# THE SENSITIVENESS OF THE RESPIRATORY CENTRE TO CARBONIC ACID, AND THE DEAD SPACE DURING HYPERPNŒA.

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In a recent paper[1] attention has been drawn to the great sensitiveness of the respiratory centre to $CO_2$. The actual experiments described in that paper indicated that a rise of about 0·3 % in the alveolar $CO_2$-pressure was sufficient to cause the alveolar ventilation of the lungs to be increased by 100 % above the resting value. At the same time arguments were advanced to show that in all probability this observed value was really too high, as, owing to the technique adopted, it was impossible to make allowance for any increase in the metabolism during the experiments, the alteration in the alveolar ventilation being deduced from a comparison of the differences of the concentration of $CO_2$ in the alveolar and inspired airs.

Supposing that the metabolism had been increased while air containing $CO_2$ was being breathed the actual hyperpnœa would have been greater than the calculated value indicated, and it was finally concluded that a rise of about 0·22 % or 1·6 mm. of $CO_2$-pressure in the alveolar air was really sufficient to cause an increase of 100 % in the alveolar ventilation. It was also shown that erroneous conclusions were likely to be drawn if the observations were made before the body had got into equilibrium with the particular $CO_2$ mixture breathed.

In the course of some other experiments it became necessary to verify these conclusions as to the sensitiveness of the respiratory centre to $CO_2$, and to obtain some more precise quantitative relationship between the alveolar ventilation and the alveolar $CO_2$-pressure than is implied by the somewhat casual expression of 100 % increase above the resting ventilation.

[1] Campbell, Douglas, Haldane and Hobson. This *Journal*, XLVII. p. 301. 1913.

Our experiments were made in an air-tight chamber of about 250 cub. ft. or 7000 litres capacity. The size of this chamber was sufficient to enable the observer to manipulate all the necessary apparatus while the subject of the experiment, who was in all cases C. G. D., remained sitting at rest in a deck chair. Two series of experiments were made in atmospheres containing different amounts of $CO_2$ so as to cause different degrees of hyperpnœa.

In the first series of experiments (nos. 1 to 3) our procedure was as follows. The subject first of all sat at rest in the chamber with the door open and an electric fan blowing fresh air into it. After the expiration of a quarter of an hour a pair of samples of the alveolar air was taken by the Haldane-Priestley method in vacuous tubes, and three minutes later a sample of the expired air was collected in a gas bag for the determination of the volume of air breathed and the total respiratory exchange by the Douglas method[1]. These two observations were repeated about 10 minutes later, *i.e.* about half an hour after entering the chamber. After this the door of the chamber was shut, and 11 cub. ft. of $CO_2$ were passed into it through a gas meter by the second observer who was stationed outside, thorough mixture of the $CO_2$ with the air in the chamber being ensured by the fan. The percentage of $CO_2$ in the air in the chamber was thereby raised to about 4·5 %, the oxygen percentage being reduced to about 19·8 %: during the course of the experiment the $CO_2$ percentage rose at the rate of about 0·6 % per hour, the oxygen percentage being correspondingly reduced. In order that the subject might get into full equilibrium with the mixture breathed a period of half an hour was allowed to elapse and then another pair of alveolar samples was taken, followed two minutes later by a sample to allow of the determination of the total respiratory exchange. About half an hour later, *i.e.* one hour after running the $CO_2$ into the chamber, these observations were repeated. A further period of about ten minutes was allowed to elapse and then another pair of alveolar samples was taken. After this the door of the chamber was opened and the fan so placed as to direct a large current of fresh air through the chamber. In two of the experiments two further pairs of alveolar air samples were taken 10 minutes and 20 minutes respectively after the door of the chamber was opened. The subject of the experiment remained seated throughout practically the whole of the experiment, and endeavoured to keep himself in a uniform condition of rest especially in the 15 minutes immediately preceding the collection

[1] This *Journal*, XLII. p. xvii. 1911.

of the samples. The samples of the expired air collected in the bag were measured in the chamber by the observer, all analyses being done subsequently after leaving the chamber. Samples of the inspired air were taken between the two sets of observations made before closing the chamber, immediately after taking each pair of alveolar samples (and therefore just before taking each sample for the determination of the total respiratory exchange) while the chamber was closed, and finally just after the first pair of alveolar samples had been taken after opening the chamber.

