

OBSERVATIONS ON THE PATHOLOGIC PHYSIOLOGY OF CHRONIC PULMONARY EMPHYSEMA *

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The object of this paper is to record the results obtained from experiments on two patients with chronic pulmonary emphysema, of the so-called "large lunged" type. The work was undertaken in an effort to ascertain facts which might lead to a clearer appreciation of the disturbance in respiratory physiology in emphysema.

The gross and microscopic appearance of the lungs in this condition is well defined; also the impediment to the mechanics of respiration afforded by the loss of the elastic tissue of the lungs is appreciated. Further investigation, however, is necessary to show to what extent the degenerative process interferes with the aeration of the blood and the manner in which the body adapts itself to the altered conditions.

The work of Siebeck,¹ Porges, Leimdorfer and Markovici,² Hoover³ and others established the fact that the residual air and the functional dead space are increased, while the vital capacity is much diminished. Such changes naturally interfere with the alveolar ventilation and cause the patient with emphysema to suffer from a certain amount of pulmonary insufficiency particularly evident when a demand for increased gaseous exchange is to be met, as in exercise.

Another fact noted by most workers is the abnormally high tension of carbon dioxide maintained in the alveolar air. Different explanations have been offered for this. Recently, in experiments on dogs, Friedman and Jackson⁴ found that there was an elevation in the carbon dioxide content of both the alveolar air and blood, when expiration was obstructed. This was attributed to the interference to the pulmonary circulation from the high intrabronchial pressure produced. Such elevations in intrabronchial pressure are not seen in patients with emphysema, except during an attack of asthma, or a paroxysm of coughing, when the impairment in the lesser circulation is probably an important factor in diminishing the gaseous exchange in the

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* First Hamilton Fiske Biggar Prize Essay of the Cleveland Medical Library Association.

1. Siebeck, R.: *Deutsch. Arch. f. klin. Med.* **102**:390, 1911.

2. Porges, O., Leimdorfer, A., and Markovici, E.: *Ztschr. f. klin. Med.* **77**:446, 1913.

3. Hoover, C. F.: *Arch. Int. Med.* **11**:52 (Jan.) 1913.

4. Friedman, E. D., and Jackson, H. C.: *Arch. Int. Med.* **19**:767 (June) 1917.

lungs. Other causes, therefore, must be considered in order to explain the high carbon dioxide content of the alveolar air in subjects with emphysema. These individuals may be comfortable and able to walk about tolerating in the alveolar air a percentage of carbon dioxide which would cause profound hyperpnea in a normal person. With no convincing evidence to the contrary it may be assumed that in such individuals the alveolar carbon dioxide is in equilibrium with the free carbon dioxide in the arterial blood. Recalling the well established physiologic relation between the activity of the respiratory center and the level of free carbon dioxide in the blood, it is at once apparent that the subject with emphysema represents a wide departure from the normal. For example, such patients have been observed to be perfectly comfortable when breathing from 8 to 10 liters of air per minute, with the alveolar carbon dioxide about 8 per cent.

After noting the unusual tolerance to carbon dioxide in several patients it was decided to study quantitatively the respiratory response to increasing percentages of carbon dioxide in the inspired air. The data thus obtained were compared to those found under similar experimental conditions in normal resting individuals. Two hospital patients with well marked chronic pulmonary emphysema were selected for this study. They were free of myocardial disease as far as could be determined clinically and with the aid of the electrocardiograph and at no time, since first observed, have any myocardial symptoms appeared. Particular attention has been paid to the circulation to eliminate as far as possible the effect of pulmonary stasis on the experimental results. The frequent association of myocardial disease with pulmonary emphysema has obviously limited the number of available subjects.

REPORT OF CASES

CASE 1.—Eli B., male, aged 46 years, first came under observation in March, 1913, suffering from an attack of acute bronchitis. At that time he had definite pulmonary emphysema with a slight degree of cyanosis which persisted after recovery from bronchitis. He was not seen again until March, 1919, when he was admitted to the hospital complaining of cough and shortness of breath. The chest presented the typical "barrel-shaped" conformation with an increase in all diameters, particularly the anteroposterior diameter. There was narrowing of the subcostal angle during inspiration. The expiratory phase of respiration was prolonged and on auscultation numerous râles were heard throughout both lungs. No cardiac enlargement was demonstrable. The heart sounds were normal and there was no evidence of venous stasis, except during a paroxysm of coughing when the veins of the neck became very prominent. The blood pressure was 130 mm. systolic and 90 mm. diastolic. There was definite clubbing of the fingers. The cyanosis of the face and hands was quite marked for a few days after admission to the hospital but appreciably diminished as he recovered and was able to walk about comfortably, but even then the lips and finger nails presented a dusky, blue appearance. The patient had no fever at any time and the urine was normal.

CASE 2.—Peter W., male, aged 49 years, has been in the hospital since first admitted in January, 1919. His complaint was shortness of breath and cough. Inspection showed the typical emphysematous thorax, with cyanosis of the face and hands. No pulmonary consolidations were found but a diffuse bronchitis was present throughout both lungs. The patient was apparently having much difficulty in ventilation, and expiration lasted about three times as long as inspiration. Marked narrowing of the subcostal angle occurred with inspiration. The blood pressure was 120 mm. systolic and 80 mm. diastolic. After ten days in bed the patient was much improved and has since been able to walk about fairly comfortably. A slight degree of cyanosis of the lips and mucous membranes of the mouth has persisted. Figure 1 shows the conformation of the thorax.

