THE RESPONSE TO RESPIRATORY RESISTANCE.

A Comparison of the Effects Produced by Partial Obstruction in the Inspiratory and Expiratory Phases of Respiration.

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The liability to fatigue of the respiratory center is a subject which needs to be studied. Davies, Haldane, and Priestley (1) were the first to investigate the manner in which breathing adapts itself to increased resistance, and the point at which the adaptation begins to fail. They showed that the normal response in man to respiratory resistance in both phases of respiration is slow and deep breathing. When the resistance is excessive respirations become progressively shallower and more frequent and the subjects then become cyanotic. Haldane and his coworkers believe that this is due to fatigue of the respiratory center. They believe anoxemia hastens greatly the onset of fatigue and the ease with which it is produced. They conclude that the mechanism involved in the immediate response is the Hering-Breuer reflex, pointing out that as a result of resistance, the time required for inflation or deflation of the lungs to reach the point at which the Hering-Breuer stimulus becomes effective is prolonged, that CO_2 accumulates in the meantime, and that the next respiration is deep and vigorous. The more or less sudden onset of rapid, shallow breathing Haldane interprets as evidence of fatigue of the respiratory center, with a resulting predominance of the peripheral stimuli over the central impulses normally governing breathing.

A study of these effects in animals was undertaken by us with several points in mind. We hoped for additional information as to the nature and origin of rapid and shallow breathing, which we have previously considered in both clinical and experimental studies (2–5). It seemed highly desirable to learn something about the liability to fatigue of so vital a structure as the respiratory center. Transferring the problem

to experimental animals rather than man, though it introduced such complications as the use of anesthetics, afforded the opportunity of allowing the experiments to go to their natural conclusion. It made it possible, too, to study the end-results of more or less prolonged periods of anoxemia and rapid and shallow breathing. It was soon learned that the response to resistance in inspiration is strikingly different from the response to resistance in expiration, both as regards functional and structural changes.

Method.

Dogs anesthetized with barbital-sodium were used. The dogs varied in weight from 6.8 to 23.5 kilos, but in every instance except one the weight of the animal was above 10 kilos. The barbital-sodium was dissolved in physiological sodium chloride solution and given intravenously in an amount sufficient to produce complete relaxation and a slow, steady respiratory rate. The initial dose was calculated on a basis of 0.3 gm. drug to 1 kilo body weight and the additional drug was given in repeated small quantities as necessary.[1] The rectal temperature was recorded at frequent intervals throughout the course of each experiment. As a precaution against the loss of heat each animal was wrapped snugly in woolen blankets and surrounded by warm air.[2]

When the animal had reached the desired state of anesthesia, tracheotomy was done, and a properly fitting rubber tube was tied firmly into the trachea. This tube, which was of such a length as not to increase the dog's natural dead space, communicated with one arm of a four-way metal tube. Two of the other branches of the four-way tube were connected by corrugated tubing of the usual type used in respiration experiments to inspiratory and expiratory valves. Low resistance valves of the kind recently described by Dr. C. V. Bailey[3] (6) were used in all experiments.

The fourth opening in the metal tube was connected to a rubber tambour by means of a short length of rubber pressure tubing. This tambour, moving with expiration and inspiration, activated a make and break contact in an electrical circuit which included an electromagnet "telephone" counter. By this arrangement the respiratory rate was automatically counted. Intratracheal pressure was measured by a water manometer communicating by means of a Y-tube with the

[1] A 5 per cent solution was used for this purpose.

[2] A cradle made by covering an arch of thin metal with hair felt was placed over the animal. Heat was supplied by an electric bulb suspended from the top of the arch. We have found that this is a much more efficacious way of maintaining the warmth of an animal than by use of an electric pad.

[3] These valves were kindly supplied us by Dr. Bailey.

four-way tracheal tube. The expired air was collected in a large Tissot spirometer.