In the second series of experiments (nos. 4–7) about 8½ cubic feet of $CO_2$ were passed into the chamber raising the initial $CO_2$ percentage to about 3½ %, and there was therefore considerably less hyperpnœa than in the first series. We consequently modified the technique a little as the differences in the composition of the various air samples were likely to be smaller, and we were anxious to minimise the chances of error in taking the alveolar air samples.

Instead of taking a single alveolar sample in a vacuous tube we took four equal small samples from the last portion of four different deep expirations into the same gas sampling tube by allowing equal amounts of mercury, with which the tube had previously been filled, to run out. Separate composite samples were obtained from deep expirations given, as in the original Haldane-Priestley method, at the end of a normal inspiration and of a normal expiration. We felt that by this means we should obtain a fairer average composition of the alveolar air, and since there were only two analyses to be made instead of eight, as there would have been if we had followed the original Haldane-Priestley method, much labour was saved. In practice the deep expirations were given alternately at the end of a normal inspiration and of a normal expiration.

After taking a composite sample of the alveolar air and a sample for the determination of the total respiratory exchange before the chamber was closed we waited, as in the previous series, for 30 minutes before commencing observations in the atmosphere containing $CO_2$. We then took in succession a composite sample of the alveolar air, a sample for the determination of the total respiratory exchange, another composite sample of the alveolar air, and another sample for the respiratory exchange, allowing an interval of three minutes between the different samples. In experiments 6 and 7 further samples for determining the composition of the alveolar air and the respiratory exchange were taken commencing 20 minutes after opening the door of

the chamber. As it took 12 minutes to collect the composite samples of the alveolar air, since time had to be allowed for the breathing to become normal after giving each deep expiration before giving the next one, we took samples of the inspired air in the middle of taking the samples of the alveolar air and of taking those for determining the respiratory exchange while the chamber was closed. The total time during which we breathed air containing $CO_2$ was about an hour and a quarter.

We purposely remained in the chamber for a considerable time after adding the $CO_2$ to the air in the hope of ensuring that we were in equilibrium with the mixture breathed before commencing the observations, for the first effect of breathing air rich in $CO_2$ is to cause a retention of $CO_2$ in the body, *i.e.* a diminished output of the gas from the body and consequently a smaller degree of hyperpnœa than would be obtained in the absence of such retention. As a consequence of this the respiratory quotient is at first very low and only regains its normal level slowly.

Table I contains the figures obtained for the total respiratory exchange while normal air was being breathed and during the hyperpnœa induced by the addition of $CO_2$ to the inspired air. In this and the succeeding tables the observations are arranged in the order in which they were made.

In Exps. 1 to 3 the respiratory quotients during the hyperpnœa are not materially different from those obtained while breathing normal air, with the exception of the last observation in Exp. 1 where there was a rise of the respiratory quotient. The subject had therefore attained equilibrium with the $CO_2$ mixture breathed. In Exps. 4 to 7, however, the respiratory quotients during the hyperpnœa were on the whole definitely lower than those obtained when breathing normal air, a fact which is suggestive of incomplete equilibrium, notwithstanding the long duration of the experiments. If this is true it might owe its explanation to the slight effect produced on the circulation rate by so small a rise in the alveolar $CO_2$-pressure and lung ventilation.

The total respiratory exchange was with few exceptions somewhat less during the hyperpnœa than during the preliminary periods. It is, however, not fair to compare from the point of view of the metabolism the values obtained during the early part of the experiments with those obtained during the time that the $CO_2$ mixture was being breathed, as the resting metabolism would tend to fall after sitting still for so long a time. This is confirmed by the low values obtained in Exps. 6 and 7

for the total respiratory exchange when normal air was again breathed at the close of the experiments.