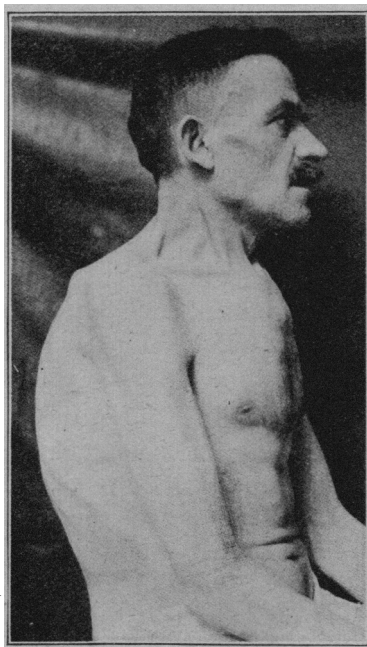


Fig. 1.—Patient Peter W., showing the conformation of the thorax.

RESPIRATORY RESPONSE TO CARBON DIOXID IN TWO NORMAL
INDIVIDUALS COMPARED WITH TWO PATIENTS
WITH CHRONIC PULMONARY EMPHYSEMA

Description of Apparatus Used.—The subject is comfortably seated in a chair before which is a small adjustable table that may be readily placed on a level with the mouth. Projecting over the edge of this table is a rubber mouthpiece connected with a pair of gut valves. These valves⁵ have been adopted in preference to others tried, because they are the most efficient and cause a minimum impediment to the

5. The technic of making the valves has been described by Pearce: *Am. J. Physiol.* **44**:369, 1917.

free ingress and egress of air. The subject inspires from a large 240 liter spirometer and expires into a smaller type of spirometer of 100 liters capacity. These spirometers are of the Tissot model, equipped with an eccentric wheel at the top so that the bell is counterpoised at all levels by means of a weight. Cylinders delivering carbon dioxid and oxygen through a Bohr meter into the inspiratory spirometer make it possible to prepare rapidly any desired concentration of the two gases for the subject to breathe. The bell of the inspiratory spirometer is so weighted that it tends to fall very slowly when opened to the air. Similarly the bell of the spirometer into which the subject expires is so balanced that it rises slowly when opened to the air, thus assisting the expiration. Attached to both spirometer bells is a small pointer which moves along a graduated scale at the side, showing the exact amount of air in the spirometers at any position of the bell. Non-collapsible rubber tubing connects the respiratory valves with the two spirometers. Both the tubing and the spirometer pipes are one inch inside diameter. On the intake pipe of the expiratory spirometer is a three way metal valve. By this arrangement the subject's expired air can be directed either into the room or into the spirometer. Samples of air for analysis are drawn off through an opening at the top of the spirometer bells. The gas analyses are made with the well known Haldane apparatus.

Technic of Experiments.—The subject is brought to the laboratory and allowed to rest for thirty or forty minutes. He then assumes a comfortable position in a chair and the small table is so adjusted that the rubber mouthpiece connected with the respiratory valve can be held in the mouth with a minimum of muscular effort. The nose is closed with an ordinary nose clip; the subject now inspires from the large spirometer filled with room air and expires through the three way valve into the room. This preliminary period in which from fifty to sixty liters of air are breathed affords the subject time to accustom himself to the experimental conditions. After inspecting the respiratory valves and other parts of the apparatus, the time is noted and the expired air is allowed to enter the spirometer. The experiment is continued usually for five minutes or less, depending on the minute volume of the subject's respiration. The nose clip and mouthpiece are now removed and the subject breathes naturally until the next experiment. This interval is about fifteen minutes during which the analysis of the expired carbon dioxid is made and the inspiratory spirometer is filled with a new mixture and analyzed. At least two observations at room air are first made to see that the carbon dioxid output is fairly constant. Other experiments with various percentages of carbon

dioxid in the inspired air are then made. Sufficient amounts of oxygen have always been added to maintain its concentration in the inspired at approximately 20 per cent.

Respiratory Response to Carbon Dioxid.—The results obtained on the two normal individuals are presented in Table 1. These data show the approximate variations that have been found in normal resting persons after they have become accustomed to the experimental conditions. Even individuals such as medical students who understand the purpose of the experiments are very likely to over-ventilate at the first few observations. The same is, of course, true of hospital patients, but after a little experience constant results are obtained.

