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RESPIRATORY REGULATION IN MAN DURING ACCLIMATIZATION TO HIGH ALTITUDE

BY C. C. MICHEL* AND J. S. MILLEDGE†

From the University Laboratory of Physiology, Oxford, and the 1960–61 Himalayan Scientific and Mountaineering Expedition

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The changes in respiratory response to carbon dioxide at high altitude have been investigated by Kellogg, Pace, Archibald & Vaughan (1957) up to 12,470 ft. (3800 m) and by Chiodi (1957) up to 14,813 ft. (4500 m). The present study was designed to measure changes in respiratory response to both hypercapnia and hypoxia and to extend existing knowledge of these changes up to a height of 19,000 ft. (5800 m) where the barometric pressure is half an atmosphere.

Control experiments were conducted in the summer of 1960 at Oxford, and the altitude experiments were carried out in two series during the winter of 1960–61 in the specially designed laboratory hut set up by the 1960–61 Himalayan Scientific and Mountaineering Expedition on a glacier at 19,000 ft. in the Everest region of East Nepal.

In conjunction with this work two experiments were carried out in a low-pressure chamber, in order to determine the effect of low barometric pressures upon the respiratory responses to CO_2 in the absence of hypoxia.

METHODS

Subjects. The subjects were all members of the scientific team of the expedition, most of them being climbers as well. Two of the subjects, J.S.M. and M.B.G., had been in Nepal for 3½ months before the experiments were started, most of the time being spent at altitudes above 15,000 ft. leading an active life while preparing the various camps and huts for the winter. The other two subjects, J.B.W. and M.P.W., arrived in the field later, having had about 1 month at intermediate altitudes before experiments on them started. All four subjects acclimatized well as judged by general climbing criteria, and all remained fit during their stay at altitude except for a steady loss of weight of from 1–3 lb. (0·45–1·36 kg)/week, which was more pronounced towards the end of the winter. Exercise was taken almost every day in the form of ski-ing and occasional climbing excursions.

Apparatus. The apparatus for use in the field was adapted from that described by Cunningham, Cormack, O'Riordan, Jukes & Lloyd (1957), Douglas bags being substituted for rotameters. The subject inhaled through low-resistance valves a gas mixture from a large (*ca.* 500 l.) capacity Douglas bag. The gas was humidified by passing it through a biscuit tin containing hot water. The exhaled gas passed through a gas meter to a second Douglas

* Christopher Welch Scholar, University of Oxford. † Present address: Christian Medical College, Vellore, Madras, India.

bag in which it was collected. The gas meter carried a simple electronic device giving a signal at every 5 l., which activated a pen recorder also carrying a time trace. From the valves a Rahn–Otis end-tidal gas sampler took gas which was drawn over a rack of sampling tubes and through a CO_2 meter by a Monaldi suction pump. The CO_2 meter was a kinetic gas analyser made and described by Wright (1959).

Gas mixtures. Gas mixtures were made up by volume before and during the experiments from room air and cylinder CO_2 and O_2. For the first 5 experiments (at altitude) only three mixtures were used, later a fourth was added. These mixtures were made up so as to have a pCO_2 between 15 and 20 mm Hg and pO_2 of approximately 54, 75, 90 and 180 mm Hg. In the last four experiments the high-oxygen mixture was pure oxygen, pO_2 300. The mixture with the lowest pO_2 was made by collecting expired air from the subject before the start of the experiment, and arranging for half the volume to pass over soda-lime. Thus a mixture having the desired pO_2 was obtained without the use of large quantities of cylinder nitrogen, which would have been impracticable.

Procedure. Experiments were all conducted in the morning except for two in the second series during a time of great pressure of work on other programmes. In view of the steady loss of weight that all the subjects suffered it was not considered justifiable to insist on the subjects being in a fasting state, but no experiments were started until at least 2 hr after a meal.

