THE CONTROL OF BREATHING AT HIGH ALTITUDE

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S Y N O P S I S

The changes in the control of breathing in man at high altitude have been studied at 5,800 m (19,000 ft). The differences between lowlanders and Sherpas were compared at 4,880 m (16,000 ft.). Ventilatory response to CO_2, hypoxia and exercise were studied, and acid-base status of the blood and CSF measured.

Acclimatization to altitude is characterized by a shift of the CO_2 response curve to the left and an increase in its slope. The hypoxic sensitivity appears unchanged. On moderate exercise there results a progressive increase in ventilatory equivalent with increasing altitude. At maximum work rate ventilation increases more rapidly due to falling Sao_2.

Sherpas show no significant difference in response to CO_2 but a remarkable lack of response to hypoxia. The CO_2 response showed little change in slope with change of Po_2 and on exercise acutely changing P_Io_2 had little effect on ventilation. Sherpas ventilate less on exercise and have higher maximum O_2 intakes per kg than lowlanders.

The arterial pH of highlanders is normal whereas in lowlanders it remains slightly elevated after 4-6 weeks at altitude. CSF pH of highlanders is about 0.04 units more acid than lowlanders at the same altitude, indicating a greater central contribution to respiratory drive and a reduced peripheral component. The role of anaerobic cerebral metabolism in respiratory acclimatization is discussed.

A C K N O W L E D G M E N T S

This work was carried out over eight years in many places and therefore I am indebted to many people who helped me as collaborators or subject: and often both. To others I am indebted for their advice, supervision and laboratory facilities.

From the first expedition (1960-61) I am chiefly indebted to Dr. L. G. C. Pugh who planned and led the scientific side of the expedition and to Sir Edmund Hillary the leader who with Dr. Pugh invited me to join the team. The work on CO_2 and hypoxic response was under the supervision of Dr. D. J. C. Cunningham and Mr B. B. Lloyd whose teaching and advice are gretefully acknowledged, together with the valuable collaboration of Dr. C. C. Michell, all of the Department of Physiology, University of Oxford. I am indebted to all the expedition team who acted as subjects, and to Dr. J. B. West who also taught me much physiology. I acknowledge my thanks to R. A. F. Institute of Aviation medicine, Farnbrough, for allowing me to use their low pressure chamber for follow-up experiments.

On the second expedition (1964) I am again indebted to Sir Edmund Hillary for all the field facilities, and to Dr. S. Lahiri who organized the scientific aspect of the expedition as well as acting as collaborator and subject. Also Mr. Battacharia who assisted us in the work and was a subject. Our Sherpas not only volunteered as subjects but also looked after our comforts (on both expeditions). Without their cheerful help nothing would have been accomplished. I acknowledge the help and facilitie

afforded by Dr. P. Zechariah in his Department of Physiology at Vellore for the follow-up studies after the expedition.

The work in Peru, briefly reported in the last chapter, was largely due to the initiative of Dr. S. Sørensen and the encouragement of Dr. J. W. Severinghaus to whom I am very grateful. I wish also to thank Dr. J. Cruz and the Institudo de Investigazione del Altura in Lima for help and facilities in Peru.

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C H A P T E R I

INTRODUCTION I

Historical

From earliest times the vital importance of breathing has been recognized. The author of the book of Genesis writes, "And the Lord God formed man ... and breathed into his nostrils the breath of life; and man became a living being" (Gen 2:7).

The Hebrew word neshema translated in the quotation as "breath of life" can mean breath or life force. In the early Hebrew philosophy man was formed from the dust and became a living being only by God breathing into him the "neshema" of life or "ruach" God's spirit. Death was the departure from man of this same "breath" and man again became dust.

In Greek philosophy of about the same era, ie. about 500 B.C. the work "pneuma" had very much the same connotation as neshema. Anaximines of Miletus (born circa 570 B.C.) said "As our soul being air, sustaining us, so pneuma and air pervade the whole world" (Perkins 1964).

The deep-rooted idea of an intimate connection between breathing and life is shown in modern language by our use of the words inspire and expire.

But although it was realized that life in some way depended entirely upon breathing, no scientific investigation of this connection was possible until the second half of the 18th century when the discovery of carbon dioxide by Black, and of oxygen by Priestly and Scheele set the stage for the brilliant work of Lavoisier showing that in respiration animals consumed O_2 and produced CO_2. The first systemic study of the effects of O_2 lack and CO_2 inhalation was by Pflüger (1868). He came to the conclusion that O_2 lack was more important in the control of respiration. This was probably because he used 30 per cent CO_2 which would produce a degree of narcosis in his dogs.

Miescher Rusch (1885) concluded that CO_2 was the more potent stimulus since in his human subjects the inhalation of CO_2 sufficient to cause dyspnoea caused the expired CO_2 concentration to rise from 5.43 per cent to only 6.0-6.4 per cent. He wrote "Thus carbonic acid spreads its protective wings over the oxygen needs of the body."

In 1877 Walter demonstrated an increase in respiration in dogs poisoned with acid thus identifying the third main chemical stimulus to breathing.

Between 1870 and 1885 Paul Bert carried out many experiments on the effects of reduced pressure and oxygen breathing and showed that "Oxygen tension is everything, barometric pressure in itself does nothing or almost nothing." Thus laying a sure foundation for all future work on chemical control of breathing and altitude physiology.

Despite the work of Miescher Rush and others, by the turn of the century there was still much controversy as to the normal control of breathing.

In 1905 Haldane and Priestly published their classical paper demonstrating the constancy of the alveolar Pco_2 over a range of barometric pressures, varying from 646 mm Hg on top of Ben Nevis to 1,260 mm in the Brompton hospital pressure chamber. They also showed the great sensitivity of man to small increments of inspired CO_2 and concluded that under normal circumstances CO_2 regulated the respiration.

Haldane realized the importance of acid and later with Douglas (1909) noted the fall in $Paco_2$ after hard exercise and attributed it to lactic acid production by the muscles. The possibility that CO_2 exerted its effect through its acidity was obvious and was proposed formally in Winterstein's "reaction theory". This theory as first proposed in 1910 was found inadequate since CO_2 had a greater effect on respiration than an equivalent quantity of infused acid. A possible cause for this was given by Jacobs (1920) who showed that living membranes, in this case the lining membrane of Arbacia eggs, can be more freely permeable to dissolved CO_2 than to hydrogen ions. Winterstein (1956) therefore modified his theory suggesting that the CSF $[H^+]$ was the controlling factor rather than the blood $[H^+]$ and that CSF $[H^+]$ was affected readily by changes in $Paco_2$ but not by arterial pH changes due to infusion or production of acids.

This reaction theory did not, of course, account for hypoxic stimulation. The discovery of peripheral chemoreceptors by Heymans and Heymans in 1927 led to the thought that whilst CO_2 and/or H^+ affected mainly central receptors near the respiratory center, hypoxia affected mainly the peripheral receptors. It seemed unlikely, therefore, that a single unique stimulus to breathing could be proposed.

In 1950 Gray published his multifactorial theory in which he took the view that all three known stimuli contributed to the total ventilation. Also that these effects could be quantitated and added algebraically to give the resultant ventilation for any given set of values for Po_2, Pco_2 and pH. He worked from data in the literature and proposed the formula:

$$VR \cdot H^+ \cdot Pco_2 \cdot Po_2 = 0.22H^+ + 0.262Pco_2 - 18 + 2.118(104 - Po_2)^{4.9}$$

This acted as a considerable stimulus to respiratory physiologists to undertake further experiments to prove or disprove his theory. Workers in Scandinavia and in Oxford examined again the effects of hypoxia and CO_2 on the ventilation. Nielsen and Smith showed in 1951 that these two well known stimuli were not additive as Gray's theory assumed, but interacted, so that the effect of hypoxia became greater as the Pco_2 was raised. The Oxford workers found the same interaction (Cunningham, Cormack and Gee 1957, and Lloyd Jukes and Cunningham 1958). The ventilatory response to CO_2 above certain critical threshold is linear. Examining this linear portion of the line, they found that as the Po_2 was lowered, a family of response lines was made, which when produced back to the Pco_2 axis came to a single point on this axis, thus forming a fan of lines. They derived an equation to describe this, relating ventilation ($\dot{V}$) to alveolar Pco_2 and Po_2 through four parameters: B, D, C and A

$$\dot{V} = D(Pco_2 - B)\left\{1 + \frac{A}{(Po_2 - C)}\right\}$$

where B is the intercept of the CO_2 response lines extrapolated to the Pco_2 axis.

D is the minimum slope of the CO_2 response lines, i.e., when Po_2 is infinite and therefore there is no hypoxic drive. It is expressed in liters per min per mm Hg Pco_2.

C is the value for Po_2 when the slope is infinite, and

A is related to oxygen sensitivity, actually to the shape of the hyperbola relating Po_2 to the slope of the CO_2 response line expressed in mm Hg Po_2.

This equation is purely descriptive and does not tell us anything about the mechanism of action of CO_2 and hypoxia, but as a quantitative statement of their separate effects on ventilation it is very useful in comparing individuals under varying experimental conditions, or in comparing one group with another.

RESPIRATION AT ALTITUDE

Early accounts of the study of respiration at altitude focus on acute mountain sickness. The first of such accounts was by the Spanish Jesuit Fr. Jose de Acosta in 1590 (Kellogg, 1967), who tells very vividly of his own and others' experiences in crossing the high Andean passes. After describing the headache, nausea, vomiting, etc. of the condition, he hints at the process of acclimatisation. He noted that those coming westward from the altoplano were less affected -- having had at least a few days at high altitude -- than those going east who came rapidly up from the coast.

Denis Jourdanet (1861), a French physician who travelled extensively in Mexico and South America noted the similarity between mountain sickness and anaemia and suggested oxygen lack as being the cause of symptoms in both conditions. It was Jourdanet who stimulated and financed Paul Bert in his work on altitude.

Although difficulty and increase in breathing was known to be part of the response to high altitude, when the first quantitative study was reported by Mosso in 1897, he apparently found resting ventilation to be reduced. The reason for his error was partly due to his methods -- he used a poorly calibrated plethysmograph to measure ventilation, and partly conceptual since he expressed his results in l/min STPD. He also found the $P_E co_2$ to be reduced and attributed mountain sickness to this cause.

Ward (1908) found a lowered $P_A co2$ in subjects on Monte Rosa, and this was confirmed in 1910 by Barcroft and Douglas on the Teneriffe expedition who noted that those members with the lowest $P_A co_2$ were most free of symptoms.

This fall in $P_A co_2$ was most intensely studied by Douglas, Haldane, Henderson and Schneider (1913) on the 1911 Pikes Peak expedition and they suggested that during acclimatization man becomes "more sensitive to CO_2." While they were up Pike's Peak Miss Fitzgerald (1914) also from the Oxford physiology school toured the mining communities of Colorado on mule back. Shj analyzed alveolar gas samples for $P_A co_2$ in the residents there. She showed in these people a fall in $P_A co_2$ that was approximately linear with decreasing barometric pressure.

The high altitude expeditions between the wars were not concerned with respiratory control beyond the collection of alveolar gas samples.

After World War II there has been greatly renewed interest in the subject; and many studies have been carried out at altitude in North and South America, Europe and a few in the Himalayas. This work is discussed in the succeeding chapters of this thesis.

INTRODUCTION II

Setting of Present Study

The work described in this thesis is mainly the result of two scientific expeditions to the Himalayas in 1960 and 1964 with preliminary results from a visit to the Peruvian Andes in 1968. Together with preliminary and follow-up experiments, the work spans a time from March 1960 to April 1968 and was carried out in the field and in the following laboratories:

The Department of Physiology, University of Oxford, U.K.

The Medical Research Council Laboritories, Holly Hill, Hampstead, U.K.

The R.A.F. School of Aviation Medicine, Farnbrough, U.K.

Department of Physiology, Presidency College, Calcutta, India

Department of Physiology, Christian Medical College, Vellore, India

The first expedition, "The 1960-61 Himalayan and Scientific and Mountaineering Expedition" was led by Sir Edmund Hillary, with Dr. L. G. C. E. Pugh as scientific leader. The area of operation was

the Everest region of Eastern Nepal known as Solu Khumbu. Besides the scientific work, physiology and glaciology, the expedition had as its mountaineering objective the assault of Mount Makalu without oxygen and an investigation into the existence of the Yeti or Abominable Snowman. The results of these are described by Hillary and Doig in the expedition book (Hillary and Doig 1962).

The physiological objective was to study the changes in the physiology of normal lowland man on ascent and prolonged stay at high altitude. A list of publications from this expedition, showing the scope of this work, is given in the appendix to this chapter.

As part of this work, two series of experiments bearing on the control of respiration were undertaken; one at rest, on the ventilatory response to changing inspired Pco_2 and Po_2, and the other at exercise, with varying rates of work. These experiments and the sea level control experiments form the basis of the first part of this thesis.

In order to spend a long period at altitude, it was necessary for us to start just after the monsoon, in September 1960, and spend the winter at high altitude, returning before the next monsoon, in June 1961. This was the first time that men have spent the winter at high altitude in the Himalayas. In order to study the effects of really high altitude, it was intended to establish a station at 20,000 ft. In the event a suitable site could not be found above 19,000 ft (5,800 m). We found that even this height was probably above that at which lowland man, even acclimatised, could live indefinitely since after the first month we began to lose weight despite an apparently adequate diet.

This high altitude station, known as the Silver Hut consisted of a prefabricated hut (see photograph) almost cylindrical in section, 22 ft long by 10 ft diameter. Inside were bunks, table, stove, laboratory space, benches, etc. The hut was specially designed and built for us in plywood sections. All parts, as well as the equipment and food had to be carried by porters for 18 days into the area, then three days up from the last village. The hut was well insulated and day-time temperatures inside varied from 60 to 80°F (21 to 29°C).

Some exercise experiments were also carried out at the Mingbo base camp (a tented camp) at 15,300 ft (4,630 m).

The physiological programme was continued in the spring during the attempted assault on Mount Makalu (27,800 ft, 8,450 m). At advanced base camp (21,000 ft, 6,400 m) and on the Makalu Col (24,000 ft, 7,440 m) exercise experiments were carried out, and alveolar gas samples were collected at these stations and at camp VI, (25,700 ft, 7,830 m).

The members of the physiology team were:

Dr. L. G. C. E. Pugh of the Medical Research Council, London

Mr. (now Dr.) M. B. Gill of Auckland, New Zealand

Dr. S. Lahiri of Presidence College, Calcutta

Dr. M. P. Ward of the London Hospital

Dr. J. S. West of the Hammersmith Post-Graduate Medical School

and the author.

The second expedition in 1964 was smaller and less ambitious than the 1960-61 expedition; this, the "Second School House Expedition" was one of a series led by Sir Edmund Hillary, primarily to continue his aid programme for the Sherpas of Solu Khumbu. The physiological

FIG. 1.1. The "Silver Hut", the main physiological station of the 1960/61 Himalayan Scientific and Mountaineering expedition. Altitude 5,800m (19,000 ft).

FIG. 1.2. Silver Hut interior, looking towards domestic end. Inhalation experiment in progress, subject Dr. John West.

FIG. 1.3. Silver Hut interior, laboratory end with portable bicycle ergometer.

team was led by Dr. S. Lahiri. The team consisted of Dr. S. Lahiri, Mr. Bhatacharia M. Sc who unfortunately could not acclimatise and left the expedition half way through, and the author. Our objective was to study the differences between ourselves, lowlanders acclimatised to altitude, and Sherpas, the local native residents.

The Sherpas are a tribe of Tibetan origin settled on the Southern slopes of the divide range of the Eastern Himalayas. They are now subdivided into groups according to location. The Khumbu, or highland Sherpas are usually regarded as the "true Sherpas" and the high altitude porters and climbers made famous through mountaineering expeditions are mostly drawn from them either direct or from Darjeeling where many have emigrated. It has long been realised by climbers that Sherpas are physically much more efficient at altitude than even the fittest and best acclimatised lowlander. For instance, we noticed on the first expedition that at 19,000 ft at a steady gradient, a well-acclimatised lowlander kept up comfortably with a Sherpa only if the latter were carrying a 60 lb load. But previously the physiological basis for this difference had been studied hardly at all.

Our physiological camp in this expedition was at an altitude of 16,000 ft (4,800 m) on the divide ridge between the Dudh Kosi and Inuku Kola vallies. It was a tented camp (see photograph). A similar programme to that of the first expedition was carried out. A list of papers published is given in the appendix to this chapter. The programme included inhalation experiments at rest, and observations on exercise, comparing ourselves -- lowlanders -- with the Sherpa highlanders.