TABLE 1.—THE RESPIRATORY RESPONSE TO INCREASING PERCENTAGES OF CARBONDIOXID IN THE INSPIRED AIR IN TWO NORMAL SUBJECTS

Inspired Air	Period Observed, Min.	Total Volume Expired Air, Liters	Minute Volume Expired Air, Liters	Carbon Dioxid				Respiratory Rate per Min.
				Expired, per Cent.	Expired per Minute, C.c.	Inspired per Minute, C.c.	Output over Intake, C.c.	
Subject C. P. H.								
Room air.....	5	25.5	5.1	4.40	224	0	224	8
Room air.....	5	25.0	5.0	4.64	232	0	232	7
1.7% CO ₂	5	35.5	7.1	5.12	363	120	243	8
3.04% CO ₂	5	44.0	8.8	5.44	479	268	211	10
4.5% CO ₂	4	48.0	12.0	5.84	701	540	161	13
6.16% CO ₂	3	58.5	19.5	7.04	1,373	1,201	172	17
7.2% CO ₂	2	70.0	35.0	7.60	2,660	2,520	140	25
Subject P. J. C.								
Room air.....	5	35.0	7.0	3.44	241	0	241	17
Room air.....	5	35.0	7.0	3.40	238	0	238	17
1.92% CO ₂	5	40.0	8.0	4.32	346	154	192	15
4.0% CO ₂	5	56.0	11.2	5.76	645	448	197	15
6.0% CO ₂	3	52.5	17.5	7.00	1,225	1,050	175	17
7.12% CO ₂	2	44.0	22.0	7.84	1,725	1,566	159	18
8.40% CO ₂	2	64.0	32.0	8.80	2,816	2,688	128	22

Table 2 contains the results of two experiments on Eli B., a patient with chronic pulmonary emphysema. The experiment made April 5 was done shortly after his admission to the hospital and shows a sluggish respiratory response to inspired carbon dioxid. Similar results were obtained in the experiment done five months later (Sept. 13). A comparison of these two experiments shows the constancy with which the abnormal response to carbon dioxid is maintained. A further illustration of this is given by the data in Table 3. These experiments were performed several months apart on Peter M. This patient has been in the hospital all this time and frequent observations at intervals have yielded similar results. His respiratory response to carbon dioxid and that of the normal subject, P. J. C., is shown graphically in Figure 2.

After observing the respiratory response to carbon dioxid in normal individuals and particularly in patients with heart disease, the subjects

TABLE 2.—THE RESPIRATORY RESPONSE TO INCREASING PERCENTAGES OF CARBON DIOXID IN ELI B., A PATIENT WITH CHRONIC PULMONARY EMPHYSEMA

Inspired Air	Period Observed, Min.	Total Volume Expired Air, Liters	Minute Volume Expired Air, Liters	Carbon Dioxid				Respiratory Rate per Min.
				Expired, per Cent.	Expired per Minute, C.c.	Inspired per Minute, C.c.	Output over Intake, C.c.	
Experiment 1								
April 5, 1919								
Room air.....	5	45.0	9.0	3.88	349	0	349	17
Room air.....	5	44.5	8.9	3.84	342	0	342	18
1% CO ₂	5	45.5	9.1	4.32	393	91	302	19
2.32% CO ₂	3	27.5	9.2	5.44	500	213	287	18
5.52% CO ₂	4	44.0	11.0	7.52	827	607	220	18
7.08% CO ₂	3	42.5	14.2	8.68	1,233	1,005	228	19
8.00% CO ₂	3	50.0	16.6	9.32	1,547	1,328	219	21
9.12% CO ₂	3	57.0	19.0	10.32	1,960	1,732	228	22
Experiment 2								
Sept. 13, 1919								
Room air.....	5	40.0	8.0	4.20	336	0	336	11
Room air.....	5	37.5	7.5	4.28	321	0	321	12
1.6% CO ₂	4	35.0	8.8	5.12	450	140	310	15
3.84% CO ₂	4	36.0	9.0	6.80	612	346	266	12
6.32% CO ₂	3	37.5	12.5	8.40	1,050	790	260	18
7.00% CO ₂	3	36.5	12.2	8.80	1,074	854	220	14
8.32% CO ₂	3	44.0	13.7	9.68	1,326	1,140	186	15
9.50% CO ₂	3	49.5	16.5	10.64	1,756	1,568	188	17

TABLE 3.—THE RESPIRATORY RESPONSE TO CARBON DIOXID ON DIFFERENT DATES IN PETER W., A PATIENT WITH CHRONIC PULMONARY EMPHYSEMA

Inspired Air	Period Observed, Min.	Total Volume Expired Air, Liters	Minute Volume Expired Air, Liters	Carbon Dioxid				Respiratory Rate per Min.
				Expired, per Cent.	Expired per Minute, C.c.	Inspired per Minute, C.c.	Output over Intake, C.c.	
Experiment 1								
Feb. 22, 1919								
Room air.....	5	37.5	7.5	3.84	288	0	288	20
Room air.....	5	39.5	7.9	3.48	275	0	275	20
1.96% CO ₂	5	39.0	7.8	4.88	381	153	228	20
3.92% CO ₂	5	49.0	9.8	6.16	604	384	220	21
6.08% CO ₂	4	42.5	10.6	7.88	835	644	191	21
7.28% CO ₂	3	33.5	11.2	8.88	994	815	179	21
8.36% CO ₂	3	34.5	11.5	9.80	1,127	961	166	21
9.60% CO ₂	3	35.0	11.7	10.92	1,278	1,123	155	21
Experiment 2								
Sept. 16, 1919								
Room air.....	5	37.5	7.5	4.24	318	0	318	20
Room air.....	5	42.0	8.4	3.76	314	0	314	18
2.64% CO ₂	7	68.5	9.8	5.40	529	259	270	21
3.92% CO ₂	5	53.0	10.6	6.32	670	415	255	21
4.96% CO ₂	5	58.5	11.7	7.44	870	580	290	20
6.44% CO ₂	5	61.0	12.2	8.60	1,049	785	264	21
7.52% CO ₂	4	53.5	13.4	9.33	1,250	1,008	242	22
10.45% CO ₂	2	28.0	14.0	11.30	1,639	1,515	124	20
Experiment 3								
Oct. 5, 1919								
Room air.....	5	51.5	10.3	3.20	330	0	330	22
Room air.....	5	51.5	10.3	3.24	334	0	334	22
4% CO ₂	3	33.5	11.2	6.16	690	448	242	22
6.12% CO ₂	3	35.5	11.8	8.04	949	722	227	22
8.08% CO ₂	3	38.5	12.8	9.76	1,249	1,034	215	22
9.28% CO ₂	3	39.5	13.2	10.56	1,394	1,225	169	21
10.24% CO ₂	3	42.0	14.0	11.56	1,618	1,434	184	22
11.44% CO ₂	3	42.0	14.0	12.48	1,747	1,607	145	22