The subject was seated on a bunk and made comfortable with sleeping bags and encouraged to read. After a steady state had been reached with the subject breathing room air, as indicated by a steady reading on the CO_2 meter, usually after 7–10 min on the valves, a sample of alveolar air was taken and the first mixture switched on. The subject breathed this until he emptied the Douglas bag. During this time, when the CO_2 meter indicated a steady state, an alveolar sample was taken. After the bag was exhausted, the two Douglas bags were reversed so that the subject inhaled his expirate. Thus a mixture having a higher pCO_2 and slightly lower pO_2 was then inhaled, resulting in a higher ventilation. This process was continued until a ventilation of about 50 l./min was reached, and then repeated, starting with a different gas mixture. Usually 3–4 runs were necessary. The process could be shortened by adding a small quantity of CO_2 to the first exhalate. Experiments started with the lowest oxygen mixture proceeding in order to the highest. The experiments lasted about 1½–2 hr. The gas samples were analysed later in Lloyd's (1958) development of the Haldane gas analysis apparatus.

Sea-level experiments. The sea level experiments were similar to those carried out at altitude, though here the subject was seated in a dentist's chair which could be adjusted to suit his comfort. For all sea-level determinations on M.B.G., and for experiment 3 on J.S.M., the apparatus was the same as that used at high altitude. In other sea-level experiments the unmodified methods of Cunningham *et al.* (1957) were employed, gas mixtures being made up from rotameters, etc.

Pressure-chamber experiments were carried out on two subjects, one of which (J.S.M.) was a member of the expedition and a subject in the other experiments. A considerable amount of sea-level data was available for the other subject (C.C.M.) and could be used for comparison with his responses here.

The apparatus was of a very simple form. Gas mixtures were made up in cylinders with CO_2 concentrations of 3·9, 5·4 and 6·4 % in 40 % O_2 for use at a barometric pressure of 760 mm, and 7·5, 10·2 and 13·1 % in 80 % O_2 for use at a barometric pressure of 380 mm. There was no CO_2 meter and no recorder; the expired gas was passed through a gas meter and the readings continually recorded by a clerk.

The subject inhaled each gas mixture in turn, starting with the low-CO_2 mixture, end-tidal samples being taken into mercury-filled gas sampling tubes when ventilation became constant. In the first experiment, the 'ground level' run was performed first and followed, after a 30 min rest, by the 'altitude' run, the pressure in the chamber having been reduced to 380 mm for this. In the second experiment the order was reversed.

RESULTS

Ten experiments were performed at sea level and sixteen at altitude on four subjects. These are shown in Fig. 1. The problem of comparing results of experiments at sea level and at altitude when looking for changes in responses to a raised alveolar pCO_2, and to lowered alveolar pO_2 was overcome by making use of the equation of Lloyd, Jukes & Cunningham (1958) relating ventilation ($\dot{V}$) and the alveolar gas pressures.

They showed that where the CO_2 response is linear,

$$\dot{V} = S(pCO_2 - B), \tag{1}$$

where S is the slope of the $\dot{V}$–pCO_2 line, B the intercept on the pCO_2 axis, and partial pressures are those in the alveolar gas.

Furthermore $$S = D\{1 + A/(pCO_2 - C)\}, \tag{2}$$

where D is the minimum slope of the $\dot{V}$–pCO_2 line, i.e. when pO_2 is infinity and there is no hypoxic drive, C is the value for pO_2 when the slope is infinite, and A is a parameter related to oxygen sensitivity.

By combining equations (1) and (2) we get

$$\dot{V} = D(pCO_2 - B)\{1 + A/(pO_2 - C)\}. \tag{3}$$

By obtaining values for these 4 parameters, B, C, D, and A, by suitable experiments it is possible to compare respiratory regulation in various situations such as acidosis, alkalosis, noradrenaline administration, raised body temperature, or, as in the present study, acclimatization to high altitude.

The results were first plotted on a $\dot{V}$–pCO_2 diagram.

Figure 1 shows all the experiments performed on our four principal subjects, the sea-level experiments being plotted together with altitude experiments. Figure 2 is an enlargement of experiment 2 on subject J.B.W. in Fig. 1. It will be seen in Fig. 1 that

(1) The trend is towards a fan of isoxic $\dot{V}$–pCO_2 lines radiating from a single point, B, on the pCO_2 axis, as shown by Lloyd *et al.* (1958). The assumption that this is so is basic to the use of the equation and the calculation of the parameters. For this reason points which are suspected of being below the CO_2 threshold of Neilsen & Smith (1952) are neglected in this treatment.

