experiment, the remaining 2 minutes of the 5 being given to counting the pulse rate and writing down the figures. At exactly the middle of the 3 minute period a sample of inspired air was taken for analysis. In those experiments in which the Douglas bag contained pure oxygen to begin with, the carbon dioxide alone was estimated and the sample was taken directly into the burette of the Haldane gas analysis apparatus. The analysis could be satisfactorily completed and the apparatus cleared in sufficient time for the next sample 5 minutes later. In experiments in which room air was used and oxygen added to replace that utilized, the samples were collected in exhausted sampling tubes and subsequently analyzed for carbon dioxide and oxygen. The experiments were carried out in the morning, from 1 to 2 hours after a light breakfast. During half an hour prior to the experiment the subject sat quietly in a chair in such a position that the only movement required in commencing the experiment was the insertion of the mouthpiece and adjustment of the nose clip.

At the commencement of each experiment, from three to five periods of observation were taken with the subject breathing room air. The average minute volume of pulmonary ventilation obtained from these observations was taken as the normal and formed the basis for calculation of the "ventilation coefficients" in the subsequent experiment, after the manner described by Peabody (2). This author takes the average normal minute volume as 100, and the subsequent minute volumes as percentage increases over this figure. Thus, when the ventilation is doubled, the coefficient is 200. A coefficient of 400 indicates that the ventilation has increased to fourfold.

III.

The Normal Response to Carbon Dioxide.

Six experiments were made on different days in order to determine the limits of variation and average normal response to increasing concentrations of carbon dioxide in a single individual. Table I gives the findings in a typical experiment. In this experiment oxygen was added to the bag during the rebreathing period at a rate slightly greater than 250 cc. per minute. In spite of the fall in the oxygen percentage of the inspired air, it is probable that the alveolar oxygen percentage remained approximately normal, owing to the greatly increased minute volume of pulmonary ventilation.

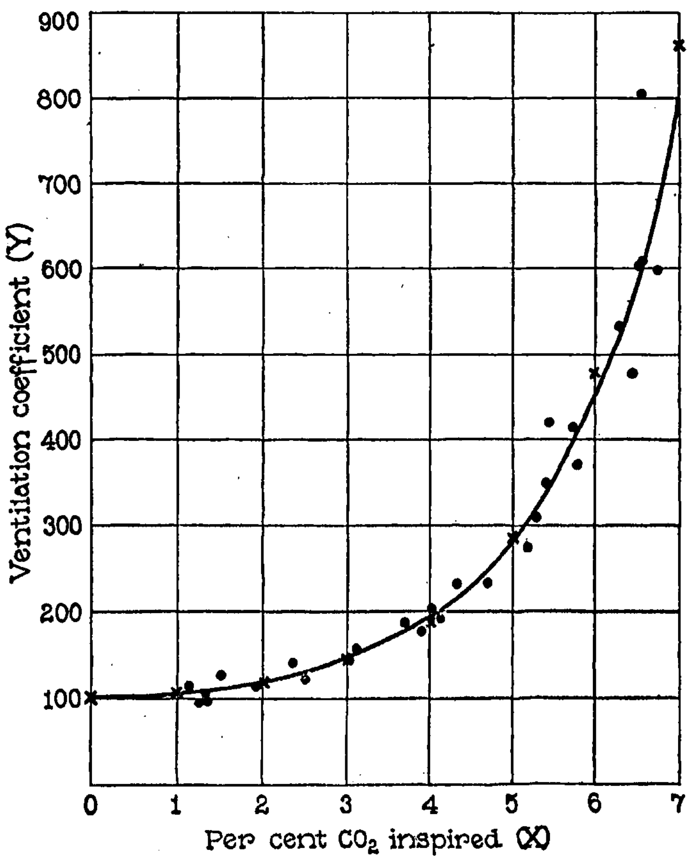
It will be noted that in the subject under investigation the rate of respiration increased but little until the inspired carbon dioxide increased to approximately 5 per cent. The response was mainly manifested by increase in depth. In a few experiments on another subject the results were less clear-cut, rate sometimes increasing earlier and more markedly than depth. This variation in response has been previously noted by Hough (3), who found that twenty-three out of twenty-five normal individuals showed an early increase in depth while in the remaining two the respiratory rate increased prior to an increase in depth.