To introduce resistances we used a specially constructed metal tap with an

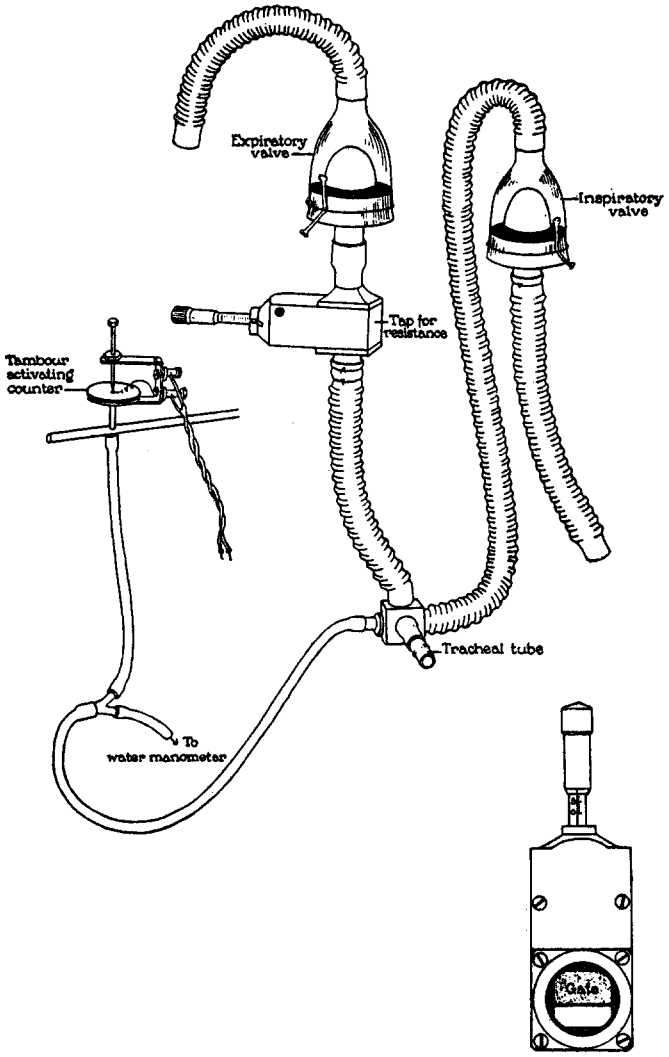

FIG. 1.

internal bore of 4 sq. cm. The tap was closed by means of a gate which was gradually lowered into its seat by a screw of such a pitch that one turn lowered the gate 1 mm. and accordingly diminished the lumen by 0.2 sq. cm. A scale permitted one

to read off at any time the cross-section area in sq. cm. This tap was introduced into the system at a point between the trachea and one of the respiratory valves. According to its position, resistance could be created either in the inspiratory or expiratory phases of respiration. The apparatus which we used is shown in diagram in Fig. 1.

When resistance to respiration is introduced by a tap of this sort the velocity of air flow varies as the square root of the driving pressure. With cotton wool resistance, however, which Haldane and his coworkers used, the air flow varies directly as the driving pressure. The intratracheal pressure may be assumed to represent the driving pressure. Velocity of air flow can thus be calculated if desired. We have chosen tap resistance because it is easier of manipulation and quantitative control. It was found that great reduction in the cross-section area of the tap was necessary before any change in type of breathing occurred.

All experiments were conducted on the same general plan and the observations fall into three periods; first, the period of control; second, the period of resistance; and, third, the period following release.

The observations include a record of respiratory rate, tidal air, minute volume of pulmonary ventilation, intratracheal pressure, cross-section area of the tap, and in some instances an additional study of the O_2 content, O_2 capacity, percentage oxygen saturation, CO_2 content, CO_2 tension, and pH of the arterial blood. The blood samples were withdrawn through a cannula in the femoral artery and collected without exposure to air in sampling tubes over mercury. The analyses of oxygen content and capacity, and of CO_2 content of the separated plasma or serum were made by the method of Van Slyke and Neill (7). The pH was estimated on serum by the colorimetric method of Hastings and Sendroy (8). From these data and the following formula (9) the partial pressure of carbon dioxide expressed in mm. Hg was calculated, assuming pK' to be 6.115.

$$pCO_2 = \frac{[CO_2]}{0.031 \times (1 + 10^{pH - 6.115})}$$

where CO_2 content is given in terms of millimols per liter.

The records of respiratory rate and pulmonary ventilation were made over 5 minute periods, and were repeated several times under each condition. During the time of resistance the cross-section area of the tap was reduced to a degree that created a negative or positive intratracheal pressure of from 10 to 20 cm. of H_2O, and this was maintained over intervals ranging from 20 to 145 minutes. The readings in the final period were taken when the respiratory rate had reached a constant, or approximately constant, level.