TABLE I.

| | Normal air | | | Air containing $CO_2$ | | |
|---|---|---|---|---|---|---|
| | Respiratory exchange in c.c. per min. at S.T.P. | | | Respiratory exchange in c.c. per min. at S.T.P. | | |
| Number | $O_2$ | $CO_2$ | Respiratory quotient | $O_2$ | $CO_2$ | Respiratory quotient |
| 1 | 314 | 260 | 0·828 | — | — | — |
| | 305 | 249 | 0·816 | — | — | — |
| | — | — | — | 352 | 291 | 0·826 |
| | — | — | — | 358 | 330 | 0·921 |
| 2 | 290 | 230 | 0·793 | — | — | — |
| | 276 | 212 | 0·768 | — | — | — |
| | — | — | — | 277 | 220 | 0·795 |
| | — | — | — | 279 | 219 | 0·785 |
| 3 | 329 | 261 | 0·794 | — | — | — |
| | 312 | 237 | 0·760 | — | — | — |
| | — | — | — | 304 | 234 | 0·770 |
| | — | — | — | 310 | 242 | 0·781 |
| Average of 1–3 | 304 | 242 | 0·793 | 313 | 256 | 0·813 |
| 4 | 307 | 238 | 0·776 | — | — | — |
| | — | — | — | 345 | 235 | 0·681 |
| | — | — | — | 304 | 244 | 0·802 |
| 5 | 344 | 266 | 0·773 | — | — | — |
| | — | — | — | 304 | 217 | 0·714 |
| | — | — | — | 294 | 230 | 0·782 |
| 6 | 306 | 230 | 0·752 | — | — | — |
| | — | — | — | 296 | 217 | 0·733 |
| | — | — | — | 282 | 205 | 0·727 |
| | 280 | 225 | 0·804 | — | — | — |
| 7 | 303 | 251 | 0·828 | — | — | — |
| | — | — | — | 276 | 217 | 0·787 |
| | — | — | — | 277 | 208 | 0·751 |
| | 268 | 223 | 0·832 | — | — | — |
| Average of 4–7 | 301 | 239 | 0·794 | 297 | 222 | 0·747 |

Table II shows the concentration of $CO_2$ in the inspired, expired and alveolar airs. The figures for the alveolar air represent the mean of the determinations made at the end of a normal inspiration and of a normal expiration. We have not thought it necessary to give these latter values separately, as the difference between them was but small, and of the same order of magnitude during the quiet breathing and the hyperpnœa. In Exps. 1 to 3 the samples taken at the end of expiration

TABLE II.