The results of our six experiments are shown in Text-fig. 2, in which the ventilation coefficient has been plotted against the percentage of carbon dioxide in the inspired air. The curve is the one which was found empirically to fit the results most closely. It was so drawn that the average of the variations above the curve equals that of those below it.

TABLE I.

Apr. 28, 1924. Time.	CO_2 inspired.	O_2 inspired.	Pulse rate.	Respiration rate.	Minute volume.	Ventilation coefficient.	Volume per respiration.	Remarks.
a.m.	*per cent*	*per cent*			*liters*		*liters*	
11.45–11.48	Room air.		76	5.7	6.00			
11.50–11.53			74	5.7	6.08			
11.55–11.58			76	5.0	5.90			
p.m. 12.00–12.03			82		6.04	100	1.06	Subject coughing. Observation discarded.
12.05–12.08			76	6.3	6.18			
12.10–12.13	1.50	?	76	6.7	7.57	125	1.13	
12.15–12.18	3.70	18.3	76	6.3	11.28	187	1.79	
12.20–12.23	5.39	17.1	80	9.0	21.08	349	2.34	
12.26–12.29	6.56	16.4	96	15.0	36.77	608	2.45	

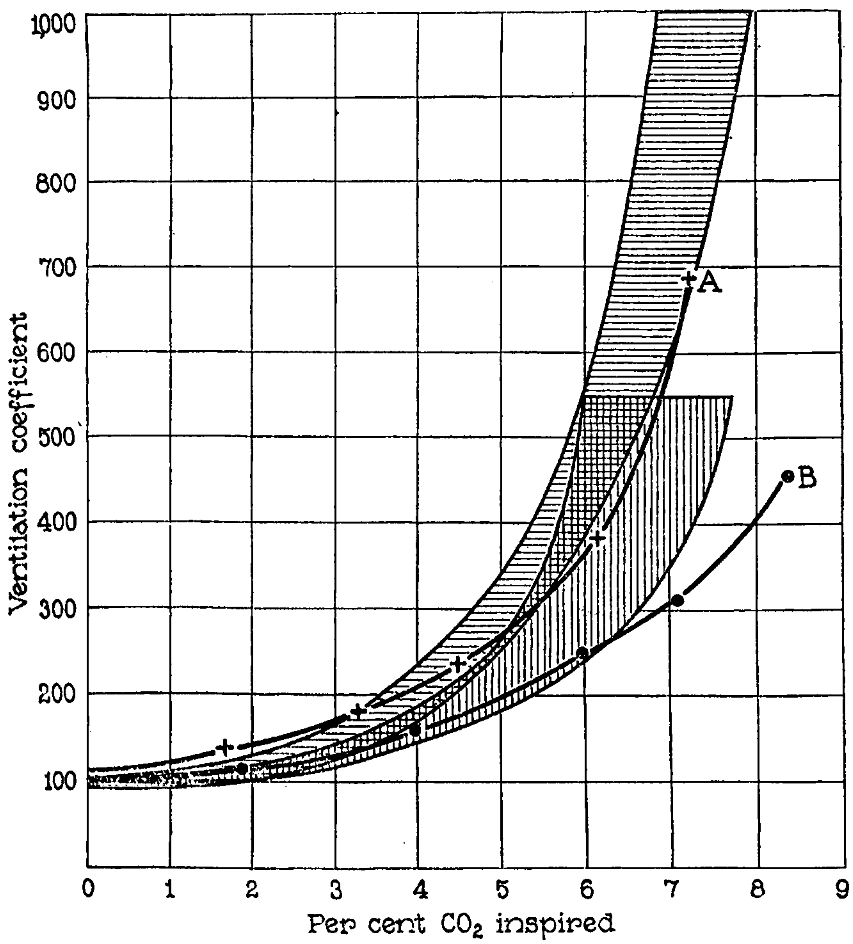
The results show a considerable divergence from those of Peabody (2) and of Scott (1). Text-fig. 3 shows the limits of normal response of the present subject in the six experiments that involved rebreathing room air and in five of rebreathing oxygen. On the same figure we have included the limits found by Peabody in nine normal individuals, and the curves of the two normal individuals investigated by Scott. None of these findings can be compared with the results of Lindhard (4) and of Campbell, Douglas, Haldane, and Hobson (5) because in these latter the minute volume of total pulmonary ventilation is not given. The reasons for the divergence between our results and those of Scott and Peabody are not evident. We must conclude, therefore, that the respiratory response to carbon dioxide in the inspired air shows marked variations in different individuals, and indeed in any given individual on different days. We have no evidence leading us