In some experiments the animals breathed room air. In others they breathed 90 to 95 per cent oxygen from a Douglas bag. After the final observations the experiment was terminated by the intravenous injection of from 20 to 30 cc. of a saturated solution of magnesium sulfate. At autopsy attention was given to the presence or absence of froth in the trachea, pleural effusions and gross edema of

the mediastinal tissues and lungs, and to the color of the lungs. The degree of hypostatic congestion, the lung weights, the heart weights, and the lung-heart ratio were also observed.

TABLE I.

Experiment 7. The Effect of Resistance in the Inspiratory Phase of Respiration.

Conditions	Time	Gas inspired	Respiratory rate per min.	Tidal air	Minute volume	CO_2	pCO_2	pH	Arterial blood		
									O_2 content	O_2 capacity	Saturation
				cc.	*liters*	*mM*	*mm. Hg*		*mM*	*mM*	*per cent*
Control period	11.57 to 12.46	Room air	19	273	5.11	25.8	32.91	7.50	8.47	9.02	93.9
During resistance	12.46 to 2.55	Room air	30	92	2.78	28.1	53.15	7.32	6.29	9.39	67.0
After release	2.55 to 3.48	Room air	40	225	9.00	24.5	28.63	7.54	8.89	9.66	92.0

Weight of animal, 23.5 kilos.
Total barbital-sodium, 0.35 gm. per kilo body weight.
Cross-section area of tap finally reduced to 0.05 sq. cm.
Negative intratracheal pressure, 20 cm. H_2O.
Duration of greatest resistance, 113 min.
Lung-heart ratio, 1.66.

EXPERIMENTS.

I. Experiments with Resistance in the Inspiratory Phase.

Five experiments were performed in which the cross-section of the tap opening was 0.05 sq. cm. In these experiments the negative intratracheal pressure during the inspiratory phase varied from 11 to 20 cm. of H_2O. In a sixth experiment a conspicuous effect on breathing was obtained with a cross-section area of 0.1 sq. cm. All animals showed an increase in respiratory rate and a decrease in tidal air. The percentage increase in respiratory rate ranged from a low extreme of 58 per cent to a high extreme of 310 per cent, and the percentage

decrease in tidal air ranged from a high extreme of 88.9 per cent to a low extreme of 56.1 per cent. The experimental data are presented in Tables I to IV.

Examination of Table I will bring out the following points. A dog anesthetized with barbital-sodium was breathing at the rate of 19 per

TABLE II.

Experiment 1A. The Effect of Resistance in the Inspiratory Phase of Respiration.

Conditions	Time	Gas inspired	Respiratory rate per min.	Tidal air	Minute volume	CO_2	pCO_2	pH	Arterial blood		
									O_2 content	O_2 capacity	Saturation
				cc.	*liters*	*mM*	*mm. Hg*		*mM*	*mM*	*per cent*
Control period	12.47 to 1.35	90–95 per cent O_2	15	189	2.73	26.29	41.8	7.40	9.46	8.77	107.8
During resistance	1.35 to 3.04	90–95 per cent O_2	47	21	1.00	32.08	80.2	7.19	5.27	10.44	50.4
After release	3.04 to 3.24	90–95 per cent O_2	139	75	10.4	25.61	49.7	7.31	5.75	10.66	54.0

Weight of animal, 14 kilos.
Total barbital-sodium, 0.37 gm. per kilo body weight.
Cross-section area of tap finally reduced to 0.1 sq. cm.
Negative intratracheal pressure not recorded.
Duration of greatest resistance, 19 min.
Lung-heart ratio, not determined.

minute. The caliber of the tap was gradually reduced until it had reached 0.05 sq. cm. This was sufficient to cause a negative intratracheal pressure at the height of inspiration equal to 20 cm. H_2O. Under these conditions the rate accelerated to 30. This was accompanied by a decrease in tidal air from 273 cc. to 92 cc. and a resulting

decrease in minute volume of pulmonary ventilation from 5.11 liters to 2.78 liters. These changes occurred while the animal was breathing room air. They were associated with a rise in pCO_2 from 32.91 mm. to 53.15 mm., a drop in pH from 7.50 to 7.32, and a decrease in the percentage oxygen saturation of the arterial blood from 93.9 to 67.0. Resistance was maintained for 113 minutes. 65 minutes after the

TABLE III.