(2) At altitude, B, the intercept of the $\dot{V}$–pCO_2 line, is much reduced, i.e. the fan is shifted to the left.

(3) The slope of the high pO_2 lines is much increased at altitude, i.e. the fan is 'folded up' from the right.

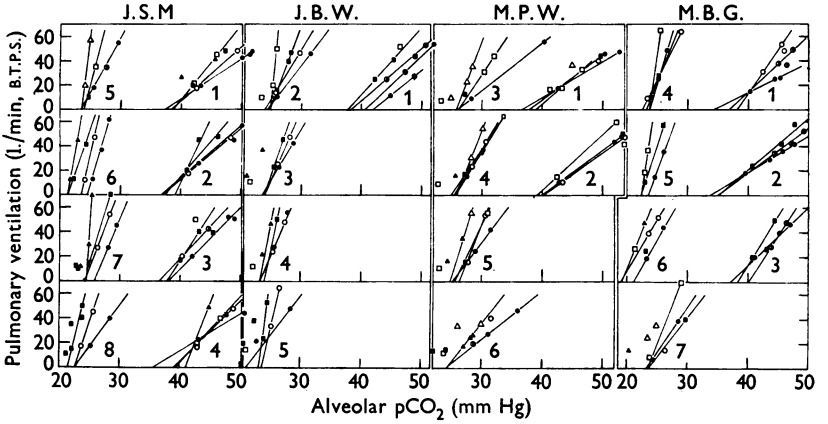

Fig. 1. The relation between pulmonary ventilation and the alveolar pCO_2 and pO_2 in subjects at sea level and at 19,000 ft (5800 m). Each small rectangle refers to one or two experiments on a particular subject and they are arranged in columns according to the subject. In the sea-level experiments the pCO_2 usually lie between 40 and 50 mm, and at high altitude the pCO_2 usually lie between 10 and 30 mm. Lines have been drawn through points of equal pO_2, the different pO_2 (mm Hg) being indicated by the different symbols: ● 115 or more; ◑ 70–90; ○ 55–60; ■ 48–54; □ 41–39; ▲ 37–39; △ 32–34.

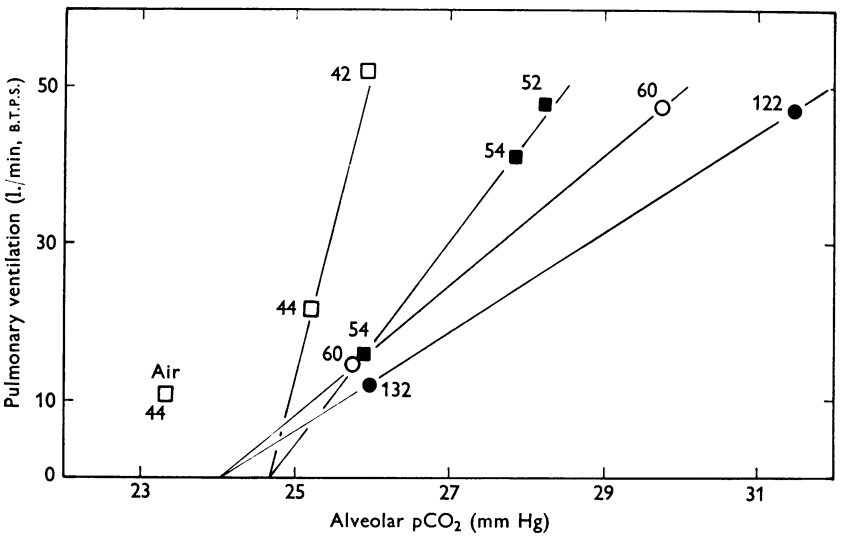

Fig. 2. The effect of hypoxia on the respiratory response to CO_2 in a single experiment carried out on J.B.W. at altitude. The figures against the points indicate the actual values of the alveolar pO_2.