with emphysema afford a very sharp contrast. The ease and apparent comfort with which emphysematous patients inspire high percentages of carbon dioxide (from 8 to 10 per cent.) for short periods is very striking. This is, of course, true only up to a certain percentage, which might be called the tolerance level. At or a little above this level, symptoms of acute distress develop quite abruptly. There is

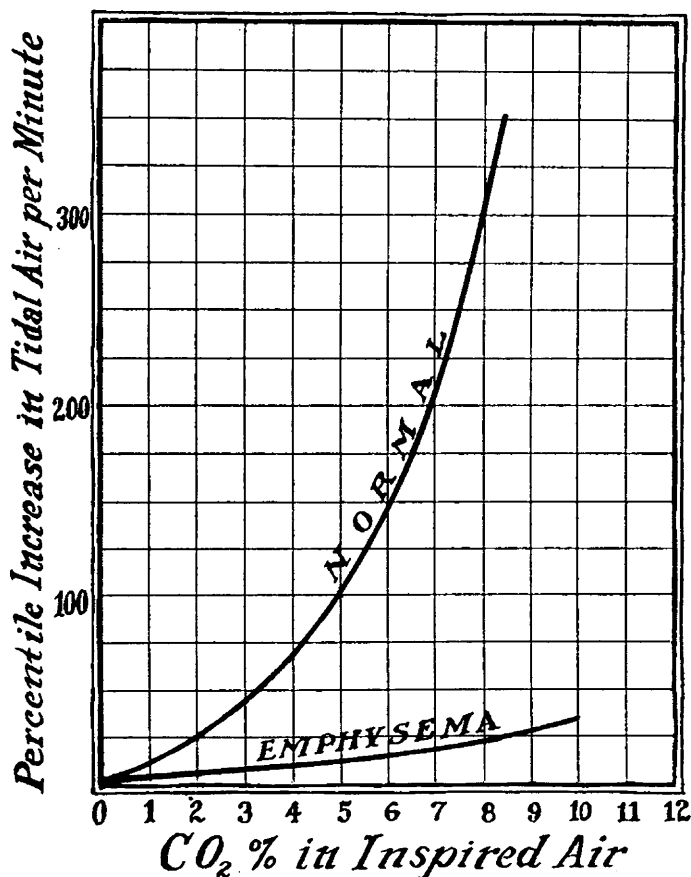


Fig. 2.—This shows the percentile increase in tidal air per minute as the percentage of inspired carbon dioxide is raised. Note that when the normal subject inspires air containing 8 per cent. carbon dioxide, the tidal air is increased about 300 per cent. and in the emphysematous subject only about 25 per cent.

headache, nausea, dizziness and the subject refuses to continue the experiment. This appearance of acute distress at a certain concentration of inspired carbon dioxide is quite characteristic and was noted in all experiments where high percentages were breathed for short periods (from 10 to 15 minutes). Take, for example, experiment 3

in Table 3, which was done particularly to find the tolerance level. While inspiring 9.28 per cent. carbon dioxide the subject was apparently comfortable and made no complaint. Breathing 10.24 per cent. carbon dioxide caused a little dizziness, but the next observation with 11.44 per cent. caused considerable distress and it was with much effort on the part of the subject that the experiment was continued to the end. At this high concentration the minute volume was 14 liters. This and other experiments have indicated that 14 liters per minute is the maximum volume of air which this subject can exchange. In other words, with a potent stimulus to respiration he has a factor of safety amounting to about 7 liters per minute as compared with about 50 liters for normal persons under the same conditions. This indicates a marked limitation in pulmonary reserve. It also shows how helpless the emphysematous subject is to combat an accumulation of carbon dioxide in the body occurring when metabolism is increased as in exercise, or when the resting metabolic carbon dioxide is retained as happens when air rich in carbon dioxide is inspired.

For a given concentration of inspired carbon dioxide the emphysema subjects take less carbon dioxide into the lungs per minute. This is obviously due to the difference in minute volume in the two cases. For example, Peter W. (Table 3) breathing 10.15 per cent. carbon dioxide actually took into the lungs less carbon dioxide per minute than the normal subject, P. J. C. (Table 1), breathing 7.12 per cent. carbon dioxide. It is further noted in both the normal and emphysematous subjects that as the per cent. of inspired carbon dioxide rises, the excess of carbon dioxide output over intake falls. These figures are obtained by simply subtracting the cubic centimeters of carbon dioxide inspired per minute from that expired per minute. Obviously, at room air the difference represents metabolic carbon dioxide but as increasing percentages are breathed more and more metabolic carbon dioxide is retained in the body.