Experiment 5. The Effect of Resistance in the Inspiratory Phase of Respiration.

Conditions	Time	Gas inspired	Respiratory rate per min.	Tidal air	Minute volume	CO_2	pCO_2	pH	Arterial blood		
									O_2 content	O_2 capacity	Saturation
				cc.	*liters*	*mM*	*mm. Hg*		*mM*	*mM*	*per cent*
Control period	12.35 to 1.31	Room air	8	249	1.98	25.26	52.05	7.28	9.37	10.34	90.6
During resistance	1.31 to 3.49	Room air	17	80	1.36	29.40	61.95	7.27	6.00	10.48	57.3
After resistance	3.49 to 4.07	Room air	8	285	2.28	25.75	53.05	7.28	9.17	10.01	91.6

Weight of animal, 17.25 kilos.
Total barbital-sodium, 0.32 gm. per kilo body weight.
Cross-section area of tap finally reduced to 0.05 sq. cm.
Negative intratracheal pressure, 11.5 cm. H_2O.
Duration of greatest resistance, 124 min.
Lung-heart ratio, 1.71.

valve was opened the respiratory rate was 40, the tidal air was 225 cc., and the minute volume was 9 liters. The pCO_2 had dropped to 28.63 mm., the pH had risen to 7.54, and the percentage oxygen saturation of the arterial blood was again normal, 92 per cent. Postmortem examination showed no froth in the trachea, no effusion into either pleural cavity, and no edema of the mediastinal tissues. The surface of the lungs appeared granular; the color was a bright pink. Hy-

postasis was limited to the dependent parts of the lobes. The lung-heart ratio was 1.66.

In Experiment 1A (Table II) the animal breathed 90 to 95 per cent oxygen. In spite of this, after inspiring against resistance for 21 minutes the percentage oxygen saturation of the arterial blood dropped from 107.8 to 50.4. The rate accelerated from 15 to 47 and the tidal air dropped from 189 cc. to 21 cc. The tension of CO_2 rose from 41.8 mm. to 80.5 mm. and the pH decreased from 7.40 to 7.19. The final estimations in this animal were made 34 minutes after the resistance was removed. It should be noted that the respiratory rate at this time was 139, the tidal air only 75 cc., the tension of carbon dioxide still above the original level, and the percentage oxygen saturation of the arterial blood only 54. Autopsy showed a considerable amount of frothy liquid in the trachea and 10 to 15 cc. of clear fluid in each pleural cavity. The lungs were boggy with fluid.

In Experiment 5 (Table III) the increase in CO_2 tension during the period of resistance was slight, and the pH did not change. The animal breathed air, and the percentage oxygen saturation of the arterial blood dropped from 90.6 to 57.3. This accompanied an increase in respiratory rate from 8 to 17 and a decrease in tidal air from 249 cc. to 80 cc. Resistance was continued 124 minutes. 41 minutes after release all functions were at the normal level. Autopsy in this case showed no froth in the trachea, no effusion into either pleural cavity, and no edema of the mediastinal tissues. The lungs were diffusely coral-pink in color. Hypostatic congestion was slight. The lung-heart ratio was 1.7.

The data for Experiments 2, 3, and 4 are grouped together in Table IV. The results in general are consistent with those obtained in Experiments 1A and 7. The increase in minute volume during the period of resistance in Experiment 3 was a single occurrence. In Experiments 2 and 3 the animals breathed 90 to 95 per cent oxygen and maintained a pink color of the tongue and mucous membranes throughout. It seems safe to conclude that resistance in these animals did not produce anoxemia. At autopsy pleural effusions were found in Experiments 3 and 4. In Experiment 3 there was in addition an excessive edema of the mediastinal tissues. The color of the lungs in all cases was a coral-pink, of varying shades of intensity, but deeper in every instance

TABLE IV.

Experiments 2, 3, and 4.

The Effect of Resistance in the Inspiratory Phase of Respiration.