TEXT-FIG. 2. Respiratory response to CO_2. Ordinates represent ventilation coefficient (Y). Abscissæ represent percentages of CO_2 (X). The dots indicate observed values for X and Y. The crosses indicate calculated values for X and Y.

to suppose that this variable response is necessarily due to variations in the excitability of the respiratory center itself. It might be due to other factors such as the hemoglobin concentration, to slight variations in the carbon dioxide-carrying capacity of the blood, or to slight changes in metabolism.

Lyon (6) has shown that the response to adrenalin as indicated by changes in blood pressure obeys the Weber-Fechner law, according to which the response is proportional to the natural logarithm of the



TEXT-FIG. 3. Comparison of respiratory response to CO_2 of the present subject with that of other normal individuals. The horizontally shaded area represents the limits of response in the present subject. The vertically shaded area represents the limits of response in cases studied by Peabody. The curves *A* and *B* are those of the two normal individuals investigated by Scott.

stimulus. It seemed of interest to determine whether the curve of response to carbon dioxide given in Text-fig. 2 also obeyed this or any other known law which can be expressed in mathematical terms. The values for X and Y are given in Table II, X representing the strength of the stimulus as expressed by the percentage of CO_2 breathed, Y the respiratory response as measured by the ventilation coefficient.

From a glance at this table it can be seen that while X is in arithmetical progression, the successive increases of Y (ΔY) are in geometric progression, at any rate for values of X up to 5. The relationship between X and Y can therefore be expressed by a formula of the type $Y = K + ab^x$. Substituting several sets of observed values for X and Y, the constants K, a, and b were found to be 94, 6, and 2, respectively, the general expression being $Y = 95 + (6)(2^x)$. The results of Peabody and of Scott can be expressed by a similar equation but one having different values for K, a, and b. It is probable that

TABLE II.

X	Y Observed (interpolated) values.	ΔY	Y Calculated values.	Difference between observed and calculated values of Y.
0	100	–	100	±0
1	106	6	106	±0
2	118	12	118	±0
3	146	28	142	+4
4	193	47	190	+3
5	282	89	286	−4
6	452	170	478	−26
7	800(±)	348	862	−62

these mathematical constants may have some physiological significance, but our present data give no indication regarding what this may be.

The formula expresses very exactly the respiratory response to carbon dioxide for percentages up to 5 per cent. Beyond this point the observed results show a progressive fall below the calculated values. There are physiological reasons for this divergence. Assuming that the equation correctly expresses the relation between carbon dioxide stimulus and respiratory response, it is evident that it can only hold within limits and that beyond a certain point the ability to respond will be progressively limited by failure of the muscles of respiration and perhaps by failure of or changes in other systems. For values of X up to 4 or 5 the respiratory response does not demand any abnormal effort, but beyond that point the effort required to maintain the greater pulmonary ventilation, together with the increased resistance in the breathing circuit, would give rise to fatigue which would manifest itself in just such a divergence as is shown between the observed and calculated response. It is noteworthy, also, that in the subject under investigation, this "breakaway" occurred at approximately the point at which increased depth alone was insufficient to take care of the demand for increased pulmonary ventilation. Obviously the facts cannot be expressed in terms of the Weber-Fechner law. They indicate rather that the natural logarithm of the response increases in proportion to the stimulus.