The almost constant respiratory rate at all concentrations of inspired carbon dioxide, particularly in the case of Peter W. (Tables 5, 6 and 7) afford an interesting illustration of the significance of the lung elasticity in breathing. Even while respiring room air there is no time interval between one expiration and the succeeding inspiration. With a potent stimulus to respiration Peter W., is unable to inflate and deflate his lungs more than twenty-two times per minute. It is a matter of common observation that most cases of emphysema have a prolonged expiratory cycle. In both Eli B. and Peter W. expiration lasted approximately twice as long as inspiration.

In comparing the data from the experiments on the two subjects with emphysema it is noted that Eli B. was a little more sensitive to

carbon dioxid. This may have been due in part to the fact that he had a lesser grade of emphysema, as indicated by the size of the lungs and by the diminished vital capacity (Table 4).

TABLE 4.—THE VITAL CAPACITY ON DIFFERENT DATES IN THE TWO EMPHYSEMATOUS SUBJECTS

Eli B., Height 5 ft. 9 in.		Peter W., Height 5 ft. 10 in.	
Date	Vital Capacity, C.c.	Date	Vital Capacity, C.c.
4/ 2/19	2,600	2/18/19	1,600
4/ 5/19	2,800	4/ 6/19	1,700
4/14/19	3,200	10/ 5/19	1,750

The Carbon Dioxid Tension of the Blood.—It has been demonstrated by others that the carbon dioxid tension in the alveolar air is abnormally high in emphysema. Several experiments were done to determine the alveolar carbon dioxid, using the original Haldane and Priestly technic and also the method brought out by Pearce.⁶ The results were usually well above the normal but they showed considerable variation. This was attributed to poor cooperation on the part of the subject. In order to obtain more constant results, the carbon dioxid tension in the blood was determined by analysis of the expired air brought into equilibrium with the venous blood. The method suggested by Henderson and Prince⁷ was found most useful in work with patients. The technic is simple and quite consistent results were obtained in both normal and diseased individuals. With this method not only the tension of carbon dioxid in the venous blood is determined, but some information is also obtained concerning the rapidity with which equilibrium is reached between the gases of the venous blood and the air in the lungs. Here, as in the foregoing observations, the data obtained in experiments on normal individuals were used for comparison with those found in the subjects with emphysema. The technic employed was as follows: A graduated Krogh spirometer of six liters capacity is used instead of a rubber bag, as recommended by Henderson. The spirometer is preferred because it affords a means of checking the total volume of each successive expiration. The outlet to the air chamber of the spirometer is through an iron pipe, 1 inch inside diameter. Attached to this pipe is a three way steam valve, one outlet of which is connected with a rubber mouthpiece.

The subject is comfortably seated before the spirometer and the nose closed with a clip. He inserts the mouthpiece into the mouth and breathes room air normally for from twenty to thirty seconds,

6. Pearce, R. G.: Am. J. Physiol. **43**:73, 1917.

7. Henderson, Y., and Prince, M.: J. Biol. Chem. **33**:325, 1918.

through one outlet of the valve. Just at the height of a normal inspiration he is told to blow, the valve is suddenly turned so that all the expired air passes into the spirometer. When the forced expiration is completed the valve is again turned, thus closing off the spirometer. A sample of this air is now drawn off and analyzed for carbon dioxide. During this analysis the subject removes the nose clip and mouthpiece and breathes naturally. After a few minutes the mouthpiece is again taken and room air is respired through the valve outlet. At the height of a normal inspiration the subject is told to blow but this time he expires into the room. At the end of the deepest possible expiration he raises his finger as a signal, the valve is suddenly turned, and the contents of the spirometer is inspired. This is held ten seconds and forcibly expired back into the spirometer. A carbon dioxide analysis of this expired air is then made. This procedure of inspiring the contents of the spirometer—holding ten seconds and expelling—is repeated until the carbon dioxide percentage of the expired air reaches a constant level.

The same technic is used to determine the rapidity with which a high concentration of carbon dioxide (from 12 to 13 per cent.) reaches the level of carbon dioxide in the venous blood. In this case a carbon dioxide-rich air mixture is first put into the spirometer, the total volume equal to that which the subject forcibly expires after a normal inspiration. The rebreathings, as described above, are performed until a constant carbon dioxide percentage is reached in the expired air.

TABLE 5.—THE RISE IN CARBON DIOXIDE FROM INTERMITTENT REBREATHINGS IN TWO NORMAL PERSONS AND TWO PATIENTS WITH EMPHYSEMA
Temperature, 20 C. Barometer, 742 Mm. Hg.

Number of Intermittent Rebreathings	Percentage of Carbon Dioxide in Expired Air			
	Normal Subject	Normal Subject	Emphysema, Eli B.	Emphysema, Peter W.
1*	4.88	4.48	5.40	6.08
2	6.40	6.0	7.52	7.52
3	7.04	7.20	8.28	8.60
4	7.08	7.28	8.92	9.23
5	7.28	7.26	9.16	9.50
6	7.20	7.28	9.22	9.45
7	7.28	7.28	9.40	9.50
8

* The first analysis in each subject is the carbon dioxide content of a forced expiration after a normal inspiration of room air.