FIG. 1.4. Physiological camp, Lung Samba, 1964 expedition. Laboratory/mess tent in center, sleeping tents along-side. Altitude 4,880m (16,000 ft).

FIG. 1.5. Dr. Lahiri running an exercise experiment on a Sherpa subject outside the laboratory tent.

FIG. 1.6. The physiology team 1964 expedition at Lung Samba. Lt. to Rt., Sherpas Penury, Hakba tsering, the author, Dr. Lahiri, and Sherpa Hakba Norbu.

The work was carried out at this one altitude over a period of two months, October to December 1964.

After the expedition one of our Sherpa subjects was studied at sea level at Calcutta and Vellore.

In March 1968 I was able to carry out some further high altitude studies in the Peruvian Andes at Cerro de Pasco (14,500 ft, 4,300 m) with Dr. Soren C. Sorensen while we were in Dr. J. W. Severinghaus's laboratory in the Cardiovascular Research Institute, University of California, San Francisco. These studies were mainly concerned with cerebral metabolism in men native to high altitude. The study included measurement of cerebrospinal fluid pH, CO_2 and cerebral A-Vo_2 differences. Preliminary results from this study are added to those of the 1964 expedition in the chapter on acid base regulation (Chapter 6).

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C H A P T E R I I

CHANGES IN VENTILATORY RESPONSE TO CO_2 AND O_2 ON ACCLIMATIZATION TO HIGH ALTITUDE

INTRODUCTION

This project followed directly from the work of the Oxford School on the chemical control of respiration (Chapter I). The aim was to study quantitatively the changes in the ventilatory response to CO_2 and hypoxia in a group of subjects, normally resident at low altitude, after sojourn at a higher altitude and for a longer time than is usual in such studies.

The 1960-61 Himalayan Scientific and Mountaineering Expedition provided the opportunity for the project (Chapter I).

EXPERIMENTS

In the summer of 1960 experiments were carried out at Oxford on members of the expedition who would serve as subjects at altitude. The altitude experiments were carried out in two series, one near the beginning and one near the end of the four months' sorjourn at 5,800 m. After the expedition two experiments were carried out in a low pressure chamber in order to determine the effect of reduced air density and viscosity alone on the ventilatory response to CO_2.

METHOD

Subjects

There were four principal subjects whose physical characteristics are shown in Table 2. 1.

Subject	Age Yr	Height cm	Weight Kg
M B G	23	180	64.4
J S M	30	175	59.9
M P W	35	178	66.7
J B W	32	183	64.0

Table 2. 1. Physical characteristics of subjects:

Weight declined during stay at altitude. Weight given is that recorded at about the mid point of stay, between the two series of experiments.

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 3 1/2 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 one 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 0.5 Kg to 1.5 Kg per week which was more pronounced towards the end of the winter. Exercise was taken almost every day in the form of skiing and occasional climbing excursions.

Apparatus

Fig. 2.1. The apparatus for use in the field was adapted from that described by Cunningham, Cormack, O'Riordan, Jukes and Lloyd (1957), Douglas bags being substituted for rotameters. The subject inhaled through low-resistance valves a gas mixture from a large capacity Douglas bag (capacity 500 litres). 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 bag in which it was collected. The gas meter carried a simple electronic device giving a signal at every 5 litres, which activated a pen recorder also carrying a time trace. From the valve 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 five 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 hours 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 minutes 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 litres/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 1 1/2 to 2 hours. The gas samples were analysed later in Lloyd-Haldane apparatus (Lloyd 1958).

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 embloyed, gas mixtures being made up from rotameters, etc.

Results

Ten experiments were carried out at sea level and sixteen at altitude. The unprocessed data of these experiments is given in Table 2. 2 (a) and (b). The results were first plotted on a $\dot{V}/Pco_2$ graph as shown in Fig. 2. 2. The graphs for all experiments are shown in Fig. 2. 3. In this figure the sea level and altitude experiments are plotted together, the altitude plots being invariably to the left.

From Fig. 2. 3 it will be seen 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, Jukes and Cunningham (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 and Smith (1951) are neglected in this treatment.

Table 2.2. a Results of experiments conducted at sea level (Oxford) on four subjects used at altitude. Ventilation, litre per min, B.T.P.S., P_ACO_2, P_AO_2 mm. Hg.

Subject: J.S.M.

Expt. 1	24/2/60	
Vl/min	P_ACO_2	P_AO_2
19.9	43.3	119.8
18.0	42.4	60.0
20.1	41.9	51.7
22	42.0	41.3
27.7	39.7	37.0
43.2	50.6	116.7
46.2	51.4	(650)
49.0	51.8	117.4
48.9	49.2	66.5
49.0	47.2	53.0
45.5	45.8	42.5
42.3	45.6	38.5

Expt. 3	30/7/60	
Vl/min	P_ACO_2	P_AO_2
18.1	40.1	45.4
20.0	40.2	64.2
20.5	42.1	118.0
50.2	42.5	43.2
40.4	43.1	48.9
30.4	45.4	54.6
42.5	44.6	73.2
52.1	48.0	112.0
51.1	49.0	(650)

Expt. 2	27/7/60	
Vl/min	P_ACO_2	P_AO_2
20.9	41.0	46.9
18.6	41.2	65.3
20.1	43.0	119.9
45.5	42.4	48.2
48.0	46.3	54.4
47.0	48.3	67.8
57.0	50.4	121.3
45.0	48.8	(650)

Expt. 4	6/8/60	
Vl/min	P_ACO_2	P_AO_2
20.3	42.9	42.1
18.0	42.8	62.4
23.2	43.1	117.9
49.0	44.7	39.0
40.0	46.7	43.4
43.0	47.8	52.4
44.5	50.8	118.5
48.0	48.8	67.8
51.0	52.1	(650)

TABLE 2.2. a contd

Subject: J.B.W

Expt.	1	22/7/60
12.6	44.1	121.1
28.3	48.8	102.8
31.4	37.2	107.5
26.4	41.1	75.5
44.0	48.9	79.3
55.3	50.6	73.0
25.4	42.2	45.2
41.3	45.3	46.4
52.5	46.3	43.9
54.0	52.1	129.7

Subject: M.P.L.

Expt.	1	6/8/60
17.4	41.3	41.8
18.6	43.1	58.9
18.3	42.8	121.5
37.5	44.9	53.7
33.0	46.6	42.5
43.9	49.7	53.0
40.8	49.3	68.5
47.6	52.8	124.2
46.7	50.4	(650)

Expt.	2	8/11/60
11.6	42.9	121.1
11.5	43.3	56.4
15,7	42.4	45.0
60.0	52.4	40.6
44.1	53.6	44.9
50.1	53.4	54.2
48.5	53.7	67.8
46.4	54.5	79.2
49.4	53.3	113.7
44.1	51.9	(650)

Subject: M.B.G.

Expt.	1	18/7/60
Vl/min	P_ACO_2	P_AO_2
15.1	40.4	115.0
24.8	44.5	104.8
26.5	45.4	106.4
37.5	46.4	96.7
38.1	45.1	79.6
43.7	47.7	87.4
55.7	48.0	85.3
31.5	43.4	57.5
48.0	46.3	65.1
53.0	45.6	60.6

Expt.	2	21/7/60
Vl/min	P_ACO_2	P_AO_2
29.0	43.6	106.1
36.5	45.4	106.5
42.0	47.8	102.1
34.0	44.5	75.2
41.8	47.5	77.2
52.5	48.3	75.6
24.5	40.8	45.4
41.7	45.6	48.8
58.0	47.9	43.1

Expt.	3	23/7/60
Vl/min	P_ACO_2	P_AO_2
19.5	40.6	46.8
27.8	43.2	40.6
50.0	44.5	47.4
28.5	43.3	75.5
47.7	46.4	63.2
20.6	41.2	120.1
39.8	44.4	102.5
46.5	47.1	104.1

Table 2.2. b: Results of experiments conducted altitude (5,300 m) Ventilation litre per min, B.T.P.S. P_ACO_2 and P_AO_2 mm.Hg

Subject: J.S.M.

Expt. 5 5/1/61			Expt. 6 22/1/61			Expt. 7 28/1/61			Expt. 8 15/4/61		
Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2
20	24.00	32.2	13	20.88	37.8	13	22.75	45.1	13	20.97	53.1
58	24.47	33.0	45.5	22.90	36.3	12	23.34	38.0	11	20.97	53.1
11	24.67	48.2	13	22.18	51.2	30	24.80	39.2	40	23.82	48.30
36	25.86	44.3	41	24.17	46.5	70	25.14	37.9	50	23.75	46.67
16	25.43	133	12	24.00	65.3	12	22.91	50.2	35	21.94	51.6
18	25.43	133	47	25.66	60.4	70	28.27	48.6	17	23.65	63.0
35	27.68	93	13	25.27	133	27	26.24	66.8	45	25.53	58.0
55	29.70	111	37	26.83	123	54	28.20	57.0	18	25.16	310
9	24.67	48.2	62	28.02	120	28	27.94	167	40	28.37	307
						45	29.40	150			

Subject: M.B.G

Expt 4 30/12/60			Expt. 5 2/1/61			Expt. 6 4/1/61			Expt. 8 14/4/61		
Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2
10	24.8	43.1	19	21.73	39.95	27	21.17	40.16	15	20.40	36.2
28	25.42	46.01	19	22.96	40.05	48	22.97	38.93	25	23.58	35.6
65	25.59	44.35	37	23.49	40.40	19	23.36	144	35	24.92	33.3
9	23.49	75	11	23.05	52.0	41	26.18	135	9	24.25	41.0
63	28.98	78	11	23.14	53.5	25	23.14	54.3	70	28.02	41.3
25	25.68	114	57	26.12	47.1	39	26.68	61.2	15	26.45	60.9
26	25.33	119	15	24.80	140	52	25.27	57.8	41	29.83	54.5
49	26.73	114	15	24.63	140	11	18.73	47.5	39	28.56	303
			36	26.20	140				8	24.42	312

Table 2.2.B. Cont.

Subject: M.P.W.

Expt. 3 16/1/61			Expt. 4 24/1/61			Expt. 5 31/1/61			Expt. 6 11/4/61		
Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2
7.5	23.24	45.8	9	22.74	43.5	11	23.07	43.3	12	23.90	45.8
10.5	24.76	35.6	16	25.65	37.2	17	24.35	38.9	14	22.14	46.7
10.5	24.76	35.6	31	28.30	34.9	35	26.80	36.8	18	27.17	37.7
23	27.50	34.7	55	30.17	32.6	56	28.28	35.2	26	28.27	36.0
36	28.55	32.4	17	27.18	52.2	16	27.03	51.9	34	26.05	34.5
13.5	27.20	62.5	65	33.63	45.8	55	30.89	46.6	15	24.16	48.8
31.0	30.32	42.9	24	28.30	65.2	16	27.70	60.9	27	28.60	36.4
44.0	32.01	40.9	94.5	30.68	58.2	54	30.69	55.9	36	30.02	33.9
9.5	29.25	136	16	27.60	142	25	29.01	155	20	28.75	86.5
56.5	40.33	103	37½	30.22	122	42	31.52	142	41	31.61	58.0
			35	29.26	132				28	31.21	300
									47	36.05	294

Subject: J.B. West:

Expt. 2 20/1/61.			Expt. 3 26/1/61			Expt. 4 2/2/1961			Expt. 5 12/4/61		
Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2
10	23.30	43.56	11	21.61	45.5	12	22.10	44.7	15	20.94	46.4
20.7	25.21	43.7	16	21.01	39.2	22	23.39	39.1	20	20.64	47.41
51.7	25.91	42.1	37	23.60	37.9	47	25.06	37.9	37	22.34	46.8
14	25.77	57.7	23	23.50	54.4	23	24.97	53.2	23	24.97	53.2
40.5	27.85	54.15	46	27.00	49.9	51	26.12	48.4	53	24.58	50.3
47.5	28.25	51.6	25	26.17	67.9	24	25.46	63.8	34	25.12	68.4
11.4	25.97	132	43	28.14	63.9	48	27.44	58.6	65	26.52	62.8
47.0	31.48	122	23	26.30	160	28	25.56	158	22	22.64	311
15.0	25.90	54.0	43	28.67	147	56	27.77	148	48	28.42	306
47.0	29.73	60.2									

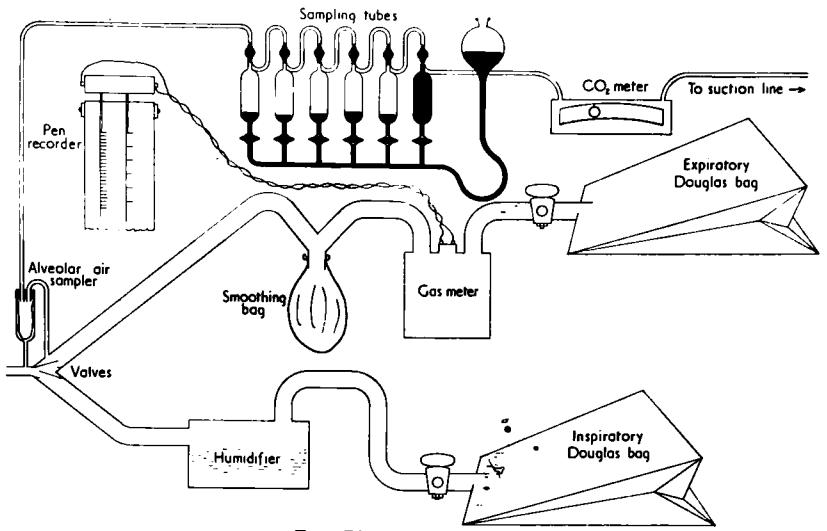

FIG. 1. Diagram of the apparatus used.

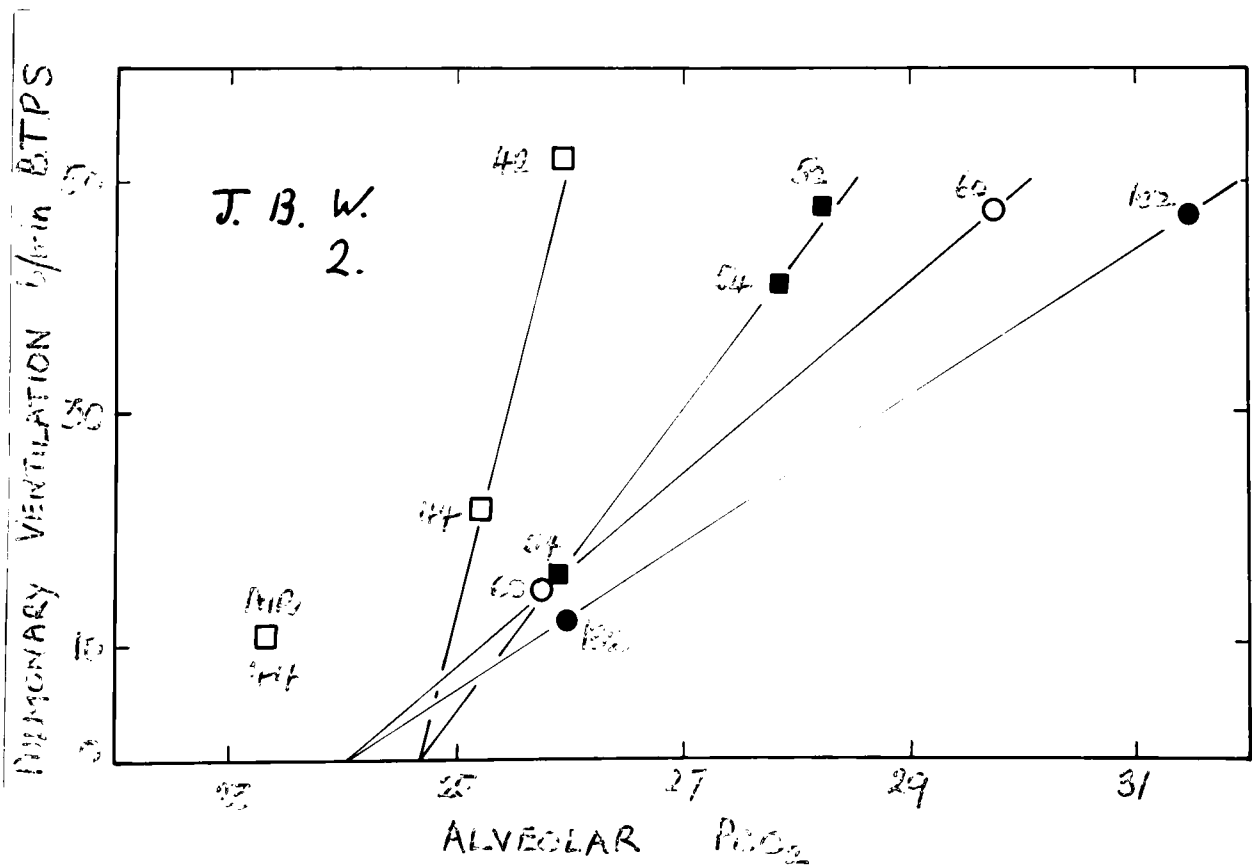

FIG. 2.2. The relation between pulmonary ventilation and alveolar Pco_2 and Po_2, the results of one experiment at 5,800m (19,000ft). The figures against the points indicate the actual PAo_2 values. Lines are drawn by eye through points of equal PAo_2. Symbols as in Fig. 2.3.