IV.

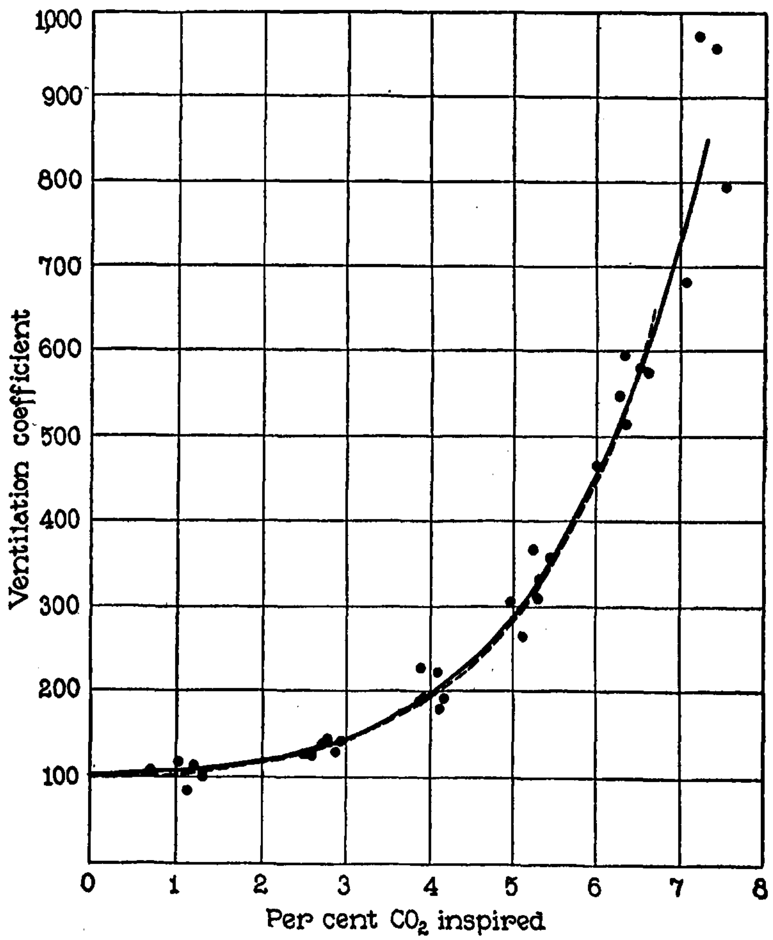
The Respiratory Response to Carbon Dioxide in the Presence of High Oxygen Percentages.

The fact has been clearly established that in conditions of anoxemia the respiratory center is abnormally sensitive to increases of carbon dioxide concentration, but the effect of increased oxygen percentages upon the respiratory response to carbon dioxide has given rise to controversy. Previous workers have studied this point with reference to the alveolar ventilation, not the total pulmonary ventilation. The alveolar ventilation cannot be determined directly, but is calculated from the percentages of carbon dioxide in the alveolar and inspired air.

Lindhard (4) considered that in the presence of a high oxygen percentage in the inspired air, the sensitivity of the respiratory center to carbon dioxide is greatly diminished, while Campbell, Douglas, Haldane, and Hobson (5) have held that the sensitivity of the respiratory center to carbon dioxide is unaltered even by wide variations in the percentage of oxygen inspired. The difference of opinion would seem to depend upon the methods used in determining the carbon dioxide percentages of the alveolar air, and calculating the alveolar ventilation.

Benedict and Higgins (7) found that the breathing of pure oxygen produced no change in the character, depth, or frequency of the respiration as recorded by means of a pneumograph.