Table 5 contains the experimental data obtained in two normal individuals and two emphysematous subjects (Eli B. and Peter W.). Tables 6 and 7 show the results of taking a high percentage of carbon dioxide into the lungs and rebreathing until an equilibrium is attained. Curves plotted from these data are shown in Figure 3.

The data obtained show that, after four or five rebreathings, the carbon dioxide in the inspired air comes practically to a constant level and this occurs when a low as well as a high concentration is first taken into the lungs. Although the number of patients studied is too small to draw definite conclusions, yet the results seem to indicate that the tonometric function of the emphysematous lung is not seriously impaired. That is, under the experimental conditions, carbon dioxide equilibrium is reached between blood and lung air in approximately the same time in the emphysematous subject as in normal persons.

TABLE 6.—THE FALL IN CARBON DIOXID FROM INTERMITTENT BREATHING IN TWO NORMAL PERSONS

Temperature, 20 C. Barometer, 742 Mm. Hg.

Number of Intermittent Rebreathings (Spirometer Filled With 12.8 per Cent. Carbon Dioxid)	Percentage of Carbon Dioxid in Expired Air	
	Normal Subject	Normal Subject
1*	10.0	9.20
2.....	8.6	8.00
3.....	7.68	7.60
4.....	7.20	7.28
5.....	7.28	7.20
6.....	7.28	7.28
7.....	7.20	7.20

* The carbon dioxide content of the air forcibly expired after first filling the lungs with air containing 12.8 per cent. carbon dioxide and holding for ten seconds.

TABLE 7.—THE FALL IN CARBON DIOXID FROM INTERMITTENT REBREATHING IN A PATIENT WITH EMPHYSEMA

Temperature, 22 C. Barometer, 738 Mm. Hg.

Number of Intermittent Rebreathings (Spirometer Filled with 13 per Cent. Carbon Dioxid)	Percentage of Carbon Dioxid in Expired Air	
	Emphysema, Eli B.	
1*	10.24	
2.....	9.72	
3.....	9.50	
4.....	9.56	
5.....	9.56	
6.....	9.45	
7.....	9.45	

* The carbon dioxide content of the air forcibly expired after first filling the lungs with air containing 13 per cent. carbon dioxide and holding for ten seconds.

It is apparent that such observations throw little light on the facility with which carbon dioxide can be eliminated from the body, because such important factors as the blood flow through the lungs, the available alveolar surface, and the efficiency of alveolar ventilation are not considered. The level at which carbon dioxide equilibrium is established is definitely higher in emphysema than in the normal.

Observations on several normal persons at rest have shown that the venous carbon dioxide as determined by the technic described above, varies between 7 and 7.4 per cent. at 20 C. and the prevailing barometric

pressure, 740 mm. Hg. Under similar experimental conditions the results have been consistently high in both Eli B. and Peter W. A few determinations of the alveolar carbon dioxide on these patients have also been high. Such abnormally high figures admit of two interpretations.

The carbon dioxide content of the venous and arterial pulmonary air (Y. Henderson) as estimated either does or does not represent the level of free carbon dioxide in the pulmonary venous and arterial blood respectively. There is little in favor of the negative side of the

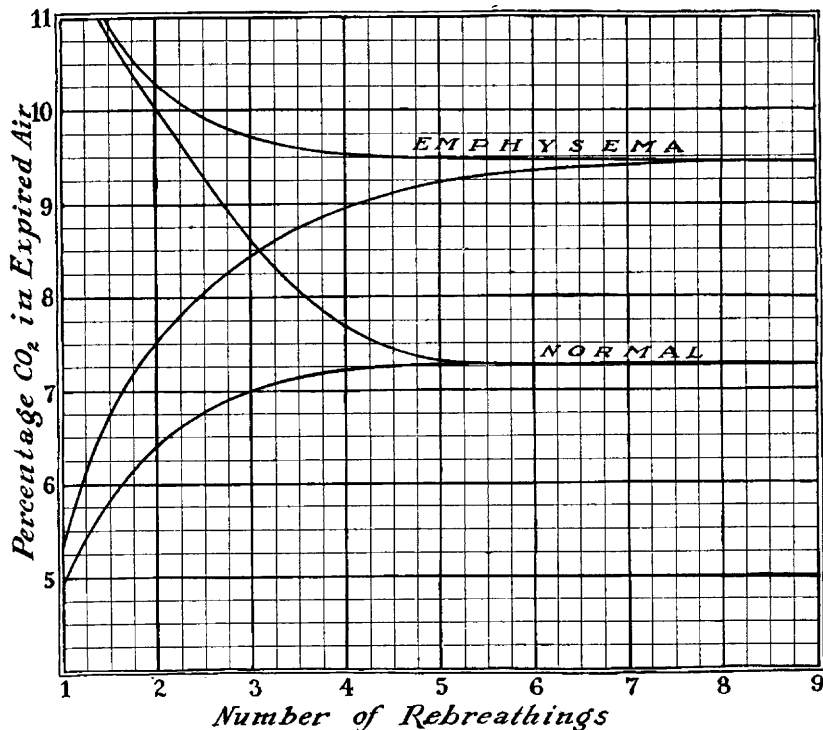


Fig. 3.—Curves plotted from experimental data to show the level at which equilibrium is established between the carbon dioxide of the lung air and the carbon dioxide tension of the venous blood in the normal and emphysematous subjects.

question unless one assumes that the methods for obtaining samples of the lung air are unreliable. On the other hand, as pointed out by Bohr, and particularly by Krogh,⁸ the diffusion constant (the diffusion at 1 mm. tension difference during 1 minute, in cm. at 0 degrees 760 mm.) for carbon dioxide is such as to render the tension of this gas the same on the two sides of the pulmonary membrane. To study

8. Krogh, A.: Skand. Arch. f. Physiol. **23**:248, 1910.

this question, H-ion concentration (p_H) and total carbonate determinations were made on the arterial and venous bloods of the emphysematous subjects. The data from the bloods of normal persons at rest served as controls.