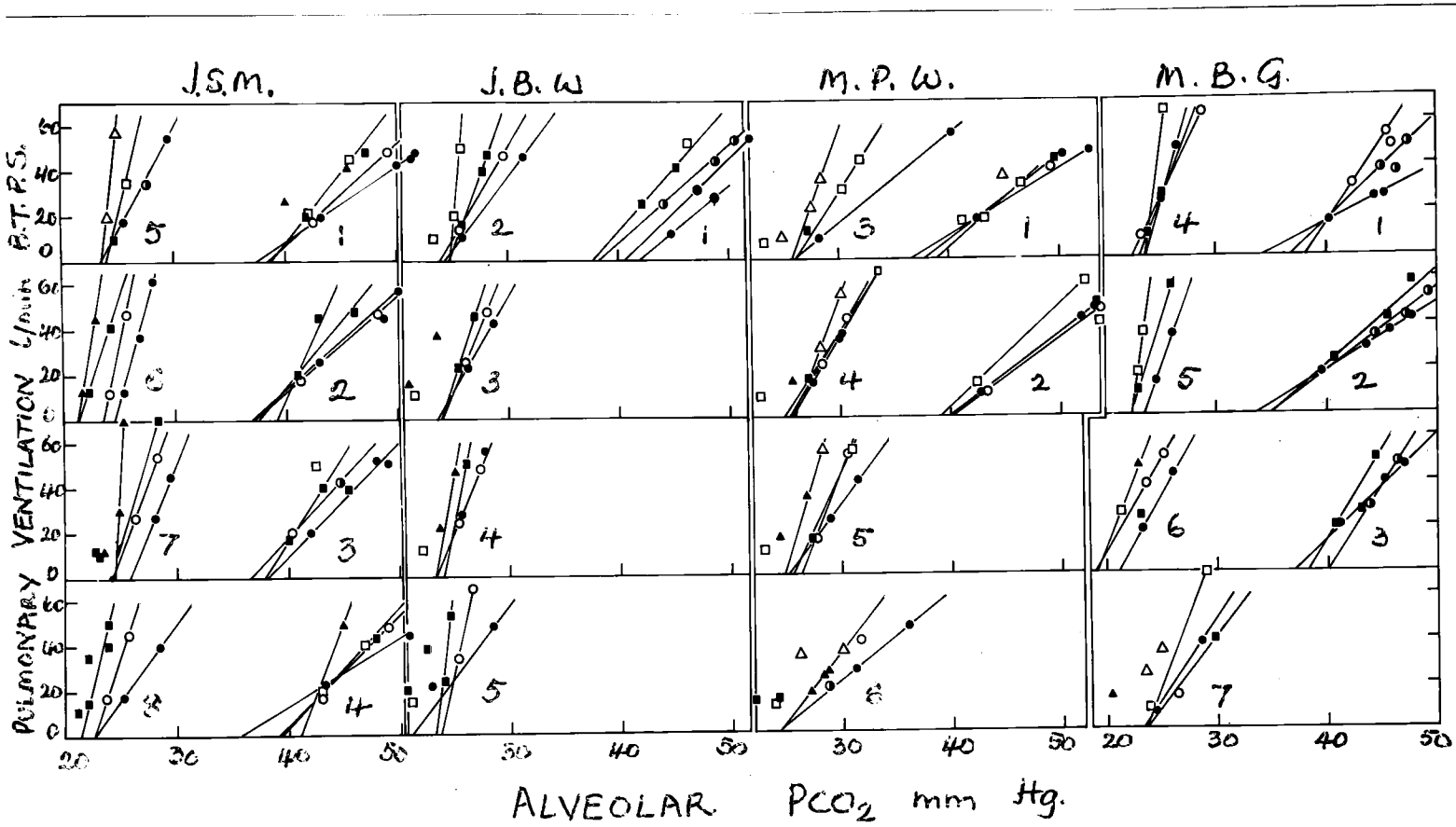

FIG. 2.3. The relation between pulmonary ventilation and the alveolar Pco_2 and Po_2 in subjects at sea level and at 19,000ft. Each small rectangle refers to one or two experiments on a particular subject. The sea level experiments lie to the right of altitude experiments in the same graph. Lines have been drawn by eye through points of equal Po_2, the different Po_2 being indicated by the different symbols:

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.

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. 2. 2 and 2. 3). 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 and Cunningham 1963) to give:

$$Pco_2 = \frac{\dot{V}}{D} + B - \left\{\frac{\dot{V}A}{D\ Po_2 - (C - A)}\right\}$$

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 VA/D and an intercept on the Pco_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. In Fig. 2. 4 the parameters of the experiment shown in Fig. 2. 2 are calculated in this manner.

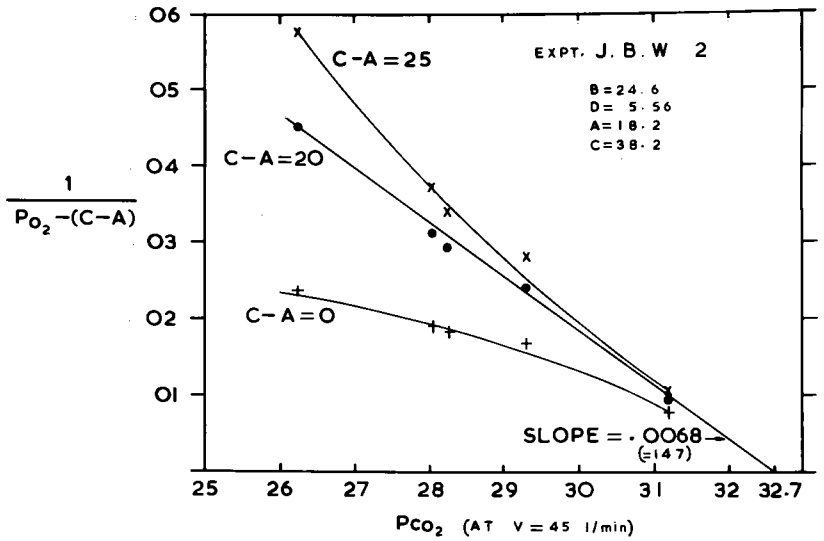

FIG. 2.4. Graph showing the method used to calculate the paramaters D,A and C of the equation relating $\dot{V}$ to Po_2 and Pco_2. The data is drawn from the experiment shown in fig 2.2. $1/Po_2-(C-A)$ is plotted against Pco_2 at constant $\dot{V}$ (45 l/min). Three different values for C-A were tried and the value C-A = 20 was found to give the best fit. From this value, the slope of the line and the intercept on the Pco_2 axis, the three paramaters can be calculated. (see text).

Parameters B, D, C and A

The results of this calculation for all the experiments are given in Table 2. 3 and Fig. 2. 5. It will be seen that the reduction in B is found in all subjects and there is very little scatter. The changes in B appear 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 three 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 the equation and consequently it is difficult to demonstrate small changes in their values.

Alveolar point on air

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 to 4 mm below B. See Figs. 2. 2 and 2. 3.

TABLE 2.3 **Results of calculated parameters**

B mm Hg P_{CO_2} C mm Hg P_{O_2}

D l/min/mm Hg P_{CO_2} A mm Hg P_{O_2}

for all experiments at sea-level (Oxford) and at altitude (5800m).

	SEA LEVEL					ALTITUDE				
Subject	Expt No	B	D	C	A	Expt No	B	D	C	A
J.S.M.	1	38.1	3.48	32.6	12.3	5	23.7	7.63	31.0	16.0
	2	37.3	3.69	35.7	10.7	6	21.3	6.18	32.2	16.2
	3	38.0	4.53	33.3	13.3	7	23.7	6.82	35.1	17.1
	4	37.8	3.36	29.4	9.4	8	21.5	5.40	33.0	22.0
	Mean	37.8	3.77	32.8	11.2		22.6	6.51	34.1	17.9
J.B.W.	1	38.7	3.71	39.7	4.2	2	24.6	5.50	38.2	18.2
						3	23.3	7.83	35.8	10.8
						4	22.6	7.76	31.6	11.6
						5	20.5	5.75	39.4	14.4
	Mean						22.8	6.71	36.3	13.8
M.P.W.										
	1	37.5	2.71	24.1	9.1	3	25.1	3.26	27.7	12.3
	2	39.4	2.63	25.5	10.5	4	24.8	6.70	-	-
						5	26.0	6.82	31.4	16.4
						6	24.0	3.40	26.8	11.8
	Mean	38.5	2.67	24.8	9.8		25.0	5.05	29.0	13.2
M.B.G.										
	1	37.6	2.92	34.5	34.5	4	23.2	7.57	29.0	24.0
	2	36.7	2.63	23.3	23.3	5	22.5	7.03	35.9	15.9
	3	39.4	4.83	33.5	13.5	6	20.4	6.43	28.5	18.5
						7	23.7	6.60	29.9	9.9
	Mean	37.9	3.46	30.4	23.8		22.5	6.91	28.1	18.4
MEAN (all subjects)		38.2	3.32	31.9	12.3		23.2	6.30	31.9	15.8
S.D.		±0.8	±0.73	±5.2	±8.1		±1.6	±1.3	±4.0	±4.2

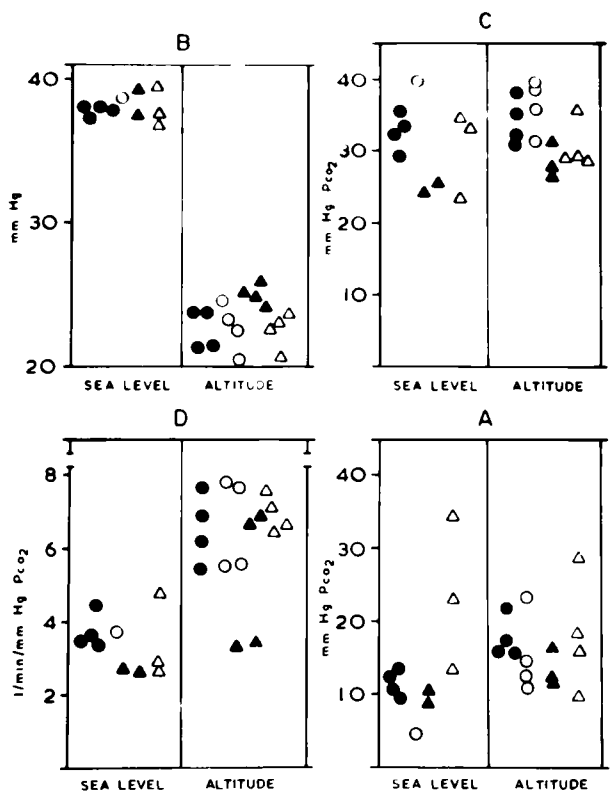

FIG. 2.5. Results of calculated respiratory paramaters on four subjects at sea level and at altitude. Each point represents one experiment. Subject JSM ●, JBW O, MPW ▲, MBJ △

In the second expedition a further six experiments were carried out on four lowland subjects (described in full in Chapter 4). These were at slightly lower altitude, but showed the same trends. At this altitude the alveolar point on air lay within the 'fan' 1 to 2 mm Hg above B, as it does at sea level.

Ideally we should have liked more sea level control experiments but this was not possible. However the results we have are within the normal range as given by Cunningham, Patrick and Lloyd (1964).

B = 37.7 ± 2.8 mm Hg D = 3.9 ± 1.4 L/min/mm Hg P_{CO_2}

C = 32.2 ± 7.6 mm Hg P_{O_2} A = 16.7 ± 11.6 mm Hg P_{O_2}

DISCUSSION

Parameter B

A reduction of B was expected from the CO_2 response studies at altitude of Rahn, Stroud, Tenney and Mithoefer (1953), Chiodi (1957) and Kellogg, Pace, Archibald and Vaughan (1957) as well as the large number of alveolar gas measurements made on air-breathing, resting, acclimatized subjects from Fitzgerald (1913) onwards.

Gilfillan, Hansen, Kellogg, Pace and Cuthbertson (1958) have shown that the fall in alveolar P_{CO_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 P_{CO_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 and 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.

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. two 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 connection 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. 2. 6 together with the determinations made on the two subjects at altitude. From the second expedition average values are also plotted for subject J.S.M. at 4,880 m. The average slope of the $B/[HCO_3^-]B$ relation 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 subject is not unexpected. Cunningham, et al. (1961) suggested that longterm adjustments in the mechanism by which acid and CO_2 affect 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

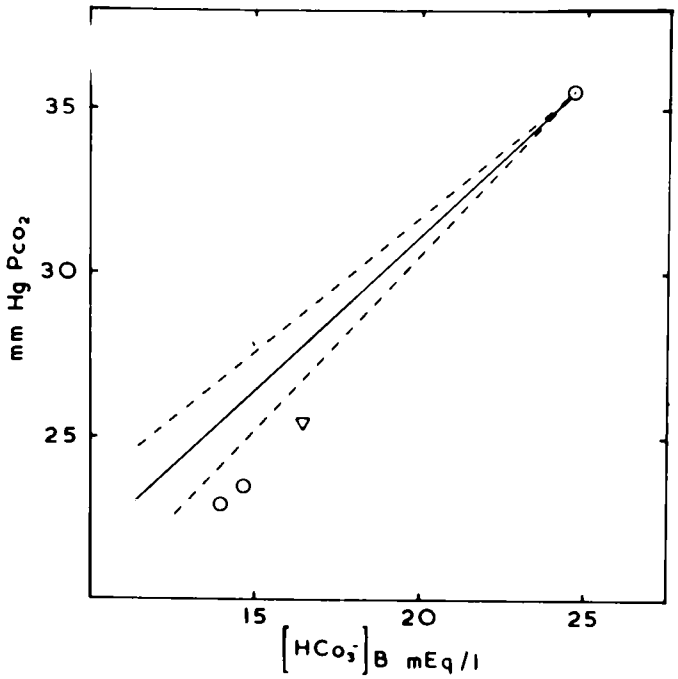

FIG. 2.6. The relation between B and arterial plasma $[HCO_3^-]$ at a PCO_2= B. The solid line represents the average slope obtained by Cunningham et al (1957) for this relationship in metabolic acidosis (NH_4Cl ingestion). Dashed lines show extreme values in their study. Measurements on JSM at 5,800m O, JSM at 4,880m Δ, value for JSM at sea level ⊙ (origin of line).

direction of the change. During metabolic acid-base imbalance, modification of the CSF $[HCO_3^-]$ is slow (Robin, Whaley, Crump, Bickelman and Travis (1958); Bradley and Semple (1962). Such changes would appear to be of considerable importance in respiratory regulation (Leusen, 1954 a,b). 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 to 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.

While adjustments of CSF pH in metabolic acidosis is slow, in respiratory acidosis it has been shown to be rapid. Merwarth and Sieker (1961) in studies on hyperventilation on dogs, although they fail to comment on it, show a loss of 5 mEq/L of HCO_3^- in CSF after only about 40 minutes over ventilation with much smaller changes in the blood. Michel and Kao (1964) made a similar finding in dogs. Severinghaus, Mitchell, Richardson and Singer (1963) studied the change in acid-base balance in blood and CSF on going rapidly to altitude, and found that in man too the CSF rapidly lost HCO_3^- even against a gradient of higher plasma $[HCO_3^-]$ so as to maintain the CSF pH at near normal values, whereas the blood remained alkaline for some 5 to 8 days.

Therefore it seems possible that in Kellogg's subjects the changes accompanying acclimatization were complete (or almost complete) as far as the CSF 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 CSF 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.