Calculation of the parameters B, C, D and A

On the $\dot{V}$–pCO_2 graph, lines connecting points of equal pO_2 are drawn by eye (Figs. 1 and 2). These give a number of values for B which when averaged give a mean B of first approximation. This value is then used to obtain by extrapolation a set of pO_2, pCO_2 values for a constant $\dot{V}$ arbitrarily selected to have a value near to the experimentally determined values at high $\dot{V}$. Equation (3) can be manipulated (Lloyd & Cunningham, 1962) to give:

$$pCO_2 = \dot{V}/D + B - \dot{V}A/D\{pO_2 - (C - A)\}, \quad (4)$$

According to this equation, at constant $\dot{V}$, pCO_2 should be a linear function of $1/\{pO_2 - (C - A)\}$, if the appropriate value of $(C - A)$ is selected. This value of $(C - A)$ is then found by trial and error to give the most linear graph of pCO_2 against $1/\{pO_2 - (C - A)\}$. The straight line drawn through the points so obtained has a slope of $\dot{V}A/D$ and an intercept on the CO_2 axis $\dot{V}/D + B$. As B and $\dot{V}$ are known, D, A and, from the final value of $(C - A)$, C can be calculated.

The calculated parameters are shown in Fig. 3. Where the sea-level and high-altitude results for each parameter and subject are averaged and plotted against each other, it will be seen that the reduction in B is found in all subjects and there is very little scatter. The change in B appears to be complete before the start of the first experimental series. The reduction is from a mean of 38·1 at sea level to 23·4 at altitude.

D is seen to be approximately doubled from a mean of 3·5 to 7·3. The values for D for J. B. W. and M. P. W., who arrived later at altitude, show a progressive increase over the first series of experiments lasting about 3 weeks, from initial values of 5·6 and 3·3 to 7·8 and 6·8 in the last pair of experiments, which then approximate to the value of D in the other two subjects who had been at 19,000 ft. about 2 months longer.

The values for C show more scatter but no definite trend. There seems to be no change in this parameter, while A shows some increase in three out of four subjects. The calculation of these parameters is more susceptible to deviations in the subject's response from that predicted by equation (3) and consequently it is difficult to demonstrate small changes in their values.

Measurements of the alveolar gas with the subject at rest breathing room air preceded two experiments on J.S.M. and all experiments on J.B.W. and M.P.W. In every case, the alveolar pCO_2 was found to lie 2–4 mm below B.

Pressure-chamber experiments

Figure 4 shows the results of the two experiments carried out in the pressure chamber. It will be seen that in neither case is the slope of the