The arterial blood was obtained by direct puncture of the radial artery, using a similar technic as that employed by Stadie.⁹ The venous blood was collected without stasis from one of the large veins at the bend of the elbow. Both samples of blood were delivered under oil into paraffin coated centrifuge tubes and immediately centrifuged at high speed. A little oxalate was added to prevent clotting. One c.c. of the separated plasma was delivered under carbon dioxid free ammonia water in the receiving cup of the Van Slyke apparatus and the total carbon dioxid content determined directly. This direct method appears to have certain advantages over the widely used technic of first exposing the plasma routinely to 5.5 per cent. carbon dioxid and determining the carbon dioxid combining power. It is simpler and with care taken to prevent the loss of carbon dioxid it gives results obviously more representative of the carbon dioxid content of the circulating blood particularly when one is dealing with pathologic conditions. Reference to and the data obtained in normal and pathologic individuals by the use of this direct method were presented in a preliminary report.¹⁰ Recently Van Slyke and Stadie¹¹ have recommended its adoption.

TABLE 8.—TOTAL CARBONATE CONTENT OF THE ARTERIAL AND VENOUS PLASMA AND p_H OF THE WHOLE BLOOD (ARTERIAL) IN FIVE NORMAL SUBJECTS AND TWO WITH EMPHYSEMA

Normal Individuals			Emphysema*		
Carbon Dioxid Reduced to 0 C. 760 Mm. in 100 C.c. Plasma		p_H Arterial Blood	Carbon Dioxid Reduced to 0 C. 760 Mm. in 100 C.c. Plasma		p_H Arterial Blood
Arterial, C.c.	Venous, C.c.		Arterial, C.c.	Venous, C.c.	
57.8	64.4	7.35	76.1	82.7	7.4
59.1	67.2	7.4	74.1	78.4	7.4
57.5	61.5	7.4	80.2	88.4	7.45
51.5	59.9	7.35	74.5	80.2	7.35
53.4	60.0	7.40	71.0	76.0	7.4

* Determinations made on different dates over a period of several months.

Table 8 contains the data for the total carbon dioxid content of the arterial and venous plasma along with the p_H of the whole arterial blood as drawn. The results on five normal individuals at rest are given to compare with similar data obtained at different dates on Eli B., and Peter W.

9. Stadie, W. C.: J. Exper. Med. **40**:215, 1919.

10. Scott, R. W.: Proc. Soc. Exper. Biol. & Med. **17**:18, 1919.

11. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **41**:191, 1920.

It is seen that the total carbonate content of both the arterial and venous plasma in emphysema is distinctly above normal, while the H-ion concentration (p_H) of the whole blood as drawn is not appreciably changed. Only one interpretation can be placed on such results in view of the well established relation between the free and combined carbon dioxide to the H-ion concentration in blood. Associated with a high carbonic acid content there is a corresponding increase in the sodium bicarbonate so that the ratio $\frac{H_2CO_3}{NaHCO_3}$ and hence the H-ion concentration is maintained at appreciably a normal level.

DISCUSSION

It is clear from the data presented that a subject with chronic pulmonary emphysema will inspire relatively high percentages of carbon dioxide for several minutes with only small increases in the minute volume over that at room air. In interpreting this, attention must first be directed to the question of whether or not the carbon dioxide taken into the lungs under the experimental conditions, actually caused a retention of metabolic carbon dioxide. From the physical laws of diffusion there must be a slight pressure gradient from the blood to the lung air. If the carbon dioxide tension in the lungs is elevated, as was done in the foregoing experiments, the metabolic carbon dioxide is retained in direct proportion to this elevation. The data indicates this to be the case in emphysema as well as in the normal. There are, of course, variations in individual experiments, but, as a rule, increasing percentages of carbon dioxide in the inspired air cause a progressive drop in the metabolic output.

When this fact was first obtained it seemed quite paradoxical to assume that the subjects with emphysema possessed an increased tolerance to carbon dioxide particularly in view of the fact that they were distressed with slight exercise. Later, experiments were conducted to test the tolerance limit, when it was found that there was a fairly definite concentration at which the subject developed acute symptoms such as headache, nausea, dizziness, etc. Further study of this point indicated that the "break" in emphysema depended on two factors, i. e., the concentration of the inspired carbon dioxide and the length of the breathing period. For example, Peter W. developed acute distress in ten minutes breathing 11.4 per cent. carbon dioxide. A similar "break," although not so sharp, occurred while breathing 6.8 per cent. carbon dioxide for twenty minutes. An attempt was made to find a definite inverse ratio between inspired carbon dioxide and time of inhalation by having the subject inspire various concentrations until symptoms of intolerance developed. The results showed clearly, as would be expected, that as the percentage of inspired carbon dioxide

was elevated the time required to produce signs of intolerance diminished, but no definite constant (carbon dioxid inspired multiplied by length of breathing period) was obtained. The failure to obtain such a constant was due in part to the difficulty of recognizing the "break" with low concentration, particularly in the longer experiments, since it is necessary to depend on the patient's subjective sensations.