| | Normal air | | | | Air containing $CO_2$ | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Alveolar air | | | | Alveolar air | |
| Number | Inspired $CO_2$ % | Expired $CO_2$ % | $CO_2$ % | $CO_2$ pressure in mm. Hg | Inspired $CO_2$ % | Expired $CO_2$ % | $CO_2$ % | $CO_2$ pressure in mm. Hg |
| 1 | 0·11 | 3·49 | 5·73 | 40·8 | — | — | — | — |
| | — | 3·34 | 5·79 | 41·2 | — | — | — | — |
| | — | — | — | — | 4·74 | 5·66 | 6·26 | 44·6 |
| | — | — | — | — | 5·04 | 5·86 | 6·35 | 45·2 |
| | — | — | — | — | 5·17 | — | 6·34 | 45·1 |
| 2 | 0·06 | 3·19 | 5·49 | 39·0 | — | — | — | — |
| | — | 3·05 | 5·60 | 39·8 | — | — | — | — |
| | — | — | — | — | 4·86 | 5·67 | 6·16 | 43·8 |
| | — | — | — | — | 5·15 | 5·92 | 6·17 | 43·9 |
| | — | — | — | — | 5·28 | — | 6·23 | 44·3 |
| | 0·10 | — | 5·56 | 39·6 | — | — | — | — |
| | — | — | 5·61 | 39·9 | — | — | — | — |
| 3 | 0·04 | 3·47 | 5·57 | 40·1 | — | — | — | — |
| | — | 3·29 | 5·36 | 38·5 | — | — | — | — |
| | — | — | — | — | 4·71 | 5·63 | 5·98 | 43·0 |
| | — | — | — | — | 5·01 | 5·81 | 6·13 | 44·1 |
| | — | — | — | — | 5·17 | — | 6·02 | 43·3 |
| | 0·10 | — | 5·25 | 37·7 | — | — | — | — |
| | — | — | 5·38 | 38·7 | — | — | — | — |
| Average of 1–3 | 0·09 | 3·31 | 5·53 | 39·5 | 5·01 | 5·76 | 6·18 | 44·1 |
| 4 | 0·05 | 3·20 | 5·77 | 40·8 | — | — | — | — |
| | — | — | — | — | 3·47 | — | 5·96 | 42·1 |
| | — | — | — | — | 3·59 | 5·03 | — | — |
| | — | — | — | — | 3·77 | — | 5·87 | 41·5 |
| | — | — | — | — | 3·77 | 5·19 | — | — |
| 5 | 0·06 | 3·51 | 5·77 | 40·1 | — | — | — | — |
| | — | — | — | — | 4·12 | — | 6·31 | 43·9 |
| | — | — | — | — | 4·28 | 5·71 | — | — |
| | — | — | — | — | 4·43 | — | 6·43 | 44·7 |
| | — | — | — | — | 4·51 | 5·86 | — | — |
| 6 | 0·07 | 3·40 | 5·73 | 39·8 | — | — | — | — |
| | — | — | — | — | 4·05 | — | 6·06 | 42·1 |
| | — | — | — | — | 4·18 | 5·58 | — | — |
| | — | — | — | — | 4·31 | — | 6·07 | 42·1 |
| | — | — | — | — | 4·45 | 5·70 | — | — |
| | 0·08 | 3·37 | 5·60 | 38·9 | — | — | — | — |
| 7 | 0·03 | 3·44 | 5·89 | 40·8 | — | — | — | — |
| | — | — | — | — | 3·75 | — | 6·03 | 41·8 |
| | — | — | — | — | 3·90 | 5·45 | — | — |
| | — | — | — | — | 4·03 | — | 6·10 | 42·3 |
| | — | — | — | — | 4·17 | 5·54 | — | — |
| | 0·08 | 3·29 | 5·67 | 39·3 | — | — | — | — |
| Average of 4–7 | 0·06 | 3·37 | 5·74 | 40·0 | 4·05 | 5·51 | 6·10 | 42·6 |

contained on an average 0·13 % more $CO_2$ when breathing normal air and 0·10 % more $CO_2$ when breathing the $CO_2$ mixture than did the samples taken at the end of inspiration: in Exps. 4 to 7 these differences were respectively 0·15 % and 0·12 %. In Exps. 1 to 3 the average oxygen percentages were 20·88 %, 16·99 % and 14·35 % in the inspired, expired and alveolar air respectively, and 19·10 %, 18·24 % and 17·59 % whilst breathing the air containing $CO_2$: in Exps. 4 to 7 these values were 20·89 %, 16·90 % and 13·57 % whilst breathing normal air, and 19·35 %, 17·50 % and 16·58 % whilst breathing the air containing $CO_2$.

It will be seen that the effect of breathing air containing about 5 % of $CO_2$ was to cause a rise in the alveolar $CO_2$-pressure of about 4½ mm., and of breathing air containing about 4 % of $CO_2$ a rise of about 2½ mm. The oxygen percentage in the expired and alveolar airs was considerably raised above its normal value while breathing the air containing $CO_2$ owing to the hyperpnœa in spite of the fall in the inspired oxygen percentage[1].

In the first series of experiments the total ventilation of the lungs was quadrupled during the hyperpnœa, and in the second series slightly more than doubled. The figures for the total volume of air expired and for the rate of the breathing are given in Table III. All volumes are expressed at 37°, saturated with moisture and under the prevailing barometric pressure, *i.e.* under the conditions which hold good within the body. During the hyperpnœa the rate of the breathing was considerably accelerated in the first series, but only slightly altered in the second series.