Alveolar point on air

In studies at sea level it appears that the resting alveolar P_{CO_2} is usually 2 mm greater than B (Lloyd, et al., 1958). In contrast with this, the resting alveolar P_{CO_2} at 5,800 m was found to lie approximately 2 mm below B on the insensitive portion of the CO_2 response curve, i.e., below the CO_2 threshold of Neilsen and Smith (1951). 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.

On the second expedition (Chapter 4) this point was found to lie as at sea level 1 to 2 mm Hg above B. So that this limit would seem to lie between 4,880 m (16,00 ft) (the altitude of our physiology camp) and 5,800 m (19,000 ft).

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 and Snidal, 1956). Cotes (1954) used the equations of Otis, Fenn and Rahn (1950) to calculate the work of breathing at maximal breathing capacity (M.B.C.) at different altitudes. His work suggested a 20 per cent reduction of respiratory work of M.B.C. at 19,000 ft. However, since the work of breathing is not a linear function of ventilation (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 to 50 l/min). No measurements of respiratory work at sea level or altitude were made in connection with the present studies. There were, however, two 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 5,800 m. Over this period a progressive rise of D was seen, although the work of breathing for a given $\dot{V}$ would have been constant.
2) A rise of CO_2 sensitivity was evident in the breath-holding studies of Rahn, et al. (1958). Work parameters were presumably not involved in the breath-holding responses.

But to test this possibility we conducted the following experiment in a low pressure chamber at Royal Air Force School of Aviation Medicine, Farnborough, after return from Nepal.

Pressure chamber experiments

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 per cent in 40 per cent O_2 for use at a barometric pressure of 760 mm and 7.5, 10.2 and 13.1 per cent in 80 per cent 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 Hg for this. In the second experiment the order was reversed.

Fig. 2. 7 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 $\dot{V}/Pco_2$ line increased by a fall in barometric pressure; in J.S.M. it is unchanged and in C.C.M. it is depressed.

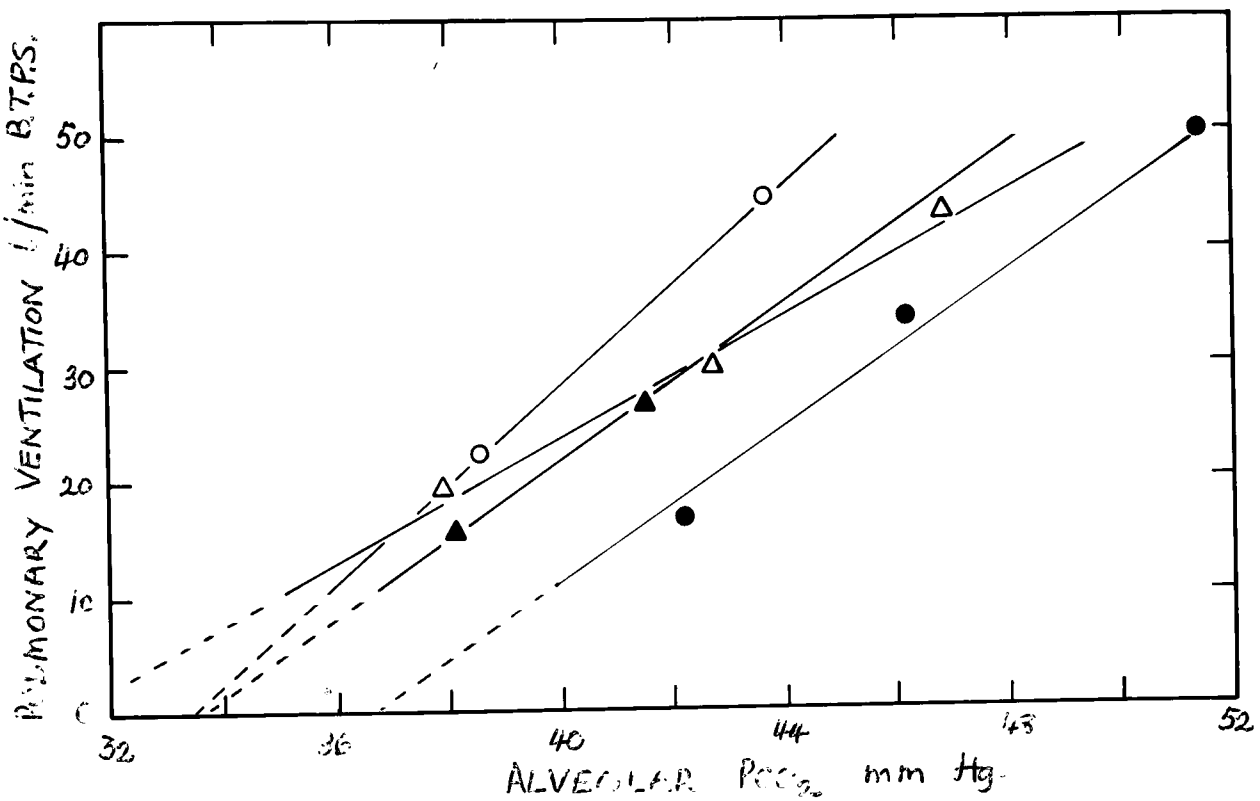

FIG. 2.7. The respiratory responses of two subjects to inhaled CO_2 at sea level and during exposure to a barometric pressure of 380 mm Hg in a low pressure chamber, when no hypoxia was present.

O	CCM at sea level;	▲	CCM at 380 mm Hg
●	JSN at sea level;	▲	JSM at 380 mm Hg

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.

Therefore we conclude that the effect of reduction in density and viscosity of air due to low barometric pressure produces a neglibible reduction in the work of breathing at this minute ventilation and does not account for any appreciable part of the change in CO_2 response which we observed on acclimatization.

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 and Visscher (1948) observed a rise of CO_2 sensitivity in normal subjects overventilated in a respirator, and Schafer (1949) and Chapin, Otis and Rahn (1955) have observed a fall in CO_2 sensitivity in subjects chronically exposed to atmospheres containing 4 per cent and 3 per cent CO_2.

A number of workers including Winterstein (1956), Luesen (1954 a) Mitchell, Loeschcke, Severinghaus and Massion (1963) and Lambertsen, Semple, Smyth and Gelfand (1961) have suggested that the CO_2 stimulus is mediated through the H^+ of CSF. For the CSF of our subjects to have a pH of 7.4 or less, the CSF $[HCO_3^-]$ would be considerably less than the normal sea level value (a difference of the order of 6 to 10 mEq/1). The change of CSF 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.

If, instead of plotting the results of the simple $\dot{V}/Pco_2$ graph, Log Pco_2 is used as the ordinate, then the slope of the CO_2 response at high oxygen is found to be almost unchanged. We could say then that ventilatory response is directly related to Log Pco_2 (Since pH is related to Log Pco_2) and the increase in sensitivity at high altitude is therefore only apparent. However, if this explanation is adopted, the situation in acute metabolic acidosis, where there is no increase in sensitivity even though the $[HCO_3^-]$ is reduced, is difficult to explain as also is our tentative finding of a longer time course for the change in D than that of B.

Until further light is thrown on this subject we prefer to use the simpler plot of $\dot{V}/Pco_2$ and the parameter D rather than one involving a logarithm base such as suggested by Lloyd (1963).

Parameters A and C

There has been considerable debate about the effect of acclimatization to high altitude on the ventilatory response to hypoxia (Heymans and Neil 1958). 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 the equation), 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 the equation. 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 overestimated 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.

Data from lowlanders in the second expedition is also rather inconclusive since sea level control experiments were not carried out on these subjects. One subject was common to both expeditions (J.S.M.), and his values for A at altitude were again higher than his original sea level value (15 altitude; 11.2 sea level). The mean for all lowlanders was 15.8 $\pm$ 4.2 compared with a normal value of 16.7 $\pm$ 11.6 given by Cunningham, Patrick and Lloyd (1964). With these reservations 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 and Teillac, 1957).

CONCLUSION

These experiments show that on acclimatization to high altitude, the control mechanism of lowland man becomes altered, in that the ventilatory response to CO_2 appears to begin to act at a lower level, i.e. B is reduced (at 5,800 m to just over half the sea level value)

and having begun to respond, the response is greater (D is increased) so that for a given rise of Pco_2 the ventilatory response is double that at sea level. But the effect of hypoxia on this CO_2 control system does not seem to change appreciably. If anything, its effect is slightly increased.

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C H A P T E R I I I

RESPIRATION DURING EXERCISE AT HIGH ALTITUDE

INTRODUCTION

Whilst experiments at rest are valuable in showing changes in the chemical control of respiration, it is on exercise that the climber is most conscious of dyspnoea. This dyspnoea is out of all proportion to the work he is doing, he feels, and one of the pleasant surprises on coming back to low altitude is to find that one can climb and talk again at the same time!

We studied this hyperpnoea of exercise at various work rates and at various altitudes from 4,650 m (15,300 ft) to 7,440 m (24,400 ft) on the 1960-61 Himalayan and Scientific Mountaineering Expedition (Chapter I).

METHODS and PROCEDURE

Particulars of the subjects studied at altitude are given in Table 3.1. They were all experienced mountaineers except J.B.W. who was however accustomed to sport and had a high work capacity.

Table 3.1. Age, height, and weight of subjects and altitude record.

Subject	Age, yr	Height, cm	Wt., kg, Before Expedition	Wt., kg, Circa 18/3/61 at 5,800 m
J.B.W.	32	183	73.9	64.0
M.P.W.	35	178	72.6	66.7
M.B.G.	23	180	70.8	64.4
J.S.M.	30	175	68.5	59.9
L.G.P.	51	183	75.3	68.0
B.C.B.	28	169	78.0	68.0
W.R.	30	178	64.0	63.0

Subject	Date of Arrival	Days at Mingbo, 4,650 m	Days at Silver Hut, 5,800 m to 18/4/61
J.B.W.	17/12/60	41	82
M.P.W.	17/12/60	43	79
M.B.G.	7/10/60	67	112
J.S.M.	20/10/60	65	113
L.G.P.	27/10/60	80	70

The experiments were all carried out on a portable bicycle ergometer weighing 20 kg, built expecially for us by the workshops of the Medical Research Council, Mill Hill.

The subjects pedaled at 50 rpm in time to a metronome. Expired air was collected in light weight rubberized fabric bags

of low CO_2 permeability and passed through a dry-gas meter. At the two highest camps and in some experiments at 4,550 m (15,300 ft) gas samples were stored in 70 ml soda-glass ampoules and analyzed in England. Otherwise all samples were drawn into Barcroft tubes over mercury and analysed in a Lloyd-Haldane analyzer (Lloyd, 1958). The reproducibility of analysis at the laboratory at 5,800 m (19,000 ft) was comparable with results at sea level; CO_2 values being expected to agree to within 0.03 per cent and O_2 values within 0.05 per cent. Two gas meters were available, both of which were recalibrated at sea level.

All experiments were preceded by a 10-min warmup at 300 kg-m/min. At sea level the subjects worked for 12 mins at each of the following work rates: 300, 600, 900, and 1,200 kg-m/min; the work periods were taken in succession without resting. Expired gas was collected over the last minute if they could keep going longer than 2 min.

At high altitude the same procedure was followed, the load being increased in 300 kg-m/min steps up to the highest work load. The subjects could perform for 6 min, expired gas being collected over the last minute. In each case, a rest was allowed before the highest work load. At 5,800 m (19,000 ft) some of the subjects attempted on separate occasions to work at 1,200 kg-m/min.

RESULTS

The experimental results are presented in Tables 3.2 to 3.5 and summarized in Tables 3.6.

TABLE 3.2 *Results of work experiments at sea level (Bar. 750 mm Hg)*

Subj.	No. of Obs.	Ventilation, l/min STPD	Ventilation, l/min BTPS	Frequency of Respiration /min	F_{ECO_2} %	F_{EO_2} %	Oxygen Intake, l/min STP	Respiratory Exchange Ratio (R)	Heart Rate, beats/min
				Rest					
JBW	1	6.1	7.5	12	4.14	16.07	0.31	0.81	64
MPW									
MBG	1	7.7	9.4		3.33	17.63	0.25	0.99	65
JSM	1	6.0	7.3	9					54
TON	1	6.0	7.3	13	3.59	16.22	0.30	0.71	88
Mean		6.6	8.1				0.29		72
				Work rate, 300 kg-m/min					
JBW	1	21.3	26.3	25	4.08	16.54	0.96	0.90	95
MPW	2	20.7	25.5		4.28	16.45	0.93	0.93	98
MBG	3	19.5	23.7	20	4.28	16.24	0.93	0.88	83
JSM	2	16.9	23.2	15	4.66	15.79	0.89	0.86	85
TON	1	16.0	19.5		5.00	15.36	0.92	0.87	108
BCB	1	24.8	30.5		3.86	16.88	1.02	0.93	90
				Work rate, 600 kg-m/min					
JBW	2	28.6	35.3	25	4.83	15.66	1.54	0.89	105
MPW	1	30.6	37.7		4.85	15.86	1.58	0.94	115
MBG	1	30.3	37.0		4.40	16.50	1.35	0.98	101
JSM	1	27.2	32.9	24	4.72	15.76	1.41	0.88	
TON	1	28.9	35.1		5.27	15.42	1.62	0.94	128
BCB	2	29.7	36.5		4.10	16.62	1.30	0.93	99
				Work rate, 900 kg-m/min					
JBW	2	43.3	53.3	24	4.64	16.17	2.08	0.96	115
MPW	1	38.0	53.9		5.22	15.35	2.12	0.93	138
MBG	5	40.8	50.1	26	4.71	15.89	2.09	0.92	129
JSM	1	37.9	46.9	25	4.84	15.75	2.01	0.91	129
TON	1	43.9	53.4		4.94	16.01	2.17	0.99	155
BCB	2	48.8	60.1	26	4.07	16.85	2.01	0.98	110
				Work rate, 1,200 kg-m/min					
JBW	2	58.3	71.8		4.73	16.16	2.80	0.98	139
MPW	1	61.4	75.7		4.72	16.19	2.93	0.98	170
MBG	5	52.2	63.3	27	4.84	15.90	2.66	0.95	150
JSM	1	57.0	70.3		4.76	16.18	2.72	0.99	154
TON	1	66.5	80.8		4.53	16.68	2.79	1.07	172
BCB	1	62.6	76.8		4.07	16.96	2.48	1.02	136
				Work rate, 1,500 kg-m/min					
JBW	1	88.6	109.2	25	4.43	16.78	3.63	1.07	198
MPW	1	87.8	107.9	34	4.18	17.25	3.14	1.16	184
MBG	2	67.0	81.9	65	4.96	16.13	3.20	1.03	176
JSM	1	65.3	80.7		5.02	16.20	3.05	1.07	174
TON	1	75.3	91.8		4.46	16.67	3.20	1.05	195
BCB	1	119.1	147.2		3.33	18.12	3.22	1.22	
				Work rate, 1,800–2,000 kg-m/min					
*MBG**	1	94.9	115.9		4.40	17.09	3.53	1.18	188
JSM†	1	121.4	146.5	46	3.66	17.89	3.65	1.21	197
JBW‡	2	125.2	153.9		3.60	17.74	3.93	1.15	177

* 2 min at 1,800 kg-m/min. † 2.5 min at 1,860 kg-m/min.
‡ 5 min at 1,950–2,000 kg-m/min (after expedition).