It is apparent from the foregoing that the length of the breathing period must be kept reasonably constant in contrasting the normal with the emphysema. However, when this factor is controlled, comparison of the data shows a sluggish response in the case of emphysema (Fig. 2). Two possibilities are suggested for this: (1) an increased capacity for storage of carbon dioxid in the body fluids; (2) a change in the sensitivity of the respiratory center. It is conceivable that the functional activity of the respiratory center may be depressed in emphysema through a slow process of adaptation. Observations bearing on this phase of the subject are under way but sufficient facts are not at present available to warrant any definite conclusions.

Evidence suggesting an increased capacity for binding carbon dioxid is afforded by the high level of blood bicarbonate (Table 8). As the buffer value of body fluids is proportional to the bicarbonate content, it appears that up to a certain limit, the emphysema subject can bind more carbon dioxid than the normal. Consequently, higher percentages of the gas may be inspired before a change occurs in the H-ion concentration in the blood of sufficient magnitude to stimulate the respiratory center. This seems to account in part for the sluggish respiratory reaction observed.

The fact that the addition of carbon dioxid to blood raises not only the carbonic acid, but also the sodium bicarbonate content was first recognized by Zuntz. Later Gürber studied the question and concluded that carbon dioxid caused a passage of chlorids from the plasma into the corpuscles. Recently Fridericia¹² confirmed the work of other investigators by showing that as the carbon dioxid tension of blood is elevated, the carbon dioxid combining power of the plasma and the red cells is also raised. His results indicate further that the increased carbon dioxid combining power of the plasma is due chiefly to the passage of chlorid ions from the plasma into the corpuscles. The sodium thus liberated in the plasma combines with carbon dioxid to form more bicarbonate.

Experimental proof that the blood bicarbonate was elevated was obtained by me¹³ in cats made to breathe varying concentrations of

12. Fridericia, L. S.: *J. Biol. Chem.* **42**:245, 1920.

13. Scott, R. W.: *Am. J. Physiol.* **44**:196, 1917.

carbon dioxid. This was later confirmed by Henderson and Haggard¹⁴ On the other hand, there is much experimental and clinical evidence to show that the blood bicarbonate is diminished when acids other than carbon dioxid are added to the blood. It is clear, therefore, that the tissue carbonate is no fixed quantity, but may undergo wide variations, the H-ion concentration being maintained within normal limits. This was recently emphasized by Henderson and Haggard.¹⁵ They showed from animal experiments that there were four theoretical alterations in the normal free and combined carbon dioxid content of the blood. One of these, in which carbonic acid and sodium bicarbonate are both at a high level but the normal ratio is apparently maintained, is illustrated in emphysema. The progressive degenerative process in the lungs in this condition causes an increasing impediment to alveolar ventilation, with the consequent interference with gaseous exchange. This ultimately leads to a retention of carbon dioxid as well as a certain amount of chronic anoxemia. The high level of free carbon dioxid of the blood in emphysema is attained gradually so that ample time is afforded for the development of compensatory mechanisms. The maintenance of the body bicarbonate at a permanent high level appears as one important illustration. This enables the emphysematous subject to tolerate a high carbon dioxid tension in the blood normally and also affords a certain protection against undue fluctuations in H-ion concentration which might otherwise occur from metabolism. Considering the body bicarbonate as a chemical factor of safety, it appears that the emphysema subject can tolerate for short periods higher concentrations of inspired carbon dioxid than the normal. When, however, the tissue buffer is exceeded, there is little mechanical factor of safety as represented by pulmonary ventilation and acute distress develops suddenly. The normal subject on the other hand has a considerable pulmonary reserve and compensates for carbon dioxid retention by increasing ventilation. Consequently no sudden "break" occurs but discomfort develops gradually.

SUMMARY

1. Two patients with chronic pulmonary emphysema of the so-called "large lunged" type have been studied over a period of several months and compared with normal persons as controls.

2. It was found that the emphysematous patients breathed high percentages of carbon dioxid (from 8 to 10 per cent.) for ten and fifteen minute periods with relatively little increase in the minute volume, and without subjective symptoms of distress. Slightly higher

14. Henderson, Y., and Haggard, H. W.: *J. Biol. Chem.* **33**:343, 1917.

15. Henderson, Y., and Haggard, H. W.: *J. Biol. Chem.* **39**:163, 1919.

percentages were intolerable and caused a sharp "break" with symptoms of acute distress such as headache, nausea and dizziness. The concentration of inspired carbon dioxide necessary to produce signs of intolerance was found to vary inversely with the length of the breathing period.

3. There was a definite elevation in the free and combined carbon dioxide of the blood in emphysema, but the ratio $\frac{\text{H}_2\text{CO}_3}{\text{NaHCO}_3}$ was such as to maintain the H-ion concentration within normal limits.

4. It is suggested that the increased buffer of the body fluid in emphysema compensates to some extent for the impairment of pulmonary ventilation and offers a certain protection against undue fluctuations in H-ion concentrations which might otherwise occur.