So far as the supply of oxygen and the discharge of $CO_2$ are concerned the effectiveness of the respiration depends on the alveolar ventilation. The alveolar ventilation per minute is obtained by subtracting the volume of the dead space from the volume of an expiration, measured at 37° and saturated with moisture, and multiplying the result by the number of breaths per minute. The volume of the dead space is given by the volume of an expiration measured at 37° and saturated with moisture × (the $CO_2$ percentage in the alveolar air − the $CO_2$ percentage in the expired air) ÷ (the $CO_2$ percentage in the alveolar air − the $CO_2$ percentage in the inspired air).

Proceeding by this method Douglas and Haldane[2] determined the dead space during muscular exercise and found it to be considerably

[1] See Loewy, *Untersuch. u. d. Resp. u. Zirkul.*, Berlin, 1895.

[2] This *Journal*, XLV. p. 235. 1912.

TABLE III.

| | Normal air | | | Air containing $CO_2$ | | |
|---|---|---|---|---|---|---|
| Number | Expired air per minute in litres | Breaths per minute | Volume of each breath in c.c. | Expired air per minute in litres | Breaths per minute | Volume of each breath in c.c. |
| 1 | 9·32 | 17·7 | 526 | — | — | — |
| | 9·34 | 19·6 | 476 | — | — | — |
| | — | — | — | 38·8 | 30·4 | 1276 |
| | — | — | — | 48·9 | 32·4 | 1510 |
| 2 | 8·94 | 21·0 | 426 | — | — | — |
| | 8·60 | 21·2 | 406 | — | — | — |
| | — | — | — | 33·3 | 31·3 | 1064 |
| | — | — | — | 34·9 | 30·0 | 1163 |
| 3 | 9·12 | 18·3 | 498 | — | — | — |
| | 8·75 | 18·5 | 473 | — | — | — |
| | — | — | — | 30·9 | 26·5 | 1166 |
| | — | — | — | 37·0 | 27·5 | 1345 |
| Average of 1–3 | 9·01 | 19·4 | 468 | 37·3 | 29·7 | 1254 |
| 4 | 9·20 | 18·9 | 487 | — | — | — |
| | — | — | — | 20·2 | 24·3 | 831 |
| | — | — | — | 21·1 | 21·9 | 964 |
| 5 | 9·60 | 16·9 | 568 | — | — | — |
| | — | — | — | 19·1 | 17·8 | 1071 |
| | — | — | — | 21·4 | 19·9 | 1075 |
| 6 | 8·61 | 16·2 | 532 | — | — | — |
| | — | — | — | 19·6 | 18·2 | 1076 |
| | — | — | — | 20·8 | 19·0 | 1095 |
| | 8·52 | 15·5 | 550 | — | — | — |
| 7 | 9·16 | 16·8 | 545 | — | — | — |
| | — | — | — | 17·6 | 17·9 | 983 |
| | — | — | — | 19·1 | 18·2 | 1050 |
| | 8·66 | 17·0 | 509 | — | — | — |
| Average of 4–7 | 8·96 | 16·9 | 532 | 19·9 | 19·7 | 1018 |

increased. Krogh and Lindhard[1] have however recently criticised these experiments, and have themselves come to the conclusion as the result of employing another method that the dead space is unaltered during the hyperpnœa of muscular work.

Their main criticism is that during the sharp expiration which is necessary when sampling the alveolar air by the Haldane-Priestley method the $CO_2$ percentage in the alveolar air is rising. During muscular work, when the rate of $CO_2$ output from the body is greatly

[1] This *Journal*, XLVII. p. 30. 1913. *Ibid.* p. 431. *Skand. Arch. f. Physiol.* XXX. p. 375. 1913.

increased, the error thus introduced becomes of very appreciable importance, even though the sharp expiration does not occupy more than half a second. The consequence is that the mean alveolar $CO_2$ percentage during expiration is estimated too high by the Haldane-Priestley method during muscular work, and as this value forms the basis for the calculation of the volume of the dead space the error will entirely explain the apparent great increase of the dead space.