Conditions	Experiment 2					Experiment 3					Experiment 4				
	Time	Gas inspired	Respiratory rate per min.	Tidal air	Minute volume	Time	Gas inspired	Respiratory rate per min.	Tidal air	Minute volume	Time	Gas inspired	Respiratory rate per min.	Tidal air	Minute volume
				cc.	*liters*				*cc.*	*liters*				*cc.*	*liters*
Control period	2.27 to 2.41	90–95 per cent O_2	18	114	2.09	11.01 to 11.22	90–95 per cent O_2	10	184	1.84	12.03 to 1.29	Room air	19	203	3.86
During resistance	2.41 to 5.15	90–95 per cent O_2	35	50	1.76	11.22 to 2.18	90–95 per cent O_2	41	64	2.62	1.29 to 4.30	Room air	39	80	3.24
After release	5.15 to 6.04	90–95 per cent O_2	44	90	3.98	2.18 to 3.40	90–95 per cent O_2	118	105	12.42	4.30 to 5.14	Room air	34	172	5.84

Weight of animal, 6.8 kilos.

Total barbital-sodium, 0.46 gm. per kilo body weight.

Cross-section area of tap finally reduced to 0.05 sq. cm.

Negative intratracheal pressure, 14.5 cm. H_2O.

Duration of greatest resistance, 38 min.

Lung-heart ratio, 1.75.

Weight of animal, 17 kilos.

Total barbital-sodium, 0.30 gm. per kilo body weight.

Cross-section area of tap finally reduced to 0.05 sq. cm.

Negative intratracheal pressure, 15.5 cm. H_2O.

Duration of greatest resistance, 145 min.

Lung-heart ratio, 2.12.

Weight of animal, 16.5 kilos.

Total barbital-sodium, 0.33 gm. per kilo body weight.

Cross-section area of tap finally reduced to 0.05 sq. cm.

Negative intratracheal pressure, 15 cm. H_2O.

Duration of greatest resistance, 70 min.

Lung-heart ratio, 1.53.

than the shade of a normal lung. Hypostatic congestion in Experiments 3 and 4 was moderate. The lungs in Experiment 2 were completely free of hypostasis.

The results of these experiments may be summed up as follows: Resistance to inspiration results in a fall in intratracheal pressure which is associated with an increase in respiratory rate and a decrease in tidal air. In most instances these are accompanied by a severe limitation of the minute volume of pulmonary ventilation. The effects come on suddenly when the cross-section area of the inspiratory passageway is reduced to 0.1 sq. cm. or 0.05 sq. cm. Anoxemia accompanies these changes, but may be prevented by the inhalation of 90 to 95 per cent oxygen. Associated with the anoxemia there is a retention of carbon dioxide and usually a drop in pH.

When resistance is removed the respiratory rate continues to be rapid. In the majority of instances the rates were higher following release than they were during the period of resistance. Release, however, permits an increase in tidal air and minute volume, and as a result of this, there is a fall in pCO_2, a rise in pH, and in some cases a complete disappearance of anoxemia. On only one occasion when resistance was removed did the respiratory rate return to the control level, with a corresponding change in CO_2 tension and oxygen saturation. The postmortem picture found in these dogs may be characterized by congestion and edema of the lungs.

II. Experiments with Resistance in the Expiratory Phase.

In striking contrast to the experiments with resistance in the inspiratory phase, partial obstruction to expiration slows the respiratory rate. This occurs with varying effects on tidal air, but with a constant decrease in minute volume of pulmonary ventilation. The results of four experiments are presented in Tables V to VII.

In Experiment 11 (Table V) the dog breathed at the rate of 25 before resistance was introduced in expiration. In the presence of restriction equal to 0.1 sq. cm. the rate dropped to 12 and the tidal air increased from 85 cc. to 122 cc. This was accompanied by a decrease in minute volume from 2.12 liters to 1.46 liters with only slight changes in pH and blood gases. The animal exhaled against resistance for 96 minutes. 24 minutes after the tap was opened the

respiratory rate had returned to the original level—thus distinguishing this type of experiment from the ones in which resistance was introduced into inspiration. No other conspicuous changes occurred. The data are given in Table V.

In Experiment 12 (Table VI) a drop in the respiratory rate from 22 to 11 was accompanied by a decrease in tidal air from 70 cc. to 49

TABLE V.

Experiment 11. The Effect of Resistance in the Expiratory Phase of Respiration.