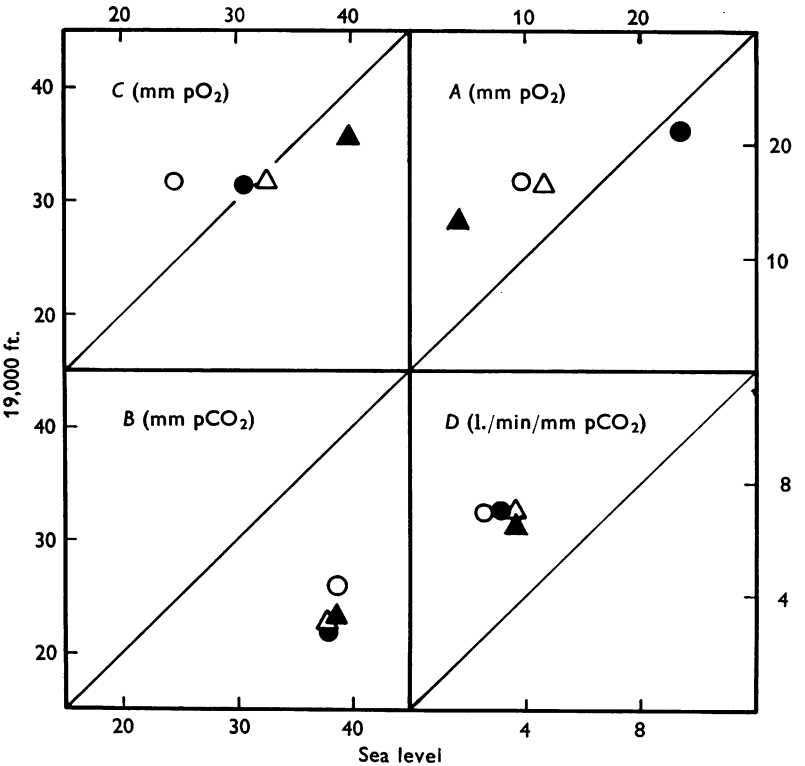

Fig. 3. The effect of altitude acclimatization on the parameters B, D, C and A of equation (3). Each point represents one subject and has been derived by averaging the results at sea level and at high altitude and plotting them against each other. The different subjects are indicated by the different symbols: J.B.W. ▲, M.B.G. ●, M.P.W. ○, J.S.M. △. Points evenly distributed around the line of equality indicate no effect of acclimatization on the parameter in question.

$\dot{V}$–pCO_2 line increased by a fall in barometric pressure; in J.S.M. it is unchanged and in C.C.M it is depressed.

DISCUSSION

Parameters A and C

There has been considerable debate about the effect of acclimatization to high altitude on the ventilatory response to hypoxia (see Heymans & Neil (1958) for review of literature). The parametric approach of Lloyd *et al.* (1958) would appear to be particularly well suited for analysing this problem, as it clearly distinguishes between the hypoxic and hypercapnic responses. From our results it would appear that the critical alveolar pO_2, at which CO_2 sensitivity would become infinite (parameter C in equation 3),

is unchanged after several months at altitude. A, the parameter related to the subject's sensitivity to hypoxia, was increased in three of our subjects. As mentioned earlier, the calculation of this parameter is very susceptible to deviations in the subject's response from that predicted by equation (3). Subject M.B.G., whose A decreased at high altitude, generally gave scattered results. This was particularly true of the sea-level experiments, and the sea-level value of A may have been over-estimated in him. On the other hand, only one sea-level experiment was carried out on J.B.W., in whom the largest change of A was observed. With these reservations in mind it would appear that if any change of A does occur during acclimatization it is a small increase. There is no evidence of a decrease of oxygen sensitivity during acclimatization. This is strong evidence for the view that the hypoxic drive to breathing is maintained in the acclimatized subject (Astrand, 1954*a*, *b*; Dejours, Girard, Labrousse, Molinard & Teillac, 1957).

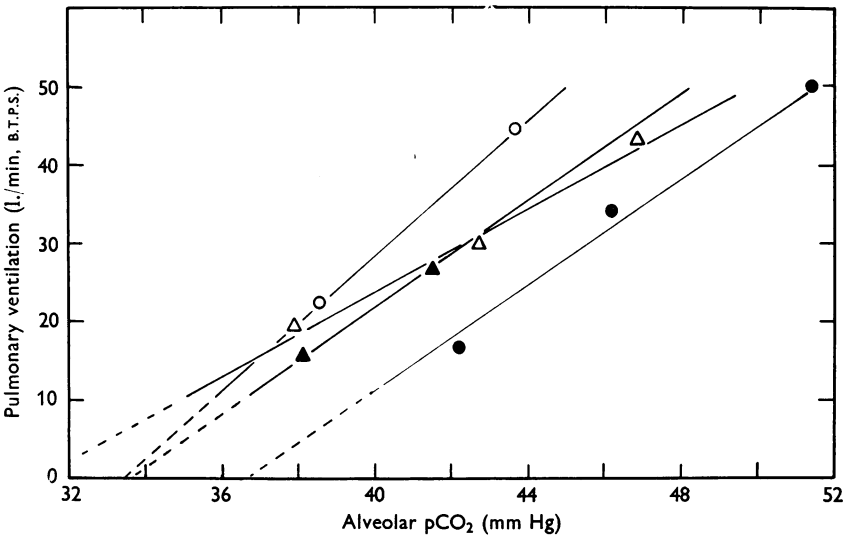

Fig. 4. The respiratory responses of two subjects to inhaled CO_2 at sea level and during acute exposure to a barometric pressure of 380 mm Hg when no hypoxia was present. ○ C.C.M. at sea level; △ C.C.M. at 380 mm Hg; ● J.S.M. at sea level; ▲ J.S.M. at 380 mm Hg.