We have performed six experiments in which pure oxygen was rebreathed. The results are shown in Text-fig. 4. In this figure the curve of Text-fig. 2 is reproduced by means of a broken line. It can be seen that the difference between the two curves is well within the limits of normal variation. It is to be noted, however, that the respiratory response to inspired carbon dioxide is slightly greater in the presence



TEXT-FIG. 4. Comparison of respiratory response to CO_2 when breathing normal and high oxygen mixtures. Each curve represents a composite of six experiments. The broken line is the curve for normal O_2, the continuous line that for high O_2 concentration.

of high oxygen percentages. We have also compared the minute volumes when breathing room air and pure oxygen. The results are shown in Table III which gives the average minute volumes,—each one based upon from three to five 3 minute periods of observations,—

together with the mean deviations. The average percentage difference for the whole six experiments is + 2.6. In view of the fact that in some cases the percentage increase differed but little from the mean deviation we are unwilling to lay any stress on this increase. We would point out, however, that it might be accounted for by an attempt on the part of the respiratory center to compensate for the slight fall in pH resulting from the increased oxygen saturation of the arterial blood when pure oxygen is breathed. This, however, can only be regarded as a possibility. In view of the very small difference in the respiratory response to carbon dioxide with normal and increased oxygen percentages this matter can be definitely decided only through statistical methods based upon a large amount of data collected under carefully standardized conditions.

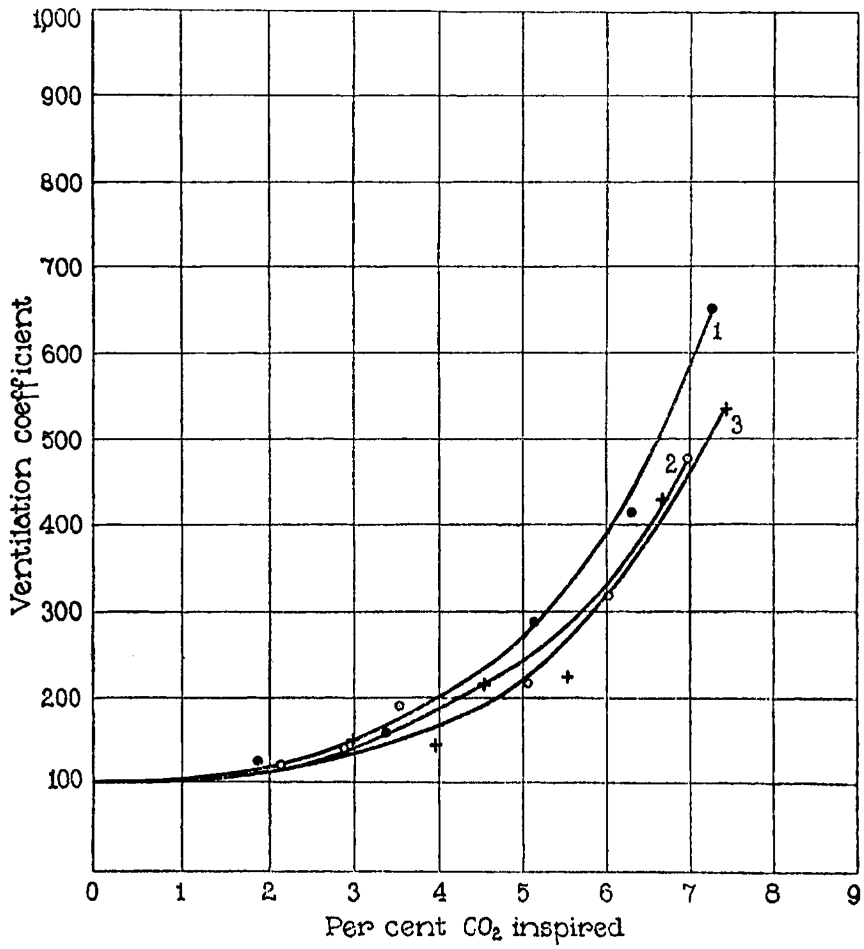
TABLE III.