Conditions	Time	Gas inspired	Respiratory rate per min.	Tidal air	Minute volume	CO_2	pCO_2	pH	Arterial blood		
									O_2 content	O_2 capacity	Saturation
				cc.	*liters*	*mM*	*mm Hg*		*mM*	*mM*	*per cent*
Control period	12.08 to 12.39	Room air	25	85	2.12	26.62	45.15	7.37	6.35	6.68	95.1
During resistance	12.39 to 2.30	Room air	12	122	1.46	25.87	40.23	7.41	6.69	7.15	93.6
After release	2.30 to 3.12	Room air	24	110	2.64	24.51	35.72	7.44	6.24	6.59	94.7

Weight of animal, 10.5 kilos.
Total barbital-sodium, 0.32 gm. per kilo body weight.
Cross-section area of tap finally reduced to 0.1 sq. cm.
Positive intratracheal pressure, 13 cm. H_2O.
Duration of greatest resistance, 96 min.
Lung-heart ratio, 1.51.

cc. and a decrease in minute volume from 1.56 liters to 0.48 liter. The animal breathed room air, and, as could be anticipated from the great reduction in pulmonary ventilation, developed a severe anoxemia. The CO_2 content of the serum rose from 29.13 mM to 32.48 mM, the pCO_2 from 51.1 mm. Hg to 70.0 mm., and the pH dropped from 7.36 to 7.26. The period of resistance was 96 minutes. When the resistance was removed the respiratory rate returned to within five

breaths of the control level. Coincident with the recovery in rate there was an increase in tidal air and minute volume, with the result that the anoxemia was completely relieved and the pCO_2 and pH returned to their previous values.

In Experiments 1B and 10 (Table VII) there was likewise a noticeable decrease in respiratory rate and minute volume.

TABLE VI.

Experiment 12. The Effect of Resistance in the Expiratory Phase of Respiration.

Conditions	Time	Gas inspired	Respiratory rate per min.	Tidal air	Minute volume	CO_2	pCO_2	pH	Arterial blood		
									O_2 content	O_2 capacity	Saturation
				cc.	*liters*	*mM*	*mm. Hg*		*mM*	*mM*	*per cent*
Control period	12.40 to 1.14	Room air	22	70	1.56	29.13	51.1	7.36	7.01	7.53	93.1
During resistance	1.14 to 2.50	Room air	11	49	0.48	32.48	70.00	7.26	4.41	8.18	53.9
After release	2.50 to 3.31	Room air	17	84	1.42	28.71	48.23	7.38	7.43	7.70	96.5

Weight of animal, 11.5 kilos.
Total barbital-sodium, 0.30 gm. per kilo body weight.
Cross-section area of tap finally reduced to 0.1 sq. cm.
Positive intratracheal pressure, 12 cm. H_2O.
Duration of greatest resistance, 96 min.
Lung-heart ratio, 1.14.

The postmortem examinations in this group of experiments brought out the following points: None of the animals showed pleural effusions, frothy fluid in the trachea, edema of the mediastinal tissues, or gross edema of the lungs. The color of the lung surface in all instances was a diffuse coral-pink, with the same slight variations in intensity as were noted in the previous series. Perhaps the most striking observation was a complete absence of hypostatic congestion in Ex-

TABLE VII.

Experiments 1B and 10. The Effect of Resistance in the Expiratory Phase of Respiration.

Conditions	Experiment 1B					Experiment 10				
	Time	Gas inspired	Respiratory rate per min.	Tidal air	Minute volume	Time	Gas inspired	Respiratory rate per min.	Tidal air	Minute volume
				cc.	*liters*				*cc.*	*liters*
Control period	3.15 to 3.43	90–95 per cent O_2	12	166	2.03	1.40 to 2.22	Room air	16	162	2.53
During resistance	3.43 to 6.07	90–95 per cent O_2	9	184	1.59	2.22 to 4.10	Room air	9	138	1.24
After release	6.07 to 6.26	90–95 per cent O_2	8	200	1.68		Room air	—*	—	—

Weight of animal, 13.5 kilos.

Total barbital-sodium, 0.32 gm. per kilo body weight.

Cross-section area of tap finally reduced to 0.1 sq. cm.

Positive intratracheal pressure not recorded.

Duration of greatest resistance, 20 min.

Lung-heart ratio, not determined.

Weight of animal, 11 kilos.

Total barbital-sodium, 0.37 gm. per kilo body weight.

Cross-section area of tap finally reduced to 0.1 sq. cm.

Positive intratracheal pressure, 10 cm. H_2O.

Duration of greatest resistance, 74 min.

Lung-heart ratio, 1.04.