Parameter B and the alveolar pCO_2

A reduction of B was expected from the CO_2 sensitivity studies at altitude of Rahn, Stroud, Tenney & Mithoefer (1953), Chiodi (1957) and Kellogg *et al.* (1957) as well as the large number of alveolar gas measurements made on air-breathing, resting, acclimatized subjects from Fitz-Gerald onwards.

Gilfillan, Hansen, Kellogg, Pace & Cuthbertson (1958) have shown that the fall in alveolar pCO_2 of chronically hypoxic dogs is dependent on intact chemoreceptors. They have concluded that this is direct evidence for the belief that the low alveolar pCO_2 seen in acclimatized subjects even after hypoxia has been abolished is a secondary response to the hypocapnia (and consequent alkalaemia) resulting from the hyperpnoea of hypoxia.

Cunningham, Shaw, Lahiri & Lloyd (1961), in studies on the effects of ammonium chloride acidosis on the respiratory parameters, have correlated B with the arterial plasma $[HCO_3^-]$, calculated for a $pCO_2 = B$.

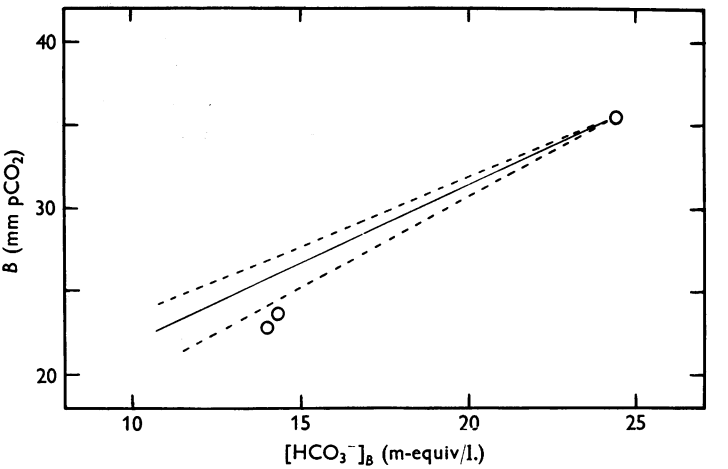

Fig. 5. The relation between B and the arterial plasma $[HCO_3^-]$ at a $pCO_2 = B$. The solid line represents the average slope obtained by Cunningham *et al.* (1957) for this relation in subjects undergoing dietary acidaemia. The interrupted lines indicate the extreme values found in their study. The points are based on measurements made on J.S.M. and J.B.W. at high altitude and on J.S.M. at sea level.

Unfortunately no blood gas measurements were made in conjunction with the sea-level experiments reported here, and at altitude the necessary information is available only for J.S.M. and J.B.W. However, two experiments were carried out on J.S.M. 2 months after his return to England. Whilst these were done for a different purpose, they did involve an estimate of this subject's parameters in conjunction with measurements on the blood, and so provide information on the sea level B–$[HCO_3^-]_B$ relations of this subject. The averaged value from these experiments has been plotted in Fig. 5, together with the determinations made on the two subjects at altitude. The average slope of the B–$[HCO_3^-]_B$ relations of the acidotic subjects of Cunningham *et al.* (1961) has been drawn through the sea-level point, the extreme values being indicated by the interrupted lines. It is seen that in the acclimatized individuals the fall in B for a given

fall in $[HCO_3^-]_B$ is greater than that found by Cunningham *et al.* in subjects during ammonium chloride acidosis.