Date.	Average minute volume.		Percentage difference.
	Room air.	Pure O_2.	
	liters	*liters*	
Apr. 14	5.36 (±0.15)	5.60 (±0.48)	+4.5
" 15	5.49 (±0.21)	5.62 (±0.21)	+2
" 16	6.05 (±0.27)	6.18 (±0.33)	+2
" 17	5.41 (±0.34)	5.41 (±0.29)	0
" 21	6.08 (±0.35)	6.27 (±0.34)	−3
May 22	5.40 (±0.46)	5.96 (±0.24)	+10

V.

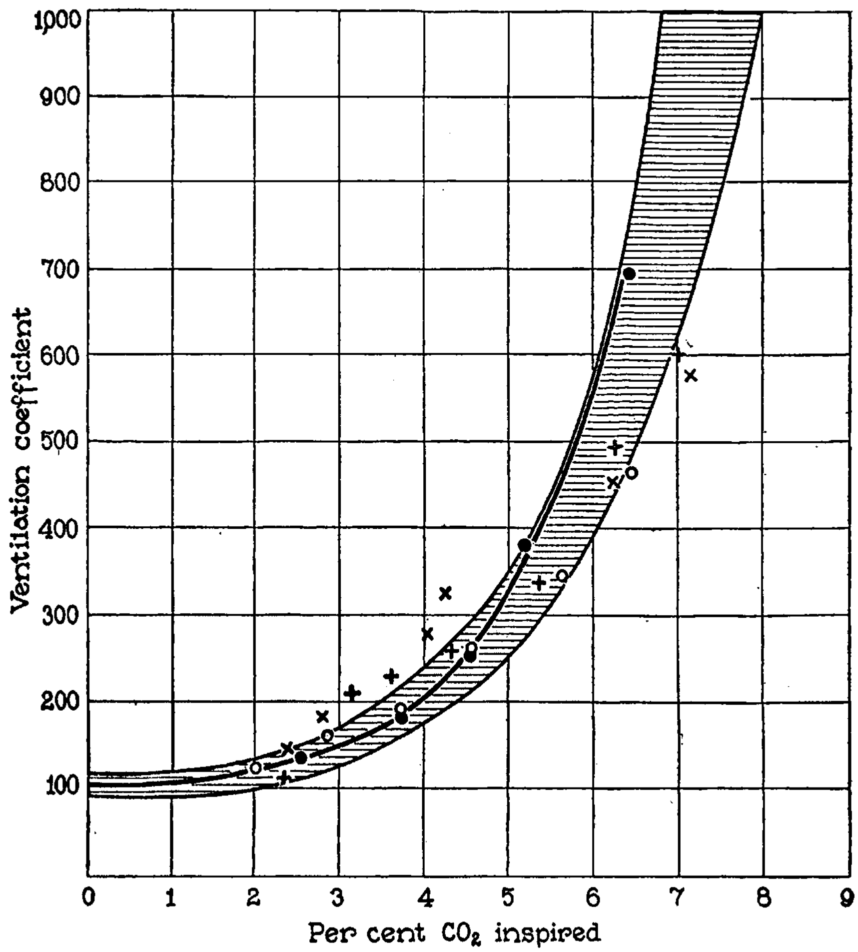
The Influence of Fatigue upon the Respiratory Response to Carbon Dioxide.

In order to determine whether the respiratory response to carbon dioxide was altered by fatigue, we attempted to compare the minute volume of respiration before and after a period of breathing through resistances while the subject was breathing a mixture containing 5.84 per cent of CO_2. The minute volume with this percentage was less after the resistance period than before, but so also was the minute volume with ordinary room air, the ventilation coefficient being actually greater. Owing to our inability to interpret this result, as well as the difficulty in obtaining a satisfactory resistance, we abandoned this method of inducing fatigue, and resorted to a comparison of the results in several successive rebreathing periods. By this means it was found that the response was definitely less in the second, third,



TEXT-FIG. 5. Successive rebreathing periods showing evidence of fatigue. Curve 1 represents response in first rebreathing period. Curve 2 represents response in second rebreathing period. Curve 3 represents response in third rebreathing period.