We freely acknowledge the justice of Krogh and Lindhard's criticism that the Haldane-Priestley method fails to give correct values during muscular work, and it seems that the true mean alveolar $CO_2$-pressure under these circumstances must for the time remain a matter of speculation. We are, however, far from convinced that the method which they advocate for the determination of the dead space gives true results.

This method consists of taking a single measured breath of hydrogen and calculating the dead space from the volume of a subsequent expiration and the percentage of hydrogen in the inspired gas and in the expired and alveolar air. They have found that the distribution of the gas in the alveolar air after a single breath of hydrogen is not uniform, and their figures show that even at rest the calculated volume of the dead space shows very great variations according to the depth of the expiration and the composition of the gaseous mixture inspired. In order to obtain concordant results by their method it is necessary to limit the volume of the expiration. These facts seem to us likely to militate seriously against the chances of obtaining true values for the dead space, quite apart from the considerations mentioned below, and with limitation of the expiration any actual increase in the calibre of the respiratory passages may be masked owing to failure to wash out these passages completely with the small volume of air available.

After all, the effective dead space, as understood in physiology, is an abstraction, not an anatomical reality. The values of the dead space which we calculate are expressed as though we have to deal only with the air in the alveoli and with the air in the upper respiratory passages, both having certain definite and ascertainable compositions, and as though the air in the upper respiratory passages is moved *en bloc* in inspiration or expiration towards or away from the alveoli. Such an expression is convenient, but it conceals the factors which underlie our conception of the dead space—the calibre of the bronchial tubes, the different rates of flow of the axial and peripheral streams of air in these tubes, the character and degree of penetration of air into

the alveoli or adjacent parts of the air passages, and the liberation of appreciable quantities of $CO_2$ in other parts of the air passages than the alveoli. When so many factors may be concerned it would seem that any method based on the introduction into the lungs of some gas which is foreign to the body must give dubious results.

Krogh and Lindhard however agree that during rest the Haldane-Priestley method gives the most accurate results for the mean percentage of $CO_2$ in the alveolar air, and we have therefore an opportunity of studying in our present series of experiments the behaviour of the dead space during hyperpnœa when the rate of the metabolism is practically identical during the quiet breathing and during the hyperpnœa.

Table IV shows the values we have obtained for the dead space and the alveolar ventilation.

In Exps. 1 to 3 these values are calculated from the individual determinations of the volume of air breathed and the corresponding inspired, expired and alveolar analyses in those cases where all the data are complete. In Exp. 2 the alveolar $CO_2$-pressure was practically the same both before and after exposure to the atmosphere containing $CO_2$, but in Exp. 3 the alveolar $CO_2$-pressure whilst breathing normal air was slightly lower at the close of the experiment than it was at the commencement. If the dead space is calculated in the latter experiment from the mean volume of each breath at the commencement of the experiment and from all four alveolar $CO_2$ determinations made whilst breathing normal air it gives the value of 132 c.c.

In Exps. 4 to 7 it is rather more difficult to obtain the true value for the dead space during the hyperpnœa, since, owing to the time taken to collect the composite samples of alveolar air, a sufficient interval of time separated the collection of these samples from that of the samples for determining the respiratory exchange to cause a material alteration in the composition of the inspired air. The fairest way to proceed seems to be (1) to take the mean of the two alveolar $CO_2$ percentages and to calculate the dead space from the figure so obtained and the results of the first determination of the total respiratory exchange: (2) to calculate the dead space from the mean results of the two determinations of the respiratory exchange and the second determination of the alveolar $CO_2$ percentage. In this way we obtain in each case values for the inspired air for comparison with the alveolar air or total respiratory exchange, which are either identical or practically identical. The only exception to this close agreement is found in the second calculation in Exp. 4, where however the occurrence of the two

TABLE IV.