* The resistance was not released in this experiment.

periments 1B and 12, with only a slight degree of hypostasis in Experiments 10 and 11. The lung-heart ratios, calculated in three out of the four instances (Experiments 10, 11, and 12) were 1.04, 1.51, and 1.14, respectively. All of these figures are lower than those

obtained with resistance in the inspiratory phase, though at times the difference is very slight.

These experiments may be summarized thus: Resistance to expiration slows the respiratory rate and limits the minute volume of pulmonary ventilation. These changes may or may not be accompanied by a retention of carbon dioxide and a low oxygen saturation of the arterial blood. The effects come on suddenly when the cross-section area of the tap is reduced to 0.1 sq. cm. With removal of resistance all functions return to their normal, or approximately normal, levels. No characteristic pulmonary pathology occurs as the result of resistance to expiration.

DISCUSSION.

The second group of experiments is easier of interpretation than the first. With resistance to expiration there is a mechanical limitation to pulmonary ventilation which may result in carbon dioxide retention and insufficient oxygenation of the blood in the lungs. When the mechanical limitation is removed both the breathing and the state of the blood return to normal and no apparent damage to the lungs has occurred.

The interpretation of the first group of experiments, those dealing with resistance to inspiration, is not so clear. Here, too, we have a mechanical limitation to pulmonary ventilation, but the result in this case is rapid and shallow breathing rather than slow and shallow. There is, as in the other group, inadequate ventilation of the blood. But, even after the resistance had been removed, in many experiments the respiratory rate continued to be rapid, and in some this was true even though the blood had returned to the state found during the control period.

What has happened to the animal which causes it to maintain a rapid respiratory rate in spite of the fact that no longer is there any resistance to the free passage of air into the lungs? The explanation must be sought for in alterations to one of the organ systems having to do with respiratory rhythm. Has the respiratory center itself been damaged or fatigued? There does not appear to be any direct evidence for this assumption. The more or less prolonged period of anoxemia and acidosis which existed in the inspiratory ex-

periments was present in one of the expiratory experiments as well, and yet in this animal there was no accelerated rate after release of resistance. Have the muscles which have to do with inspiration become fatigued as the result of resistance? This hardly seems to be a plausible explanation because in none of the experiments was there a fall in the negative pressure produced in the trachea. Such a fall would have suggested a lessened effort at expansion of the lungs.

The explanation may be sought for more probably in the state of the lungs themselves. The decreased expansion may give rise to a state of pulmonary congestion and this, together with the heightened negative pressure, may result in a seepage of fluid into the pulmonary parenchyma and pleural sacs, as has been suggested by Graham (10). Indeed, it has been experimentally shown by Huggett (11) that inspiratory obstruction increases the minute and stroke volumes of the heart, while expiratory obstruction produces a reverse effect. An augmented blood flow through the lungs may be responsible for the congestion and fluid transudation which were actually observed. It was not unlike that seen in dogs with multiple experimental emboli of the pulmonary capillaries and arterioles (2), nor unlike the changes found after clamping and releasing the artery to one lung (4). In these conditions, too, persistent rapid and shallow breathing occurred.

The local changes in the lung may then perhaps be regarded as responsible for this phenomenon. The normal Hering-Breuer stimuli are increased and predominate. Whether this in itself is evidence of fatigue of the respiratory center, as Haldane believes, is a matter for conjecture.

SUMMARY AND CONCLUSIONS.

1. A study has been made of the effects of resistance to respiration in the inspiratory and expiratory phases.

2. Resistance to inspiration caused an increase in respiratory rate, a decrease in tidal air, and in most instances a severe limitation of the minute volume of pulmonary ventilation. Anoxemia and acidosis accompanied these changes.

3. When resistance was removed the respiratory rate continued to be rapid, but the tidal air and minute volume increased. As a result of this there was a fall in pCO_2, a rise in pH, and in some cases a complete disappearance of anoxemia.

3. Resistance to expiration slowed the respiratory rate and produced a constant decrease in the minute volume of pulmonary ventilation. Anoxemia and carbon dioxide retention occurred, but were less pronounced than in the inspiratory experiments. Release of resistance to expiration resulted in a return of all functions to their normal, or approximately normal, levels.

4. A difference in the gross pulmonary pathology found at autopsy in these two types of experiments has been described, and an attempt has been made to correlate changes in function with changes in structure.

5. No direct evidence has been supplied for the liability to fatigue of the respiratory center.

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