TABLE 3.3 *Results of work experiments at 15,300 ft (4,650 m) (Bar. 440 mm Hg)*

Date	Subj.	Ventilation, l/min STPD	Ventilation, l/min BTPS	Frequency of Respiration/min	F_{ECO_2}, %	F_{EO_2}, %	Oxygen Intake, l/min STP	Respiratory Exchange Ratio (R)	Heart Rate, beats/min	Duration of Work, min
Work rate, 300 kg-m/min										
11/12/60	*MBG*	17.3	38.1	25	4.94	15.63	0.94	0.91	113	15
13/12/60	*JSM*	15.0	32.9	25	5.06	15.26	0.88	0.86	100	15
10/12/60	*TON*	13.3	29.4	22	5.02	15.42	0.79	0.88	101	10
7/12/60	*BCB*	20.3	41.9		4.07	16.51	0.92	1.12	103	17
9/12/60	*WR*	17.7	38.6	15	5.13	15.73	0.93	0.97		17
Work rate, 600 kg-m/min										
11/12/60	*MBG*	24.8	54.6	25	5.15	15.37	1.41	0.90	127	5
13/12/60	*JSM*	23.7	51.9	25	4.60	15.93	1.41	0.86	127	5
10/12/60	*TON*	22.8	50.0	24	5.31	15.22	1.33	0.91	120	3
9/12/60	*WR*	25.5	55.6	20	5.29	15.39	1.44	0.93		5
Work rate, 900 kg-m/min										
11/12/60	*MBG*	35.1	77.2	25	5.00	15.65	1.88	0.92	139	7
13/12/60	*JSM*	38.0	83.2	36	4.60	15.93	1.95	0.89	147	7
7/12/60	*BCB*	51.3	113.5		3.95	17.03	2.01	1.00	127	7
9/12/60	*WR*	47.8	104.2	60	4.25	16.67	2.05	0.98		6.5
Work rate, 1,200 kg-m/min										
11/12/60	*MBG*	77.3	170.1	50	3.35	17.83	2.31	1.14	155	2
9/12/60	*WR*	64.5	140.6	60	4.15	17.12	2.41	1.10		4.5
Work rate, 1,500 kg-m/min										
11/12/60	*MBG*	85.5	188.1	50	3.06	17.95	2.51	1.02	165	2
13/12/60	*JSM*	79.7	174.5	54	3.63	17.44	2.78	1.03	161	2
10/12/60	*TON*	70.6	156.0		4.05	17.22	2.58	1.10	174	2
9/12/60	*WR*	69.9	152.5		3.93	17.31	2.49	1.10		2.5

TABLE 3.4 *Results of work experiments at 5,800 m (19,000 ft) (Bar. 380 mm Hg)*

Subj.	No. of Obs.	Ventilation, l/min STPD	Ventilation, l/min BTPS	Frequency of Respiration/min	F_{ECO_2}, %	F_{EO_2}, %	Oxygen Intake, l/min STP	Respiratory Exchange Ratio (R)	Heart Rate, beats/min	Duration of Work, min
Rest, sitting on ergometer										
JBW	2	4.8	12.4				0.32	0.87		
MPW	2	6.6	17.4				0.33			
MBG	2	6.7	17.4				0.37	0.87		
JSM	2	5.2	13.6				0.31	0.85		
Mean		5.8	15.2				0.33			
Work rate, 300 kg-m/min										
JBW	5	17.4	45.2	25	5.31	15.26	0.99	0.91	107	
MPW	7	16.5	43.4	25	5.44	15.18	0.96	0.92	114	
MBG	7	18.5	48.4	26	5.02	15.62	1.01	0.91	111	
JSM	7	17.5	45.7	25	4.99	15.73	0.91	0.91	104	
Work rate, 600 kg-m/min										
JBW	3	26.9	69.6	25	5.33	15.41	1.52	0.94	122	
MPW	3	29.4	76.8	50	5.22	15.37	1.61	0.95	123	
MBG	3	29.2	79.2	38	4.53	16.20	1.39	0.94	132	
JSM	3	26.2	68.0	25	5.22	15.55	1.42	0.96	119	
Work rate, 900 kg-m/min										
JBW	3	51.6	134.1	36	4.56	16.36	2.12	1.03	124	
MPW	4	49.0	128.5	45	4.44	16.58	2.09	1.06	145	
MBG	5	52.4	135.6	50	3.94	16.94	1.96	0.99	141	
JSM	4	41.6	107.7	52	4.69	16.22	1.89	0.95	151	
Work rate, 1,200 kg-m/min										
JBW	2	72.5	187.6	50	3.75	17.50	2.45	1.19	125	3.5 to 4.0
MPW	1	60.0	156.0		4.33	17.60	1.85	1.39	155	3.0
MBG	1	71.5	185.0	50	3.41	17.85	2.14	1.14	145	2.75

TABLE 3. 5 *Results of work experiments at 6,400 m (21,000 ft) and 7,440 m (24,400 ft)*

Date	Subj.	Ventilation, l/min		Frequency of Respiration/min	F_{ECO_2}, %	F_{EO_2}, %	Oxygen Intake, l/min STP	Respiratory Exchange Ratio (R)	Heart Rate, beats/min	Duration, min
		STPD	BTPS							
Altitude 6,400 m (21,000 ft) (Bar. 344 mm Hg)										
					Work rate 300 kg-m/min					
4/5/61	*JBW*	16.2	46.93	25					123	12.0
5/5/61	*JBW*	17.4	50.9	25	4.82	15.80	0.91	0.91	122	12.0
2/5/61	*MPW*	17.1	50.2	25	5.39	15.18	1.00	0.91	128	12.0
5/5/61	*MPW*	20.6	60.3	25	4.26	16.30	0.98	0.89	113	12.0
2/5/61	*MBG*	18.3	53.9	25					132	12.0
6/5/61	*MBG*	17.9	52.1	25	4.49	16.00	0.91	0.88	115	12.0
4/5/61	*JSM*	16.2	47.0	25	5.11	15.32	0.93	0.88		12.0
4/5/61	*JSM*	16.6	48.3	25					118	7.0
					Work rate 600 kg-m/min					
4/5/61	*JBW*	23.4	82.6	25					129	6.0
2/5/61	*MPW*	26.4	77.7		4.92	15.94	1.33	0.97	145	6.0
2/5/61	*MBG*	36.4	107.3	50					148	6.0
4/5/61	*JSM*	28.4	82.4	37					133	6.0
					Work rate 900 kg-m/min					
4/5/61	*JBW*	56.0	162.6	50					142	5.0
5/5/61	*JBW*	57.2	167.4	50	3.61	17.53	1.92	1.07		5.0
2/5/61	*MPW*	50.9	149.8	50	3.91	17.16	1.91	1.04	161	5.0?
6/5/61	*MPW*	46.2	135.0	50	3.33	17.76	1.45	1.05	133	2.75
2/5/61	*MBG*	60.3	177.5	50	3.16	17.8	1.90	0.99	144	4.75
6/5/61	*MBG*	59.3	172.8	50	3.10	17.9	1.82	1.00	129	5.0
4/5/61	*JSM*	50.5	146.8	50					143	5.0
5/5/61	*JSM*	51.2	149.4		3.84	17.2	1.90	1.03		4.5
					Work rate 1050 kg-m/min					
5/5/61	*JBW*	69.1	202.3	50	3.22	17.86	2.11	1.05	133	4.5
Altitude 7,440 m (24,400 ft) (Bar. 300 mm Hg)										
					Work rate 300 kg-m/min					
13/5/61	*JBW*	15.2	51.8	25	5.03	15.25	0.90	0.85	129	12.0?
14/5/61	*JBW*	16.5	56.0	25	5.28	15.18	0.97	0.89	131	12.0
13/5/61	*MPW*	14.7	50.0		4.12	16.05	0.75	0.80		12.0
					Work rate 600 kg-m/min					
13/5/61	*JBW*	37.0	125.7	50	3.86	16.97	1.48	0.96	143	6.0
14/5/61	*JBW*	36.6	124.6	50	3.91	17.04	1.43	0.99	138	6.0
13/5/61	*MPW*	33.6	114.3		3.05	17.42	1.33	0.83	129	5.0

TABLE 3.6 *Summary of results at sea level and at various altitudes*

	Rate of Work, kg-m/min	Ventilation, l/min		F_{ECO_2}, %	F_{EO_2}, %	Oxygen Intake, l/min STP	Respiratory Exchange Ratio (R)	Heart Rate, beats/min
		STPD	BTPS					
Sea level (Bar. 750 mm Hg)	300	19.6±2.8(10)	24.5±3.5(10)	4.36±0.40(10)	16.20±0.56(10)	0.94±0.05(10)	0.90±0.04(10)	92±9(10)
	600	29.2±2.3(8)	35.8±3.0(8)	4.64±0.40(8)	16.01±0.54(8)	1.46±0.14(8)	0.92±0.04(8)	109±10(8)
	900	42.3±4.0(12)	52.0±4.8(12)	4.68±0.36(12)	16.05±0.51(12)	2.08±0.10(12)	0.94±0.06(12)	126±16(12)
	1,200	56.8±5.3(11)	69.4±6.7(11)	4.69±0.21(11)	16.19±0.43(11)	2.72±0.14(11)	0.98±0.05(11)	151±15(11)
	1,500	79.7±18.5(8)	97.7±23.3(8)	4.54±0.59(8)	16.67±0.73(8)	3.23±0.17(8)	1.08±0.07(8)	185±10(8)
	1,800–2,000	113.8±16.5(3)	138.8±20.2(3)	3.89±0.45(3)	17.54±0.39(3)	3.70±0.21(3)	1.18±0.03(3)	187±10(3)
4,650 m (15,300 ft) (Bar. 440 mm Hg)	300	16.7±2.7(5)	36.8±5.9(5)	4.84±0.44(5)	15.71±0.48(5)	0.89±0.06(5)	0.99±0.14(3)	104±6(4)
	600	24.2±1.2(4)	53.0±2.6(4)	5.25±0.09(3)	15.33±0.09(3)	1.40±0.05(4)	0.92±0.02(2)	125±3(3)
	900	43.0±7.8(4)	94.5±17.2(4)	4.45±0.45(4)	16.32±0.64(4)	1.97±0.07(4)	0.95±0.05(4)	139±9(4)
	1,200	70.9±9.0(2)	155.4±20.9(2)	3.75±0.57(2)	17.50±0.53(2)	2.36±0.07(2)	1.10±0.03(2)	155(1)
	1,500	76.4±8.0(4)	167.8±15.9(4)	3.67±0.44(4)	17.48±0.33(4)	2.60±0.13(4)	1.06±0.04(4)	167±7(3)
5,800 m (19,000 ft) (Bar. 380 mm Hg)	300	17.5±1.5(26)	45.8±4.1(26)	5.13±0.31(17)	15.49±0.41(17)	0.98±0.08(26)	0.91±0.04(26)	109±6(14)
	600	28.2±2.7(12)	73.2±7.1(12)	5.12±0.37(11)	15.64±0.42(11)	1.49±0.10(11)	0.95±0.02(11)	124±7(10)
	900	46.3±13.5(16)	126.1±20.7(16)	4.28±0.41(9)	16.63±0.42(9)	2.01±0.13(14)	1.04±0.15(14)	139±11(8)
	1,200	67.0±7.4(5)	173.7±19.0(5)	3.81±0.41(4)	17.61±0.17(4)	2.25±0.27(5)	1.16±0.14(5)	143±16(5)
6,400 m (21,000 ft) (Bar. 344 mm Hg)	300	17.5±1.5(8)	51.2±4.4(8)	4.81±0.45(5)	15.72±0.47(5)	0.95±0.04(5)	0.90±0.02(5)	122±7(7)
	600	28.7±5.6(4)	87.5±13.3(4)	4.92(1)	15.94(1)	1.33(1)	0.97±(1)	139±9(4)
	900	55.0±4.1(7)	160.9±12.4(7)	3.53±0.38(5)	17.51±0.33(5)	1.89±0.04(5)	1.03±0.03(5)	144±11(5)
7,440 m (24,400 ft) (Bar. 300 mm Hg)	300	15.5±0.9(3)	52.6±3.1(3)	4.81±0.61(3)	15.49±0.48(3)	0.87±0.11(3)	0.85±0.04(3)	130(1)
	600	35.8±1.8(3)	121.5±6.3(3)	3.61±0.48(3)	17.14±0.24(3)	1.42±0.08(3)	0.92±0.09(3)	140±3(3)

Figures in parentheses represent number of observations.

Oxygen intake and work rate

Fig. 3.1 shows the relation of oxygen intake to work rate at sea level and at various altitudes up to 7,440 m (24,400 ft). The relation is a straight line and independent of altitude. Data from shorter tests in which the subjects failed to keep going for 5 min are not shown, because the duration and O_2 increments were highly variable; some subjects failed before their O_2 intakes had reached the level attained at the preceding work rate, while others increased their oxygen intake, but never by as much as 0.5 liters/min unless they kept going for 5 min (Table 3.2). These results are of value when determining maximum O_2 intake, but not when the relation between oxygen intake and work rate is under consideration.

The results obtained at Mingbo (4,650 m, 15,300 ft) were unfortunately poorly controlled, and owing to a misunderstanding, the subjects did not exercise for the minimum period of 5 min at 1,200 kg-m/min, although they could have done so, and the O_2 intakes do not show the expected increase over the 900 kg-m/min values (Table 3.3). The only other aberrant value is the one on M.P.W. working at 600 kg-m/min at 6,400 m (21,000 ft) (Table 3.5). The gas analysis is the probable source of error, since the sample was too small to be analyzed satisfactorily.

Ventilation

Fig. 3.2 shows the relation of ventilation BTPS and ventilation STPD to oxygen intake, the results of all subjects are averaged. This relationship is often shown as a curve gradual in light exercise and steepening in heavy exercise. However, many authors including Gray, 1950; Grodins, 1950; Asmussen, Nielsen and Wieth-Pettersen, 1943 and

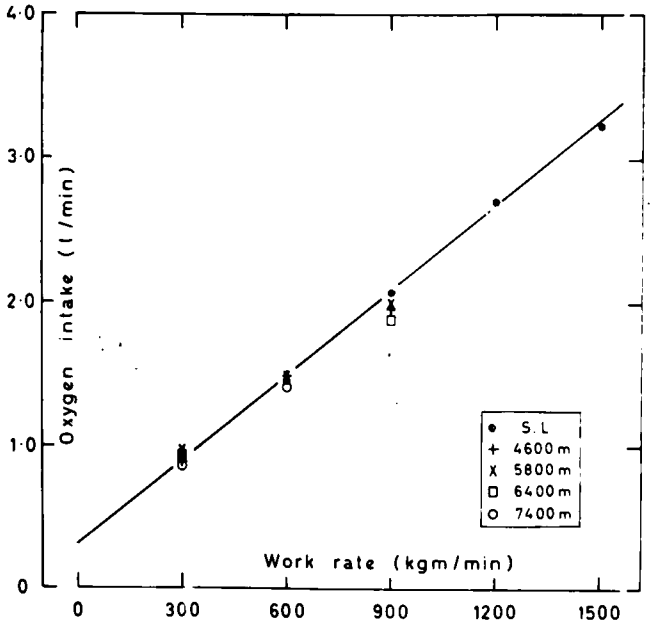

FIG. 3.1. The relation of work rate to oxygen intake at various altitudes. Each point represents the mean of all subjects studied at the given altitude.

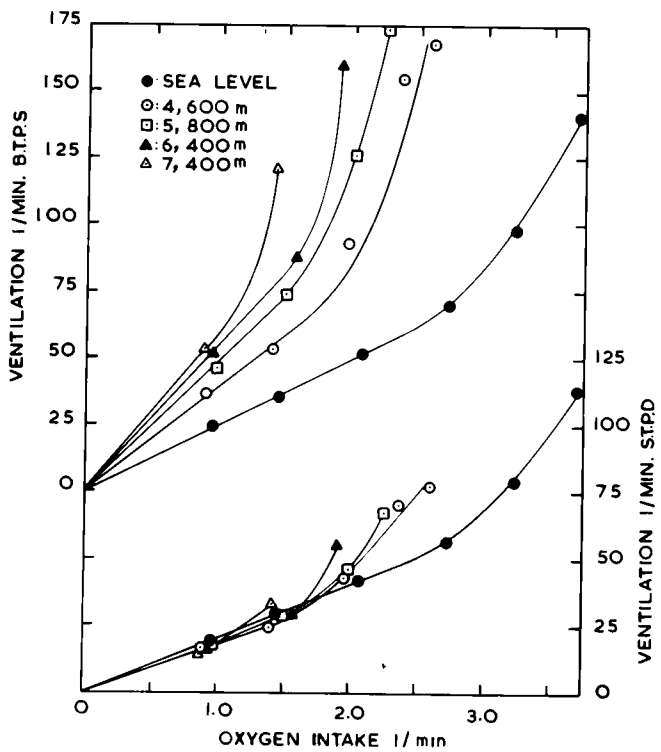

FIG. 3.2. The relation of ventilation to O_2 intake at various altitudes from sea level to 7,400m (24,400ft). Each point represents the mean of all subjects studied at that altitude.

Kao,(1963) have shown it to be a linear relationship until maximum work rate is approached when it breaks away and steepens. Our sea level data support this linear relationship and our altitude data are also consistent with it, with the proviso that as altitude is increased, and maximum work rate reduced, the breakaway point or region is shifted progressively to lower work rates.

It is seen that as altitude is increased: (i) the slope of the ventilation/oxygen intake response line steepens (at submaximum work rates), (ii) that the breakaway region is at progressively lower O_2 intakes, and (iii) beyond the breakaway region the curve steepens faster (Fig. 3.2).

The final rapid rise in ventilation for only a small increase in work-rate exactly parallels the sensation of extreme dyspnoea of even easy climbing at extreme altitude.