| Number | Normal air: Effective dead space in c.c. | Normal air: Alveolar ventilation in litres per min. | Air containing $CO_2$: Effective dead space in c.c. | Air containing $CO_2$: Alveolar ventilation in litres per min. | Rise of alveolar $CO_2$-pressure in mm. Hg required to give a rise of 10 litres in: Alveolar ventilation | Rise of alveolar $CO_2$-pressure in mm. Hg required to give a rise of 10 litres in: Total ventilation |
|---|---|---|---|---|---|---|
| 1 | 158 | 5·59 | — | — | — | — |
| | 154 | 5·29 | — | — | — | — |
| | — | — | 452 | 25·1 | 2·1 | 1·2 |
| | — | — | 513 | 30·6 | 1·7 | 1·1 |
| 2 | 128 | 5·16 | — | — | — | — |
| | 135 | 4·65 | — | — | — | — |
| | — | — | 349 | 20·8 | 2·8 | 1·8 |
| | — | — | 233 | 26·4 | 2·1 | 1·7 |
| 3 | 137 | 5·65 | — | — | — | — |
| | 132 | 5·35 | — | — | — | — |
| | — | — | 269 | 22·4 | 2·2 | 1·7 |
| | — | — | 332 | 26·4 | 2·3 | 1·7 |
| Average of 1–3 | 141 | 5·28 | 358 | 25·3 | 2·2 | 1·6 |
| 4 | 167 | 5·07 | — | — | — | — |
| | — | — | 266 (259) | 12·5 | 1·3 | 0·9 |
| | — | — | 259 (260) | 13·6 | 0·8 | 0·6 |
| 5 | 173 | 5·80 | — | — | — | — |
| | — | — | 286 (241) | 13·0 | 5·8 | 4·4 |
| | — | — | 286 (254) | 13·9 | 5·7 | 4·3 |
| 6 | 167 | 5·07 | — | — | — | — |
| | — | — | 227 (205) | 14·5 | 2·9 | 2·5 |
| | — | — | 215 (178) | 15·2 | 2·7 | 2·3 |
| | 170 | 5·08 | — | — | — | — |
| 7 | 176 | 5·33 | — | — | — | — |
| | — | — | 229 (198) | 12·6 | 2·7 | 2·3 |
| | — | — | 244 (232) | 13·0 | 2·8 | 2·3 |
| | 165 | 4·96 | — | — | — | — |
| Average of 4–7 | 170 | 5·22 | 252 (228) | 13·5 | 3·1 | 2·5 |

similar values of 3·77 % of $CO_2$ in the third and fourth inspired air samples renders some error in the sampling practically certain. In practice we have taken as inspired air values those corresponding to the total respiratory exchange in this calculation. Thus in Exp. 5: the first figure for the dead space during the hyperpnœa is calculated from the volume of each breath, 1071 c.c., the $CO_2$ percentage in the inspired air, 4·28 %, and in the expired air, 5·71 %, as found during the first respiratory exchange experiment, and from the mean of the two alveolar $CO_2$ percentages, 6·37 %: the effective personal dead space so calculated

is 286 c.c. after allowing 52 c.c. for the dead space of the valves. The figures used for the second determination of the dead space are the second alveolar $CO_2$ percentage, 6·43 %, and the mean of the values found in the two respiratory exchange determinations, viz. volume of each breath, 1073 c.c., inspired $CO_2$ percentage, 4·40 %, expired $CO_2$ percentage, 5·79 %, giving an effective personal dead space of 286 c.c.

We have also tried calculating the dead space in the same experiments in another way, viz. from each alveolar $CO_2$ percentage and the corresponding inspired $CO_2$ percentage, and the total volume of each breath and the expired $CO_2$ percentage found in the succeeding respiratory exchange determination. This method of calculation must give lower results than the previous one since the alveolar and inspired $CO_2$ percentages will clearly be too low, or the expired $CO_2$ percentage too high for strict comparison. We give, however, the results of these calculations in brackets in Table IV, and it will be seen that they indicate the same alteration in sense, though the less in degree, during the hyperpnœa.