A difference between the acidotic and the acclimatized subjects is not unexpected. Cunningham *et al.* (1961) suggested that long-term adjustments in the mechanism by which acid and CO_2 affect $\dot{V}$ had probably not occurred in their subjects, since the B–$[HCO_3^-]_B$ relations during the transition between normal and acid states were independent of the direction of the change. During metabolic acid-base imbalance, modification of the c.s.f. $[HCO_3^-]$ is slow (Robin, Whaley, Crump, Bickelman & Travis, 1958; Bradley & Semple, 1962). Such changes would appear to be of considerable importance in respiratory regulation (Leusen, 1954*a*, *b*; Loeschcke, Koepchen & Gertz, 1958). However, these changes were presumably complete in our subjects who had been at 19,000 ft. for several months at the time measurements were made.

In studies made during the first 2–3 weeks of acclimatization to altitude, Kellogg (1963) has found a much greater fall in B for a given fall in $[HCO_3^-]_B$ than was seen either in the acidotic subjects of Cunningham *et al.* (1961) or in our data. One might expect that the c.s.f. $[HCO_3^-]$ might lag behind the plasma $[HCO_3^-]$ during renal compensation for the respiratory alkalosis. Merwarth & Sieker (1961) have recently compared the pH–$[HCO_3^-]$ relations of arterial and mixed venous blood with the pH–$[HCO_3^-]$ relations of c.s.f. during over-ventilation in dogs. Although the authors failed to comment upon it, their data reveal a loss of 5 m-equiv HCO_3^-/l. from the c.s.f. after 40 min over-ventilation, whilst the $[HCO_3^-]$ of the plasma differed only slightly from the value predicted from an assumed CO_2 dissociation curve. Reciprocal changes occurred during under-ventilation. These findings, which indicate that during respiratory acid–base imbalance the choroid plexus modifies the c.s.f. more rapidly than the kidney can alter the blood, have recently been confirmed by Michel & Kao (unpublished). Furthermore, Mitchell & Severinghaus (personal communication) have found that this occurs during the early stages of acclimatization. Therefore it seems possible that in Kellogg's subjects the changes accompanying acclimatization were complete (or almost complete) as far as the c.s.f. was concerned but changes in the acid–base balance of the arterial blood were incomplete. By contrast, in our subjects, who had been at altitude for several months, changes in the c.s.f. and arterial blood may both be expected to be complete. On these grounds one would predict a considerable hysteresis in the B–$[HCO_3^-]$ relations during the early stages of acclimatization, and the early stages of recovery (contrast with Cunningham *et al.* 1961). So far no data of this kind are available for the recovery period.

In studies at sea level it appears that the resting alveolar pCO_2 is usually

2 mm greater than B (Lloyd *et al.* 1958). In contrast with this, the resting alveolar pCO_2 at altitude was found to lie approximately 2 mm below B on the insensitive region of the CO_2 response curve, i.e. below the CO_2 threshold of Neilsen & Smith (1952). This finding suggests that there may be a limit to the extent to which either B (or the arterial plasma $[HCO_3^-]$), may be lowered during acclimatization. Furthermore, it may be noted that in our subjects the resting alveolar pCO_2 was 2–4 mm below the values predicted by FitzGerald (1913) and by Rahn & Otis (1949) for alveolar gas pressures at this altitude. However, these predictions are largely based on the alveolar gas pressures of residents on high mountains, the CO_2 responses of whom are known to differ from those of acclimatized visitors. A more detailed account of alveolar gas measurements made on the expedition has been reported by Gill, Milledge, Pugh & West (1962).

Parameter D

A rise of CO_2 sensitivity in acclimatized individuals even when the hypoxia has been abolished by the inhalation of oxygen-rich gas mixtures has been observed by Neilsen (1936*a*), Rahn *et al.* (1953), Chiodi (1957), and Kellogg *et al.* (1957).