This breakaway region in our subjects is:

at sea level	about 2.6 l/min O_2 intake	(1,100 kg-m/min)
at 4,600 m	about 1.8 l/min O_2 intake	(900 kg-m/min)
at 5,600 m and 6,400 m	about 1.5 l/min O_2 intake	(600 kg-m/min)
at 7,400 m	about 1.2 l/min O_2 intake	(300 kg-m/min)

Relationship between ventilation, O_2 intake and altitude at submaximum work rates

We have confirmed that the ventilation expressed as liters per minute STPD is independent of altitude for work rates where the ventilation/O_2 intake response is linear. This was found by Christensen and Forbes 1937, quoted by Pugh, 1958.

Therefore it is possible to predict what the ventilation BTPS will be for any given altitude and work rate, or more correctly, for any given barometric pressure (PB) and O_2 intake.

For a given PB and O_2 intake,

$$\dot{V} = \dot{V}_{STPD_{SL}} \cdot f \qquad (1)$$

where $\dot{V}$ is the predicted ventilation, l/min BTPS,

$\dot{V}_{STPD_{SL}}$ is the ventilation, l/min STPD for the given O_2 intake at sea level, and

f is the conversion factor STPD to BTPS for the given P_B.

We have shown that at sea level the ventilation/O_2 intake ($\dot{V}$ O_2) response is linear, its slope being the ventilation equivalent (VE) Therefore

$$\dot{V}_{STPD_{SL}} = \dot{V}O_2 \cdot VE \qquad (2)$$

by combining the equations (1) and (2) we get:

$$\dot{V} = \dot{V}O_2 \cdot VE \cdot f \qquad (3)$$

The results of applying this equation is shown in Table 3.7 where the predicted ventilation is shown against the actual observed ventilation for the four camps where we made observations. It will be seen that with the exception of one work rate at the highest camp, all the predictions fall within one standard deviation of the observed result. In the exceptional case, the prediction is higher than the observed, possibly because the severe hypoxia was affecting the working of the respiratory muscles. Maximum ventilation at this altitude was strikingly less than at the lower camps.

TABLE 3.7. Correlation between predicted and actual ventilation at various altitudes and various sub-maximal work rates.

Altitude Bar. mm.Hg	Work Rate Kg./m./min.	Oxygen Correlation L/min.	Predicted Ventilation L/min. BTPS	Actual Ventilation L/min. BTPS	Error in Predicted ±L/min.
4,650 m. Bar. 440 f = 2.2	300	0.94	41.5	36.8 ± 5.9	+ 4.7
	600	1.44	62.0	63.5 ± 2.6	- 1.5
	900	1.99	88.0	94.5 ± 17.0	- 6.5
5,800 m. Bar. 380 f = 2.62	300	0.94	49.5	45.8 ± 4.1	+ 3.7
	600	1.44	75.5	73.2 ± 7.1	+ 2.3
	900	1.99	105.0	126.1 ± 20.7	-20.1
6,400 m. Bar. 344 f= 2.90	300	0.94	54.5	51.2 ± 4.4	+ 3.3
	600	1.44	83.5	87.5 ± 13.3	- 5.0
7,440 m. Bar. 300 f= 3.40	300	0.94	64.0	52.6 ± 3.1	+11.4

f = factor for correcting gas volumes STPD to BTPS

Effects of added inspired oxygen

At the end of the expedition a few experiments were conducted to observe the effect on ventilation of removing the stimulus of hypoxia by supplying an oxygen enriched gas so that the P_IO_2 was 150 mm Hg.

The results of three experiments, one at 4,650 m and two at 5,800 m are shown in Table 3.8 and Fig. 3.3 together with one such experiment from the second expedition (alt 4,880 m).

It is seen that the effect on breathing gas with sea level P_IO_2 was to reduce the ventilation considerably especially at high work rates. The maximum work rate was also increased by about 300 kg-m/min, and the sensation of dyspnoea was greatly reduced. But the ventilation and maximum work rate were not restored to sea level values. This is in accord with previous workers, including Astrand (1954a and b) and Dejours, Kellogg and Pace (1963).

Exercise experiments with acute hypoxia at sea level

Experiments were carried out at CMC Vellore in November 1966 and March 1967. At first gas mixtures were made up by rebreathing air and passing it through soda lime, but the small quantity of CO_2 remaining (0.1-0.3 per cent) was sufficient to significantly affect ventilation. These experiments were therefore rejected and in the last series gas mixtures were made up from cylinder nitrogen and air in 300 l meteorological balloons.

The subject (J.S.M.) was the same as for two of the altitude experiments on whom considerable data were already available. A standard bicycle ergometer and standard methods of gas collection were used.

TABLE 3.8. Effect on ventilation of adding oxygen to the inspired gas - P_IO_2 150, at various altitudes.
Compare with ventilation on ambient P_IO_2 in Tables 3.2-3.6.

Altitude	Subject	Work Rate Kg. m. min.	Ventilation L/min. BTPS	STPD
4,650 m.	J.S.M.	300	34.0	15.5
Bar. 440	"	600	50.0	22.8
	"	900	63.0	28.8
	"			
4,880 m.	J.S.M.	475	35.2	15.1
Bar. 420	"	900	54.6	23.6
	"	1265	74.5	32.2
5,800 m.	M.P.W.	300	34.9	13.4
Bar. 380	M.B.G.	300	30.3	11.6
	M.P.W.	600	54.0	20.7
	M.B.G.	600	49.2	18.9
	M.P.W.	900	85.0	32.5
	M.B.G.	900	69.4	26.6
	M.B.G.	1200	92.2	35.4
	M.P.W.	1500	122.6	47.0

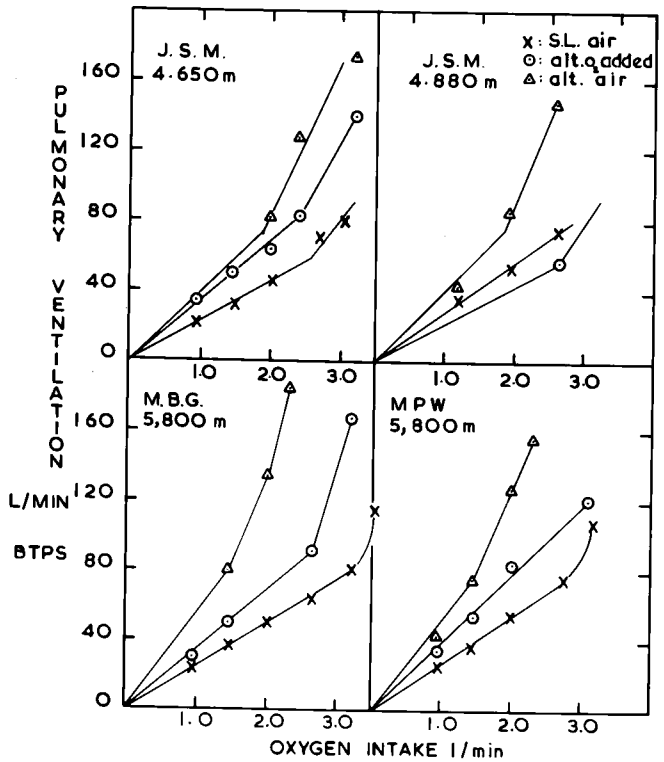

FIG. 3.3. The effect of added O_2 to the inspired gas. The relation of ventilation to O_2 intake at sea level X, acclimatized breathing air Δ and acclimatised, breathing O_2 enriched gas, PIO_2 150 mm Hg, ⊙. Each graph shows the result of one experiment at the altitude indicated

The inspired gas mixtures were made up and found by analysis to have Po_2 of: 147 (air), 105, 82, and 76.5 mm Hg. Analysis was by Lloyd-Haldane apparatus (Lloyd, 1958).

Since we had shown that at light and moderate work the $\dot{V}/O_2$ intake relationship was linear, only one work rate was adopted (300 kg-m/min) which gave an oxygen intake close to 1 l/min.

The results of these experiments are shown in Table 3.9, together with the calculated ventilation equivalents.

Acute and Chronic hypoxia

The effect on ventilatory control of hypoxia can be shown by plotting the ventilatory equivalent against the P_Io_2. This is done for both acute and chronic hypoxia in Fig. 3.4 together with two points from the literature.

For chronic hypoxia, pooled data of all subjects, it will be seen that the points lie very close to a straight line with an origin at 100 mm Hg P_Io_2 and a slope of 0.7 l/min per mm Hg Po_2 decrease. For acute hypoxia, as far as the meagre data go, a very similar relationship is found. Up to P_Io_2 100 mm Hg there is no significant increase in VE. The VE rises linearly with decreasing P_Io_2, the origin being about 91 mm Hg and the slope 1.1 l/min per mm Hg Po_2.

DISCUSSION

The results of sea level experiments are closely comparable with those of other workers with respect to oxygen intake and ventilation for a given work rate on the bicycle ergometer (Fig. 3.1) (Astrand and Astrand, 1958; Astrand, Astrand, Christensen, and Hedman, 1960).

TABLE 3.9. Results of work experiments with acute hypoxin at vellore (Bar. 746 mm. Hg). Subject J.S.M.

$P_I O_2$	Work Rate Kg./m./min.	$\dot{V}O_2$ L/min.	Ventilation L/min. STPD	BTPS	Ventilation Equivalent
147	360	0.953	19.0	23.4	24.5
105	380	0.993	20.2	24.9	25.0
82	360	0.785*	27.7	34.1	35.0
76.5	360	1.280*	32.4	40.0	41.0

*It is probable that these values are in error. They are determined by the difference between inspired and expired O_2 % which at high ventilation is small. In calculating ventilatory equivilent a $\dot{V}$ O_2 of 0.953 1/min. is assumed.

The increase in ventilation on exercise with altitude is also well known. Our subjects were able to achieve oxygen intakes comparable with those on the Mount Everest expedition (Pugh, 1958) and greater than non-mountaineers e.g. Christensen (1937) and Houston and Riley (1947).

Ventilation STPD

With changing altitude ventilation at moderate work rates was constant when reduced to STPD. Does this indicate a ventilatory control system maintaining a constant $\dot{V}_{STPD}$ directly? I think not.

The output from the respiratory center must be related to $\dot{V}_{BTPS}$ rather than to $\dot{V}_{STPD}$, a given neural output resulting in a given amount of respiratory work done which, if lung mechanics remain constant, and neglecting changes of viscosity and density of air, will result in a given volume of air ventilated, rather than a given mass or weight of air. That this expected result is true is born out by our low pressure chamber experiments with CO_2 inhalation at Farnbrough (Chapter 2). In these experiments no acclimatization was allowed to take place between runs at sea level and simulated altitude and it was found that for the same stimulus (P_Aco_2) the ventilation BTPS was the same (within the limits of experimental error).

The observation that $\dot{V}_{STPD}$ is independent of altitude indicates that the respiratory control adaptations have taken place resulting in such an increase in $\dot{V}_{BTPS}$ as to supply to the lungs at altitude the same mass of air as at sea level.

This is then analogous to the constancy of arterial oxygen content with changing altitude brought about by the increasing haemoglobin concentration as arterial oxygen saturation decreases.

Ventilation BTPS

The results of the present study allow us to look at the relationship of increasing ventilation BTPS with increasing altitude. If we concentrate on light and moderate work rates where the $\dot{V}/O_2$ intake relationship is linear, we have a family of lines with increasing slope (Fig. 3.2). The slope of these lines which is the ventilation equivalent (in l/min BTPS) can be plotted against the P_IO_2 for each altitude studied. This is done in Fig. 3.4. This a linear plot with an intercept at approximately P_IO_2 100 mm Hg and a slope of 0.7 l/min per mm Hg P_IO_2 decrease. This intercept is about the same value at which an increase in ventilation is noticed at rest at sea level when the O_2 per cent in the inspired gas is slowly reduced, i.e. about 13 per cent (Haldane and Priestly 1905).

One might have expected that the increase in slope would have been related to P_IO_2 by some exponential function but from the data we have, a linear relationship both for chronic and acute hypoxia gives the best fit.

Acute hypoxia

The effect of acute hypoxia on ventilation results in no increase in the ventilatory equivalent until a lower P_IO_2 is reached than with chronic hypoxia, via about 91 mm Hg. Thereafter the effect of further reduction in hypoxia is to increase the ventilatory equivalent more rapidly than with chronic hypoxia (slope = 1.1 l/min per mm Hg Po_2 decrease). If the extrapolation is justified, the ventilatory equivalent (VE) for acute and chronic hypoxia would be equal at a P_IO_2 of 72 mm Hg, an altitude of about 5,500 m (18,000 ft).

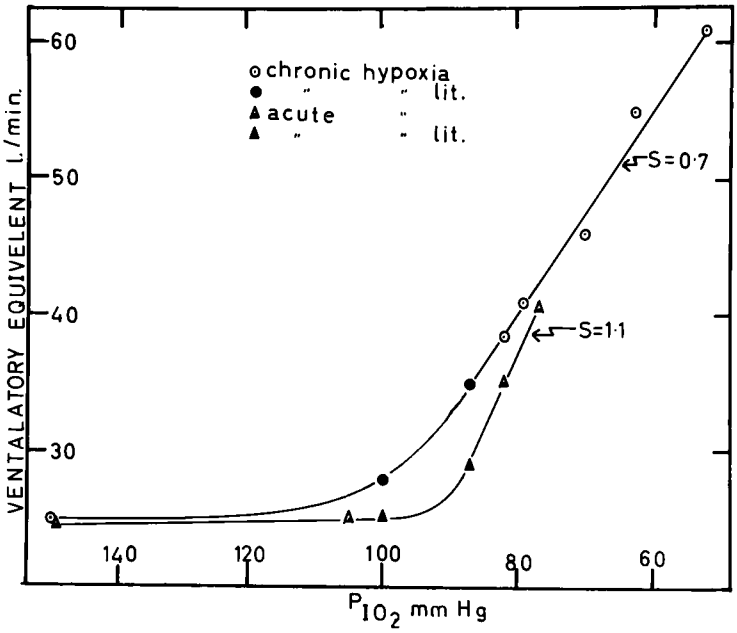

FIG. 3.4. The relation of ventilatory equivalent to PIO_2 in hypoxia; acute Δ, and chronic O. Closed symbols from the literature, (Åstrand 1954b and Dejours 1963).

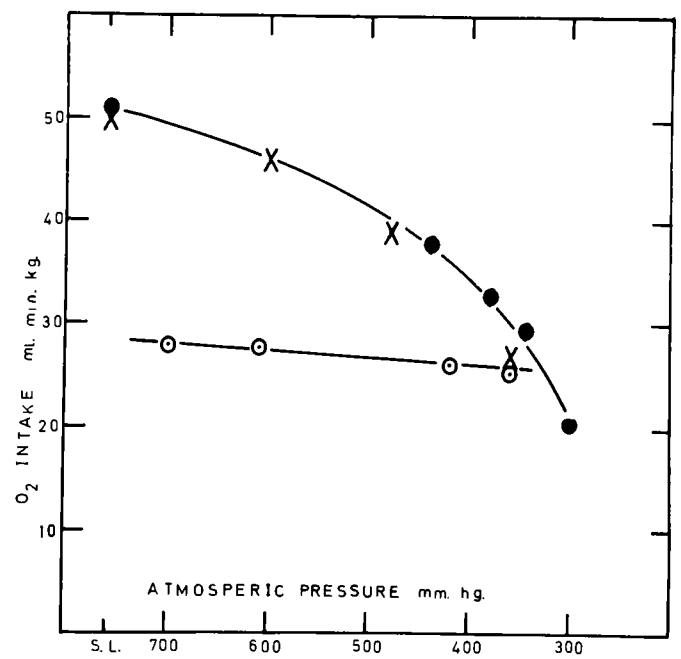

FIG. 3.5. The relation of maximum O_2 intake to atmospheric pressure, present data, ● data of Pugh (1958), X. Lower line: average values for O_2 intake of men climbing at their usual pace, O.

The ventilation on moderate exercise during acute or chronic hypoxia can therefore be predicted from the following equation:

$$\dot{V} = Vo_2 \cdot VE + s(x - P_Io_2)$$

where x is the intercept on the VE/P_Io_2 plot (the abcissa being VE for sea level)

s is the slope of this line

VE is the ventilation equivalent at sea level in l/min BTPS

For our subjects, acclimatized, x = 100 mm Hg s = 0.7 VE = 25 l/min

acute hypoxia, x = 91 mm Hg s = 1.1

Effect of added inspired oxygen (Table 3.8 and Fig. 3.3)

The reduction in ventilation on giving sea level P_Io_2 is in agreement with previous work (Astrand, 1954b) and gives some indication of the hypoxic drive present. This was rather variable and the few results preclude any quantitation of the hypoxic drive except to note that with increasing altitude the reduction in ventilation was greater. The residual hyperventilation gives an indication of the change in CO_2 sensitivity with acclimatization. This also increases with increasing altitude.