All the results agree in showing a very considerable increase in the dead space during the hyperpnœa, the average increase being 217 c.c. in Exps. 1 to 3 where the ventilation of the lungs was quadrupled, and 82 c.c. in Exps. 4 to 7 where the breathing was doubled. In spite of this increase in the dead space the relative increase during the hyperpnœa of the alveolar ventilation[1] is about 15 % greater than that of the total ventilation in each of the two series.

Though the alveolar ventilation is the factor which determines the supply of oxygen to the lungs and the removal of $CO_2$ from them the real index of the work entailed on the respiratory muscles, and therefore of the activity of the respiratory centre, is the total ventilation of the lungs which secures that alveolar ventilation. The total ventilation necessary to secure any given alveolar ventilation may, however, be a variable quantity, since it depends on the depth and frequency of the breathing and on the precise volume of the dead space.

In order therefore to express the sensitiveness of the respiratory centre we show in Table IV the rise of the alveolar $CO_2$-pressure which is required to cause a rise of 10 litres in both the alveolar and the total ventilation. In Exps. 1 to 3 these figures are obtained from a comparison of the mean values of the ventilation and alveolar $CO_2$-pressure observed in each experiment while breathing normal air with each of the values

[1] In calculating the alveolar ventilation 52 c.c. must be added to the effective personal dead space shown in Table IV to allow for the dead space of the valves.

observed while breathing the $CO_2$ mixture in the corresponding experiment, only those observations being used where all the data are complete. In Exps. 4 to 7 the mean data obtained in normal air are compared with figures derived from the data during the hyperpnœa in the manner already described in discussing the dead space.

It will be seen that an increase of 10 litres in the alveolar ventilation was caused by a rise of 2·2 mm. in the alveolar $CO_2$-pressure in the first series, and of 3·1 mm. in the second series, while a rise of 10 litres in the total ventilation was caused by a rise of 1·6 mm. in the alveolar $CO_2$-pressure in the first series and of 2·5 mm. in the second series. The individual figures show a very fair agreement, considering the small differences worked with, with the exception of those in Exp. 5, where exceptionally high values were obtained. Unfortunately we did not in this experiment make any further observations after recommencing to breathe normal air. We were at first somewhat afraid that prolonged exposure to an atmosphere containing $CO_2$ might cause some alteration in the normal threshold stimulating value of the alveolar $CO_2$-pressure, and it was for this reason that we made further observations in some of the experiments after recommencing to breathe normal air. So far as these observations went any alteration produced in the normal alveolar $CO_2$-pressure was trifling. If we except Exp. 5 the average rise of alveolar $CO_2$-pressure required to cause a rise of 10 litres in either the alveolar or total ventilations is practically identical in both series of experiments, and we do not therefore feel justified in suggesting that there was any real difference in the sensitiveness of the respiratory centre in the two series.

Taking the average of all the experiments the rise of alveolar $CO_2$-pressure required to give a rise of 10 litres in the alveolar ventilation was 2·5 mm. (a figure which is in very close agreement with that which we obtained in the earlier experiments with Haldane), and in the total ventilation 2·0 mm., *i.e.* a rise in the $CO_2$ percentage in the dry alveolar air of 0·35 % and 0·28 %. Judging from Hasselbalch and Lundsgaard's results[1] these figures would imply a rise in the $C_H$. in the arterial blood of about $0{\cdot}0163 \times 10^{-7}$, and $0{\cdot}013 \times 10^{-7}$ respectively.

[1] *Biochem. Ztschr.* XXXVIII. p. 77. 1912: XLI. p. 247. 1912.

## CONCLUSIONS.

1. During the hyperpnœa caused by breathing air containing $CO_2$ the dead space is considerably increased.

2. A rise of 2·5 mm. in the alveolar $CO_2$-pressure was found to be sufficient to cause a rise of 10 litres in the alveolar ventilation, and a rise of 2·0 mm. in the alveolar $CO_2$-pressure sufficient to cause a rise of 10 litres in the total ventilation of the lungs.

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