and fourth rebreathing experiments. In Text-fig. 5 we show the results of one of these experiments involving three successive rebreathing periods, with 15 minutes rest after each while the Douglas bag was emptied and refilled. It is to be noted that while the points determined in the first of the three periods fell close to a smooth curve, those for the subsequent periods showed a considerable amount of



TEXT-FIG. 6. Curve showing effect of repeated rebreathing periods in the subject as compared to his normal response. The shaded area indicates the normal variation in respiratory response to CO_2. The black dots represent the findings in the first rebreathing period. The circles represent the findings in the second rebreathing period. The crosses represent the findings in the third rebreathing period. The plus signs represent the findings in the fourth rebreathing period.

scattering. This irregularity was more marked when the inspired CO_2 was below 5 per cent and may possibly have been due to some

Protocol of Fatigue Experiment, June 30.

Subject quiet and comfortable throughout experiment. Light breakfast (one cup of coffee and one banana) at 8.30 a.m.

Period No.	Time.	Inspired CO_2.	Air O_2.	Pulse rate.	Respirations per min.	Minute volume of respirations.		Ventilation coefficient.	Remarks.
	a.m.	*per cent*	*per cent*			*liters*			
1	9.35								*Blood A:* pH 7.31; CO_2 52.20 vol. per cent.
	9.42½	Room air.		68	5.3	5.35	5.23	100	
	9.46½			66	5.3	5.17			
	9.51½			66	5.3	5.40			
	9.56½			66	4.7	5.53			
	10.01½			66	4.7	4.68			
	10.06½	2.56	90+	64	6.0	7.15		137	10.04 a.m. Commenced rebreathing.
	10.11½	3.75	90+	64	5.3	9.52		182	
	10.16½	4.56	90+	66	6.3	13.22		253	
	10.21½	5.17	90+	68	8.7	19.82		379	
	10.26½	6.44	90+	72	12.0	36.43		697	10.28 a.m. Back to room air.
2	10.41½	Room air.		64	4.7	4.92	4.90	94	*Blood B:* pH 7.30; CO_2 58.08 vol. per cent.
	10.46½								
	10.51½			62	4.7	4.88			
	10.56½	2.02	90+	60	5.0	6.42		123	10.54 a.m. Commenced rebreathing.
	11.01½	2.88	90+	58	7.3	8.55		163	
	11.06½	3.74	90+	58	6.7	10.05		192	
	11.11½	4.56	90+	62	8.0	13.70		262	
	11.16½	5.64	90+	62	8.3	18.12		346	
	11.21½	6.47	90+	66	9.7	24.33		466	11.23 a.m. Back to room air.
3	11.37½	Room air.		60	4.7	5.12	5.31	102	*Blood C:* pH 7.30; CO_2 59.50 vol. per cent.
	11.41								
	11.46½			58	5.0	5.50			
	11.51½	2.40	90+	58	6.7	7.50		143	11.49 a.m. Commenced rebreathing.
	11.56½	2.82	90+	58	6.3	9.57		183	
	p.m.								
	12.01½	4.05	90+	60	8.0	14.58		279	
	12.06½	4.26	90+	62	9.3	17.10		327	

Protocol of Fatigue Experiment, June 30.—Continued.

Period No.	Time.	Inspired CO_2.	Air O_2.	Pulse rate.	Respirations per min.	Minute volume of respirations.	Ventilation coefficient.	Remarks.
	p.m.	*per cent*	*per cent*			*liters*		
3	12.11½	6.24	90+	62	12.3	23.73	454	
	12.16½	7.14	90+	64	13.0	30.18	578	12.18 p.m. Back to room air.
4	12.29½	Room air.		60	5.3	5.43		
	12.32					} 5.72	109	*Blood D:* pH 7.31; CO_2 57.00 vol. per cent.
	12.37½			58	8.3	6.20		
	12.41½			58	7.3	5.53		
	12.46½	2.34	90+	54	7.3	5.90	113	12.44 p.m. Commenced rebreathing.
	12.51½	3.15	90+	58	11.7	10.95	210	
	12.56½	3.63	90+	58	8.3	12.02	230	
	1.01½	4.34	90+	58	9.3	13.55	259	
	1.06½	5.36	90+	62	11.0	17.58	337	
	1.11½	6.25	90+	64	16.3	25.88	495	
	1.16½	7.02	90+	64	16.3	31.43	602	1.18 p.m. Back to room air.
	1.33	Room air.						*Blood E:* pH 7.30; CO_2 content 58.75 vol. per cent.