Maximum work rate (oxygen intake)

The above discussion has been limited to light and moderate work loads. At heavier work loads the relationship between ventilation and work rate or oxygen consumption departs from linear and ventilation increases very rapidly. Very high ventilations are achieved at altitude e.g. 188 l/min by M.B.G. at 4,650 m and 187 l/min by J.B.W. at 5,800 m which approaches the maximum breathing capacity. It is noteworthy that at the highest altitude, 7,440 m, the ventilation at maximum work rate

was only 125 and 114 l/min for the two subjects studied suggesting that possibly the respiratory muscles are limited by hypoxia.

This great increase in ventilation is presumably due to a combination of acidosis (due to anaerobic metabolism) and the effect of hypoxia itself. We showed (West, Lahiri, Gill, Milledge, Pugh and Ward, 1962) that at high work rates the arterial oxygen saturation falls precipitously despite a rising $P_{A}o_2$ due to hyperventilation. This is because of diffusion limitations at high O_2 intake.

This reduction in maximum O_2 intake with altitude is shown in Fig. 3.5 which includes data from the Mount Everest Expedition (Pugh, 1958) and some values for O_2 intake at comfortable climbing rates for continuous climbing. This level seems to be about 15-18 ml O_2/kg/min and this is the value for maximum oxygen intake for a climber at about 6,800 m. Since maximum O_2 intake can only be maintained for a few minutes, climbers adopt an intermittent mode of climbing at altitudes well below this.

The effects of this marked hyperventilation on the acid-base balance and oxygen transport is further considered in Chapter 5.

CONCLUSION

To meet the oxygen requirements of his exercising body lowland man at altitude has to hyperventilate very considerably. At the "silver hut" the ventilation was doubled at moderate work rates, and more than doubled at high work rates. On increasing the inspired Po_2 to sea level values, the ventilation, though reduced, did not return to sea level values, indicating a change in ventilatory control with acclimatization. This change in ventilatory control presumably being a changed response to CO_2 as found in the inhalation experiments (Chapter II) is a resetting of the medullary chemostat.

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CHAPTER IV

VENTILATORY RESPONSE TO CO_2 AND O_2 IN SHERPA HIGHLANDERS

INTRODUCTION

Hurtado and Aste-Salazar (1948) and Chiodi (1957) found that the alveolar P_{CO_2} in Andean high altitude residents was significantly higher than lowlanders acclimatized to a similar altitude. Also we had noted in 1960 that for a given grade of exercise in the one Sherpa in whom we measured it, the ventilation was apparently lower. This confirmed the general impression that Sherpas hyperventilate less at altitude than lowlanders, and prompted us to plan to study their respiratory response to hypoxia and CO_2 in 1964 on the "Second Schoolhouse Expedition" (Chapter I).

The experiments were carried out during October and November 1964 at 4,880 m (16,000 ft), barometric pressure 420-425 mm Hg.

MATERIALS

There were three principal Sherpa subjects plus one used in the preliminary experiments only. All these men had been born and lived in a village at 4000 m. They had all been on previous mountaineering expeditions in which they had gone to heights of 6000 m to 7500 m. None of them could be classed as being in the top flight of climbing Sherpas and were probably representative of the Sherpa population. The four lowland subjects were all expedition members; J.S.M. and S.L. were

members of the physiological team and both had had previous Himalayan experience. They had spent about four to six weeks at 4,880 m when experiments were carried out. R.S. and J.Mc. were members of the climbing team. This was their first Himalayan expedition though they had much experience in the New Zealand Alps. They had climbed a difficult 6,400 m peak but had then spent two to three weeks at altitudes of 3,000 m 3,600 m and only one day at 4,880 m before the experiments on them were carried out. The heights, weights and ages of all subjects are shown in Table 4.1.

Table 4.1. Physical characteristics of subjects. Where weights declined during the stay at high altitude, a mean value is taken.

Subjects	Lowlanders			Subjects	Sherpa		
	Age (yr)	Height (cm)	Weight (kg)		Age (yr)	Height (cm)	Weight (kg)
S.L.	32	158	56	P.	26	155	52
J.S.M.	34	175	69	H.N.	35	165	65
R.S.	23	172	65	P.N.	42	167	60
J.Mc	28	180	81	H.T.	22	164	59
Mean	29.3	171	67.8	Mean	31.3	163	59.0

METHODS

The apparatus was the same as that used on the previous expedition (Chapter II) with the following modifications:

1) For measuring ventilation, a Wright "respirometer" (British Oxygen Co. Ltd.) was used in place of the dry gas meter. It gave a signal for every 1 liter expired which was recorded on a clockwork pen recorder. 2) Suction for drawing end-tidal gas through the sampler was by water displacement 3) There was no CO_2 meter; a steady ventilation seen on the recorder was taken to indicate a steady state, at which time a sample of end-tidal gas was drawn into a Barcroft tube.

GAS MIXTURES

Four gas mixtures were made up from air and cylinder O_2, N_2 and CO_2 so as to give a P_Ico_2 of 15-20 mm Hg and P_Io_2 of approximately 54, 76, 90 and 225 mm Hg respectively.

PROCEDURE

The procedure for the experiments was similar to the previous series. In the first group of experiments the order of bag mixtures was from low to high O_2 and the latter from high to low O_2. There was no apparent difference in results between these two procedures.

RESULTS

We carried out 14 full experiments measuring CO_2 response at 3 or 4 different O_2 levels which were technically satisfactory; 8 were on 3 Sherpa subjects and 6 were on 4 lowlanders. The results of these experiments are given in Tables 4.2 a and b, and are shown graphically in Fig. 4.1. Fig. 4.2 shows two experiments in greater detail, one on a Sherpa and one on a lowlander.

It will be seen from Fig. 4.1 and 4.2 that in general:

1. The origin of the fan of isoxic lines (B) is similar in Sherpas and lowlanders.

Table 4.2 a. Results of experiments on Lowlanders at altitude of 4,880 m. Ventilation litres per min BTPS, P_ACO_2 and P_AO_2 mm. Hg.

Subject: S.L.

Expt 1		
Vent.	P_ACO_2	P_AO_2
8.4	24.01	51.45
6.4	27.78	200 +
20.6	31.29	200 +
38.5	34.28	200 +
45.6	36.69	200 +
12.91	26.27	44.08
25.5	30.50	46.62
47.0	32.80	43.71
17.0	22.71	33.23
43.5	25.29	31.07

Expt 4		
Vent.	P_ACO_2	P_AO_2
19.8	25.02	41.89
45.2	26.93	39.83
20.7	28.84	59.99
47.3	32.50	56.14
12.6	26.93	66.24
45.2	31.53	62.50
9.8	28.76	200 +
32.0	34.67	200 +
36.6	35.46	200 +
45.7	36.65	200 +

Subject: J Mc.

Expt 1		
Vent.	P_ACO_2	P_AO_2
30.0	25.73	36.72
42	28.88	38.64
83	31.06	35.72
17	28.53	46.93
83	32.04	42.48
26.5	30.08	74.25
80	35.99	68-08
27.5	33.41	200 +
75	36.66	200 +
83	43.75	200 +

Subject J.S.M

Expt 3		
28.1	25.14	38.72
62.5	26.86	38.79
13.6	26.97	43.71
27.0	27.86	43.0*
84.3	31.67	45.65
13.9	26.15	72.77
55.8	32.86	65.64
12.2	27.90	200 +
52.0	31.44	200 +

Expt 4		
21.3	26.17	42.37
63.4	28.76	39.74
18.5	26.70	54.86
74.0	32.45	51.07
18.5	28.24	57.64
68.0	31.66	54.85
17.3	28.80	200 +
53.0	34.55	200 +

Subject: R.S.

Expt 1		
49	31.28	38.34
70	31.47	35.04
23	29.05	51.11
68	33.59	46.79
18	29.15	61.85
53	33.06	60.37
70	33.89	56.46
18	30.37	200 +
73	40.29	200 +

Table 4.2 b: Results of experiments on Sherpas at altitude of 4,880 m. Ventilation litres per min BTPS, P_ACO_2 and P_AO_2 mm. Hg.

Subject: MEN

Expt 3		
V Vent.	P_ACO_2	P_AO_2
12.2	28.99	47.46
28.5	32.56	200 +
30.6	32.45	200 +
50.6	36.91	200 +
50.6	35.59	200 +
16.5	29.59	65.6
50.5	37.92	67.43
13.7	30.54	43.47
48.5	36.3	44.45
18.0	29.56	33.97
30.6	34.04	32.35
60.8	35.02	29.73

Expt 4		
Vent.	P_ACO_2	P_AO_2
9.0	28.72	46.35
20.7	26.66	34.73
41.3	32.06	32.40
68.8	35.36	33.18
25.2	30.71	35.70
61.9	34.38	33.64
49.8	36.19	58.20
16.6	30.11	200 +
35.8	34.05	200 +
47.0	37.31	200 +

Subject: H-N

Expt 3		
Vent.	P_ACO_2	P_AO_2
18.8	28.35	200 +
54.5	36.6	200 +
21.3	29.66	63.86
68.5	38.55	62.25
24.0	29.81	46.35
68.2	37.58	44.85
22.8	27.00	37.84
46.2	31.28	33.53
75.28	38.35	30.30

TABLE 4.2 b: Cont:

Subject: H-N

Expt 4			Expt 5		
Vent.	P_ACO_2	P_AO_2	Vent.	P_ACO_2	P_AO_2
13.0	29.4	51.94	17.9	29.36	37.80
35.0	29.21	43.24	53.8	32.66	34.31
62.9	33.60	39.30	17.7	30.04	48.60
20.3	28.91	49.76	60.84	35.93	45.11
71.7	36.94	46.39	18.3	28.76	70.85
19.0	28.90	88.05	54.3	35.25	65.02
46.0	35.70	80.85	13.7	30.64	200 +
21.21	28.69	200 +	53.5	37.01	200 +
48.60	32.89	200 +			

Subject: P-N

Expt 2			Expt 3			Expt 4		
Vent	P_ACO_2	P_AO_2	Vent	P_ACO_2	P_AO_2	Vent	P_ACO_2	P_AO_2
21.4	27.56	200 +	13.0	27.52	49.20	16.6	31.64	35.85
17.8	30.64	200 +	22.4	26.93	200 +	46.7	35.51	32.36
34.6	32.07	200 +	15.14	29.29	68.63	67.0	37.31	30.19
44.6	35.31	200 +	50.0	37.20	65.36	16.4	29.66	49.16
12.6	29.93	68.32	13.8	31.13	48.64	45.1	35.25	47.44
41.0	37.75	66.55	45.9	37.20	49.35	15.7	27.64	90.30
14.9	27.11	46.25	30.5	31.65	41.18	48.0	35.74	84.20
45.9	35.95	65.83	50.8	36.68	37.2	10.0	28.50	200 +
13.6	27.90	38.88	37.6	32.66	32.89	55.2	36.94	200 +
40.4	33.65	34.48	55.5	35.93	30.75			
46.4	34.33	35.72						

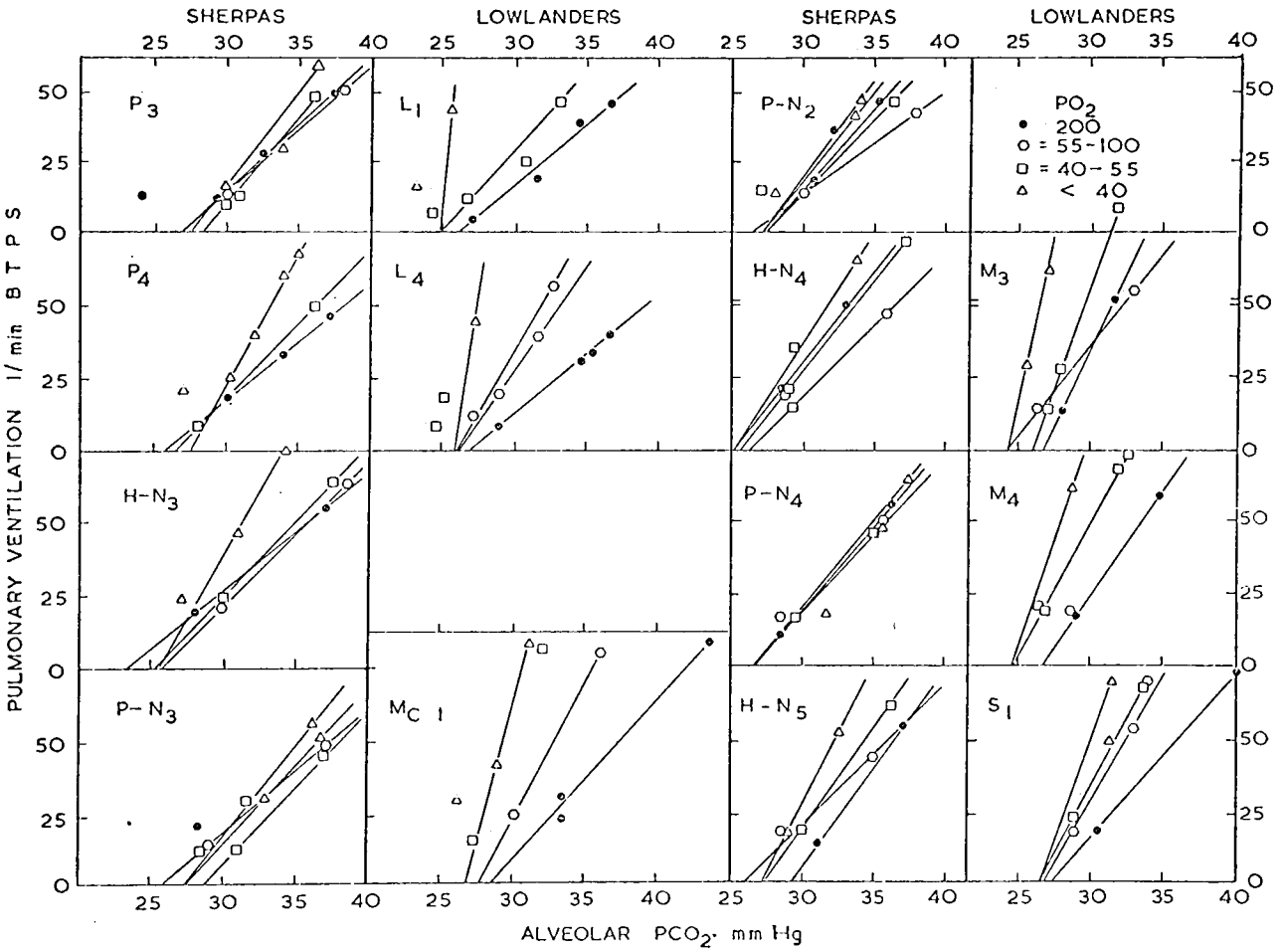
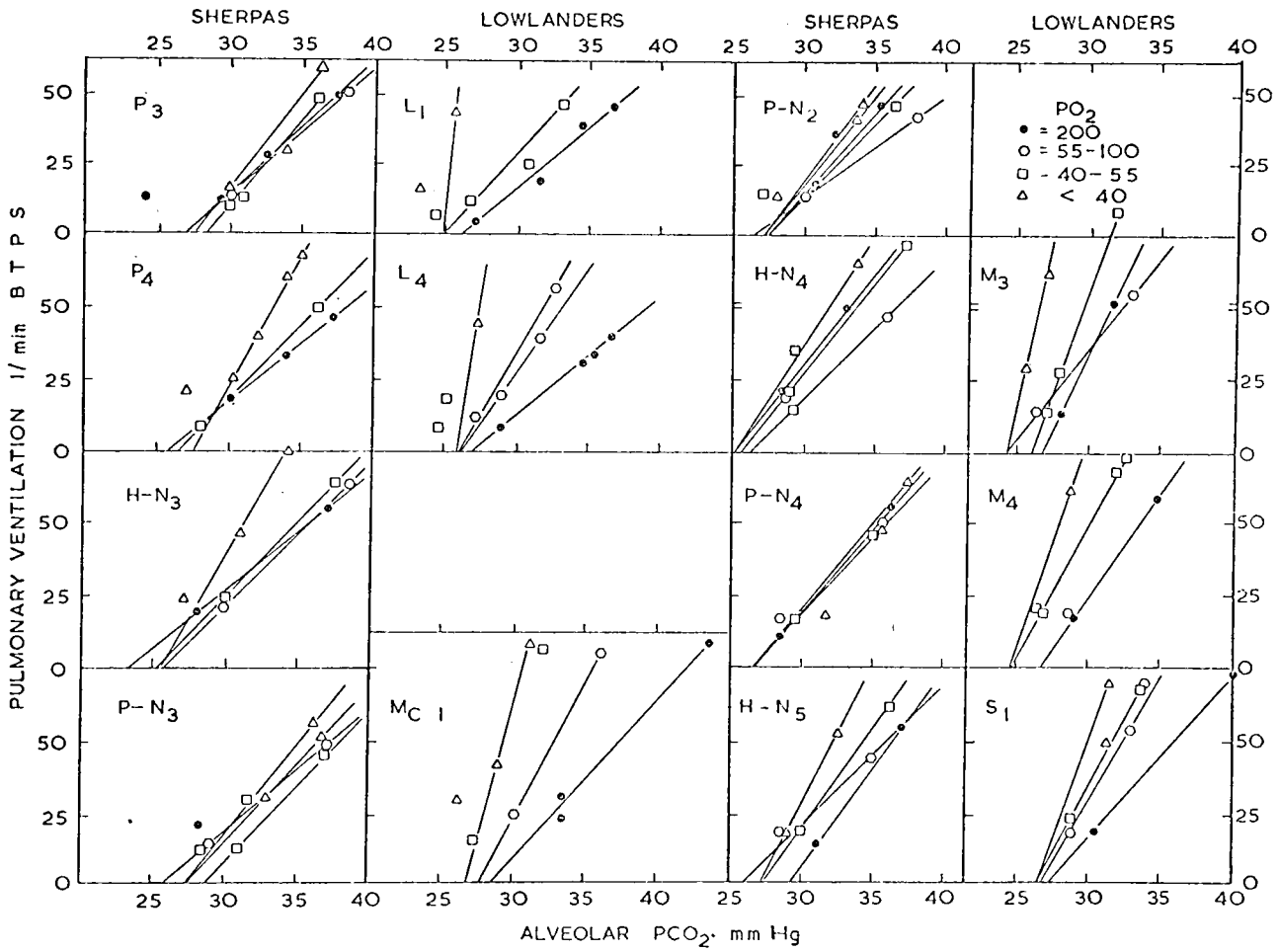