It seemed possible that the reduced density of the air at altitude might lead to a reduction in the work of breathing which might account for the rise of CO_2 sensitivity. Certainly if the respiratory work is greatly increased a fall in CO_2 sensitivity occurs (Cherniack & Snidal, 1956). Cotes (1954) used the equations of Otis, Fenn & Rahn (1950) to calculate the work of breathing at maximal breathing capacity (m.b.c.) at different altitudes. His work suggests a 20% reduction of respiratory work of m.b.c. at 19,000 ft. However, since the work of breathing is not a linear function of the level of $\dot{V}$ (Neilsen, 1936*b*), it does not follow that a similar reduction in respiratory work would occur at lower levels of $\dot{V}$ (i.e. 20–50 l./min). No measurements of respiratory work at sea level or altitudes were made in connexion with the present studies. There are, however, three reasons for believing that the change of respiratory work can have no more than a very minor contribution to the observed changes in D:

(1) Measurements were made on subjects J.B.W. and M.P.W. within a few days of the arrival at 19,000 ft. Over this period a progressive rise of D was seen, although the work of breathing for a given $\dot{V}$ was probably constant.

(2) A rise of CO_2 sensitivity was evident in the breath-holding studies of Rahn *et al.* (1953). Work parameters are presumably not involved in the breath-holding responses.

(3) No noticeable change of CO_2 sensitivity was observed in two subjects acutely exposed to a barometric pressure of 380 mm in a decompression

chamber. Although only two experiments were performed, their validity may be assessed by comparing the sea-level results with other experiments on these two subjects carried out with the more sophisticated apparatus in Oxford. The sea-level slopes in these experiments were 4·4 and 3·5 for C.C.M. and J.S.M. respectively. Their mean slopes for this high pO_2 line in experiments at Oxford were both 3·7.

No change of CO_2 sensitivity has been satisfactorily established in experimental metabolic acidosis in man. However, changes of CO_2 sensitivity have been observed to accompany respiratory acidosis and alkalosis. Brown, Campbell, Johnson, Hemmingway & Visscher (1948) observed a rise of CO_2 sensitivity in normal subjects over-ventilated in a respirator, and Schäfer (1949) and Chapin, Otis & Rahn (1955) have observed a fall in CO_2 sensitivity in subjects chronically exposed to atmospheres containing 4 and 3 % CO_2.

Lambertsen, Semple, Smyth & Gelfand (1961) have suggested that the CO_2 stimulus is mediated through the pH of the arterial plasma and the pH of c.s.f. If this is so, the $[HCO_3^-]$ of the c.s.f. may be expected to be critical in determining CO_2 sensitivity. For the c.s.f. of our subjects to have a pH of 7·4 or less, the c.s.f. $[HCO_3^-]$ would be considerably less than the normal sea-level value (a difference of the order of 6–10 m-equiv/l.). The change of c.s.f. pH per unit change of pCO_2 would now be almost double the presumed sea-level value, which compares well with the observed changes of D (cf. Heymans & Neil, 1958, Chap. 18).

The fall of D seen in two of our subjects after several months at altitude is not significant in itself, but is of interest when considered in the light of Chiodi's (1957) findings on the CO_2 sensitivities of residents in the Andes. The residents, unlike visitors to high altitudes, have CO_2 sensitivities which are average by sea-level standards. However, it is by no means clear whether a fall in CO_2 sensitivity follows prolonged residence at high altitudes or whether genetic differences between the residents and the visitors may account for this in Chiodi's experiments.

SUMMARY

1. The respiratory response to combinations of hypoxia and hypercapnia was studied in four healthy male subjects at sea level and during and after acclimatization at 19,000 ft. (5800 m).

2. Responses were compared by using the equation of Lloyd *et al.* (1898), $\dot{V} = D\,(pCO_2 - B)\{1 + A/(pO_2 - C)\}$, which relates pulmonary ventilation ($\dot{V}$) to the alveolar pO_2 and alveolar pCO_2, through the parameters B, C, D and A.

3. It was found that the parameters A and C, related to the response to

hypoxia, were affected little by several months at high altitude, C being unchanged and A being increased in three subjects but reduced in the fourth. The parameters of the hypercapnic response B and D were conspicuously changed, B being approximately half and D approximately double the sea-level values.

We are indebted to Dr D. J. C. Cunningham and Mr B. B. Lloyd under whose direction this work was carried out. We are most grateful to Professor Sir Lindor Brown, F.R.S. for laboratory facilities in Oxford and to the R.A.F. Institute of Aviation Medicine for allowing us to use their altitude chamber.

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