instability of the respiratory center brought about by fatigue. For the higher percentages of carbon dioxide the response in the second and third periods was very definitely less than in the first and fell well below the normal limits of variation for the subject.

Similar results were obtained in a second experiment. The details of this experiment are shown in a protocol and in Text-fig. 6. In this experiment the ventilation coefficients for percentages of CO_2 between 2 and 5 were markedly increased in the third and fourth rebreathing periods, rising well above the normal limits of variation, while for percentages above 5 they fell below the normal limits. These findings suggest the possibility that there may have been two kinds of fatigue involved—that of the respiratory center, involving an irritability and an increased response for the lower levels of carbon dioxide, and that of the muscles of respiration, manifested by inability to respond at the higher levels of carbon dioxide concentration when the demands for pulmonary ventilation were much greater. In this experiment samples of venous blood for estimations of pH were taken with a minimum of stasis and analyzed by the method of Hastings and Sendroy (8) and the carbon dioxide content by the constant volume method of Van Slyke (9). The pH varied by only 0.01, but the carbon dioxide content increased by from 5 to 7 volumes per cent (see protocol), indicating a considerable increase in the carbon dioxide-combining power. This increase might account partly for the diminished respiratory response at the higher levels of carbon dioxide concentration. The point requires further investigation.

SUMMARY.

1. A technique for determining the respiratory response to carbon dioxide on the Peabody principle is described.

2. The relation between minute volume of total pulmonary ventilation and percentage of carbon dioxide in the inspired air can be expressed by a simple mathematical formula, *viz.* $Y = K + ab^x$, in which Y is the ventilation rate, X is the CO_2 content of the inspired air, and K, a, and b are constants characteristic for the individual.

3. The respiratory response to carbon dioxide as expressed by the total pulmonary ventilation is slightly greater at high oxygen percentages (90 per cent $\pm$) than at normal oxygen percentages in the inspired air.

4. Respiratory fatigue may consist of two elements—one nervous, manifesting itself in increased excitability of the center and a more marked response when the demand for pulmonary ventilation is small, the other muscular and involving an inability to respond when the demand for pulmonary ventilation is great.

We are indebted to Dr. A. B. Hastings for assistance in the mathematical portion of Section III, and to Messrs. Julius Sendroy, Jr., and Tully Curitz for the pH and blood gas findings in the fatigue experiment.

BIBLIOGRAPHY.

1. Scott, R. W., *Arch. Int. Med.*, 1920, xxvi, 544.
2. Peabody, F. W., *Arch. Int. Med.*, 1915, xvi, 846.
3. Hough, T., *Am. J. Physiol.*, 1911, xxviii, 369.
4. Lindhard, J., *J. Physiol.*, 1911, xlii, 337.
5. Campbell, J. M. H., Douglas, C. G., Haldane, J. S., and Hobson, F. G., *J. Physiol.*, 1913, xlvi, 301.
6. Lyon, D. M., *J. Pharmacol. and Exp. Therap.*, 1923, xxi, 229.
7. Benedict, F. G., and Higgins, H. L., *Am. J. Physiol.*, 1911, xxviii, 1.
8. Hastings, A. B., and Sendroy, J., Jr., *J. Biol. Chem.*, 1924, lxi, 695.
9. Van Slyke, D. D., and Neill, J. M., *J. Biol. Chem.*, 1924, lxi, 523.