Fig. 41 The relation between pulmonary vantilation and $P_{A_{CO_2}}$ and $P_{A_{O_2}}$ in Sherpas and lowlanders at an altitude of 4880 m. Each small graph is the result of one experiment. The initials refer to individual subjects. The 1st and 3rd columns are Sherpa subjects, 2nd and 4th lowlanders. Lines have been drawn through points of equal $P_{A_{O_2}}$ whose value is indicated by symbols given in the key.



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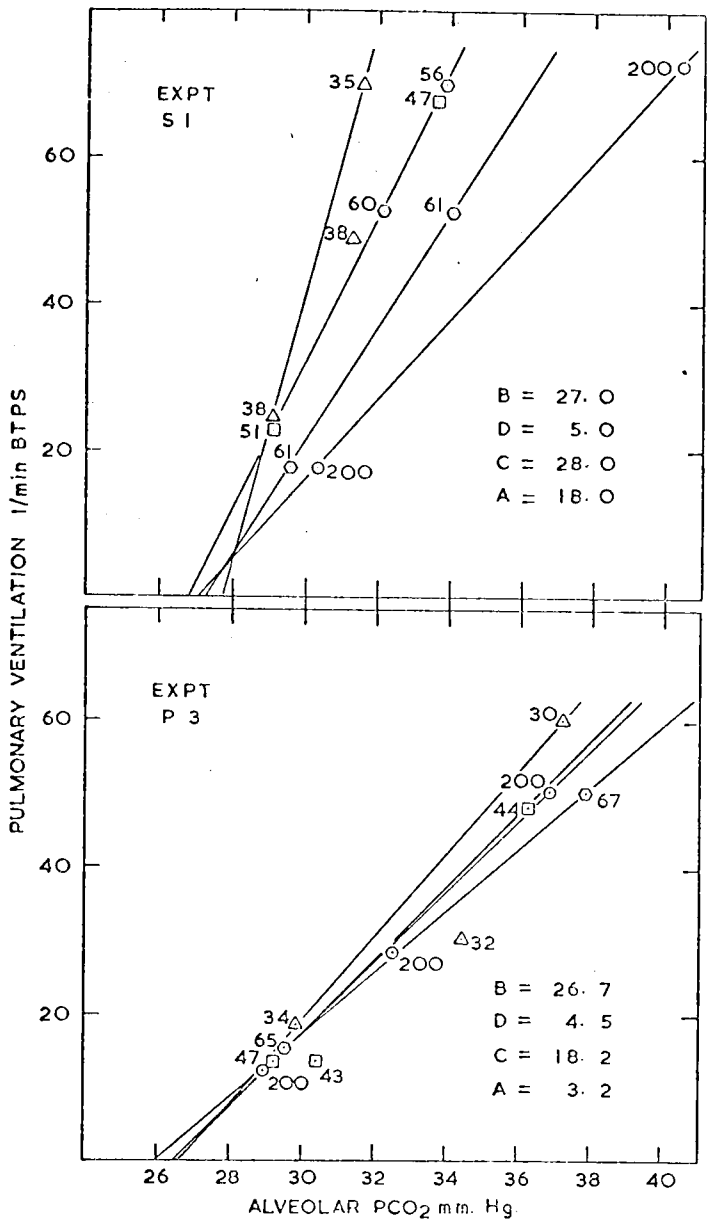

Fig. 42 The ventilatory response to CO_2 and hypoxia in one experiment each from a lowlander subject, Expt. S1, and a Sherpa subject, Expt. P3. The numbers by each point indicate the actual $P_{A_{O_2}}$ of that point. The calculated parameters of the ventilation control equation are given (see text).

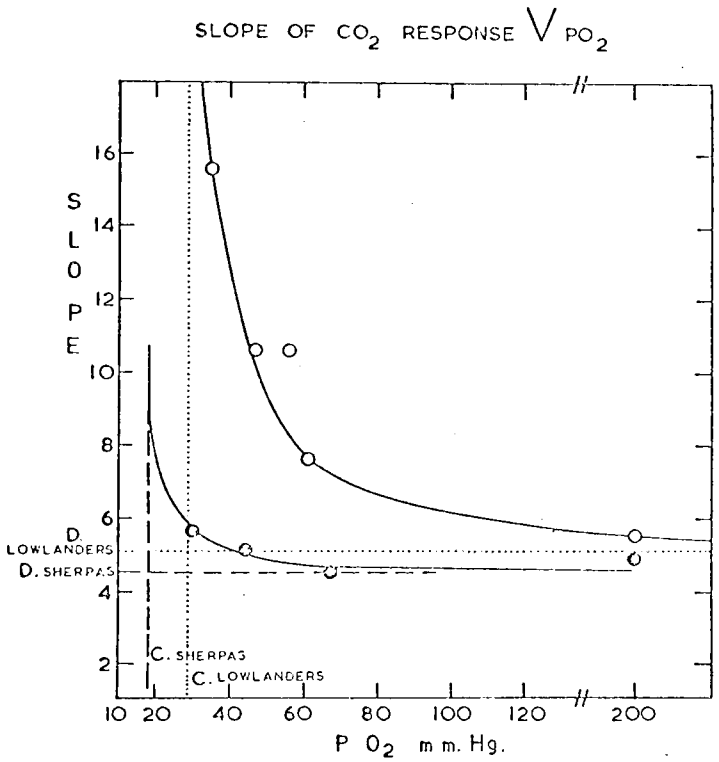

Fig. 4-3 The slopes of the CO_2 response line at various P_{AO_2} tensions are plotted against their respective P_{O_2} values for the two experiments shown in detail in Fig. 2. Sherpa subject ●, lowlander ○. The calculated asymptopes C and D of the hyperbole are drawn for each subject.

TABLE 4.3

Respiratory parameters for Sherpas and Lowlanders and (last column) change in ventilation ($\dot{V}$) on changing from Po_2 200 to 40 mm Hg at constant Pco_2 of B + mm Hg.

Sherpas	Exp-t	B mm Hg Pco_2	D 1/min mm Hg Pco_2	D ml/min mm Hg/ kg	C mm Hg Po_2	A mm Hg Po_2	$\dot{V}$ ml/min/ kg.
Pen	3	26.7	4.5	87	18	3.2	39
Pen	4	27.0	4.4	85	27	9.8	77
H.N	3	24.7	4.4	68	25	4.7	46
H.N.	4	25.1	3.3	51	20	20.0	77
H.N	5	27.1	5.2	79	32	5.1	62
P.N	2	26.1	4.0	67	22	5.0	59
P.N	3	27.0	4.2	70	25	3.2	17
P.N	4	-	-	-	-	-	17
Mean		26.2	4.3	72.5	24.2	7.3	44
Lowlanders							
S.L.	1	25.0	3.6	65	30	8.2	196
S.L.	4	25.4	3.5	63	37	26.0	890
J.S.M.	3	25.2	5.0	73	36	12.0	665
J.S.M	4	25.7	6.0	87	33	18.5	500
R.S.	1	27.0	5.0	77	28	18.2	210
J.Mc	1	27.3	5.1	63	28	24.6	320
Mean		25.9	4.7	72.9	32	17.9	450

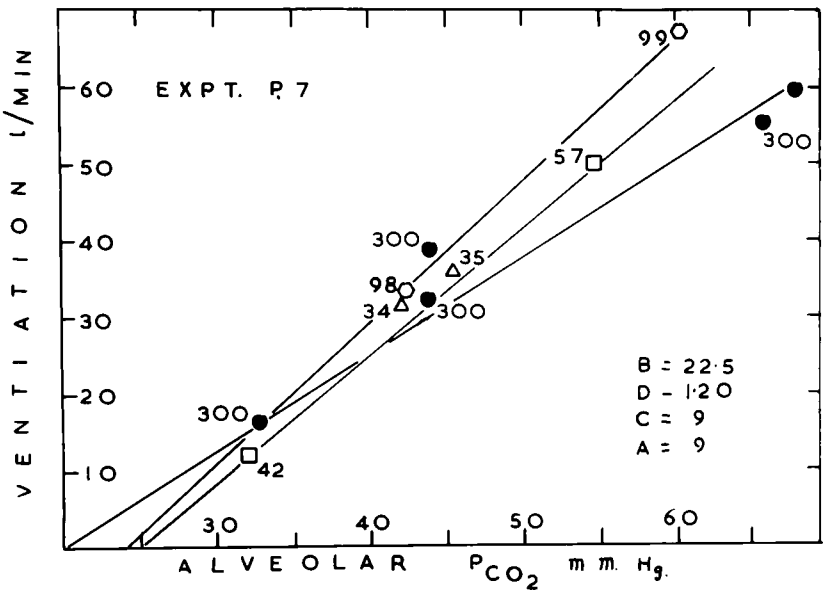

FIG. 4.4. The ventilatory response to CO_2 and hypoxia in the Sherpa, subject PEN after 3 weeks at sea level. Numbers against each point indicate PAo_2 of that point.

2. The minimum slope of the fan, i.e. the slope of the CO_2 response line for high Po_2 is similar for the two groups.
3. The outstanding difference is the closed appearance of the fan in Sherpas, i.e. the failure of hypoxia to produce in them the vivid increase in CO_2 response seen in the lowland group. This is especially seen in experiment P-N 4 but is noticeable in all experiments on Sherpas.

Another way of showing this difference is by plotting the slope of the CO_2 response line for each Po_2 against the Po_2. This is done for the same two experiments in Fig. 4.3.

CALCULATED PARAMETERS

The parameters of the equation:

$$\dot{V} = D(Pco_2 - B)\left\{1 + \frac{A}{(Po_2 - C)}\right\}$$

were calculated as described in Chapter II. The results of this calculation are shown in Table 4.3 except for experiment P-N4 where it was not possible to calculate parameters.

It will be seen that between the two groups the difference in values for B and for D are insignificant. The slight difference in D as usually expressed disappears when allowance is made for the weight of the subjects by expressing it in ml/min/kg/mm Hg Pco_2 (Table 4.3). The value for C shows a significant difference between the two groups (P 0.01), this critical minimum value for Po_2 being lower in Sherpas (mean 24 mm Hg) than in lowlanders (mean 32 mm Hg).

The reduction in A in Sherpas is also striking being about 40 per cent of the lowlanders mean value. The difference is significant ($P < 0.002$).

These results indicate no significant difference in CO_2 parameters, but definitely and consistently low values for O_2 parameters in Sherpa subjects.

Another less sophisticated but more direct way of expressing this reduced hypoxic sensitivity is by calculating the change of ventilation ($\Delta\dot{V}$) on changing the P_Ao_2 from 200 to 40 at constant P_Aco_2 of 2 mm Hg above B (chosen because the alveolar Pco_2 is usually about this value). The result of this calculation is shown in Table 4.3 last column. It will be seen that using this index the Sherpas show only about 10 per cent of the lowlanders ventilatory response to hypoxia.

High Po_2 line

In four experiments on Sherpas and one on a lowlander the point on high ventilation at high Po_2 lay to the left of points at lower Po_2. (See experiment P3 in Fig. 4.2). This is discussed later. The CO_2 response line for high oxygen often crosses over the other lines.

In a preliminary series of experiments using high Po_2 mixture alone, this effect, which was more common in Sherpas, resulted in their response lines lying to the left and having a lower slope than for lowlanders. In seven such experiments, four on Sherpas and three on lowlanders, the average intercept point on the CO_2 was: for Sherpas, 22.0 mm Hg and for lowlanders, 24.1 mm Hg, whilst the slopes were 3.6 and 5.2 respectively.

In the previous expedition (Chapter II) at 5,800 m we had found unexpectedly that the alveolar point breathing air lay to the left of the fan, i.e. the P_Aco_2 was about 2 mm Hg less than B. In this present study it was found to lie within the fan in all subjects as it does at sea level (mean value P_Aco_2, 26.5 mm Hg). Possibly there is a limit to the extent that B can be lowered by acclimatization. If this is so, it would seem to occur at an altitude of between 4,880 m and 5,880 m. This coincides with the altitude that seems to be the limit for complete altitude adjustment (Pugh, 1962).

Sea level experiments

On one Sherpa subject four satisfactory inhalation experiments were carried out at sea level, on which it was possible to calculate parameters in three. The methods were approximately the same as at altitude. The subject had been at low altitude for about three weeks before experiments started. His alveolar gas tensions (Haldane - Priestly) were P_Aco_2, 36.6 mm Hg; P_Ao_2, 100.1 mm Hg. Other variables of interest were: hemoglobin, 13.0 g per cent; arterial pH, 7.425; plasma bicarbonate, 13.8 ml and we conclude with respect to these parameters that he was deacclimatized. These results together with those of two sea level experiments on the Indian lowlander subject S.L. are shown in Table 4.4. One experiment on Sherpa P is shown in Fig. 4.4.

Although the data are rather meager they are quite self-consistent and show very low values for B (mean 25.1 mm Hg) and D (1.3 or 25 ml/mm Hg/kg) that is a very low CO_2 sensitivity. The oxygen parameter C is also very low and although the mean value for A (12.4) is higher than at altitude, this is misleading because on the experiment not calculated

TABLE 4.4

Value for respiratory parameters at sea level on Sherpa and one Lowlander (India.) $\Delta\dot{V}$ as in Table 4.3

Sherpas	Expt	B mm Hg Pco_2	D 1/min mm Hg Pco_2	D ml/min mm Hg/ kg	C mm Hg Po_2	A mm Hg Po_2	$\Delta\dot{V}$ ml/min kg.
Pen	7	22.5	1.20	23	9	9	19
Pen	8	25.8	1.24	24	17.2	17	38
Pen	9	22.8	1.42	27	16.4	11.4	19
Pen	10	22.5	-	-	-	-	-
Mean		24.2	1.3	25	14.2	12.4	25
SL	5	35.5	1.5	27	31.2	31.2	106
	6	36.2	1.8	32	26.5	23.5	89
Mean		35.8	1.65	29	28.9	27.5	125

the points for P o_2 of from 36 to 300 mm Hg fell on approximately the same line (A = 0). So the very low hypoxic sensitivity is maintained at sea level as well.

The results in subject S.L. are within the normal range except for low values for D.

DISCUSSION

CO_2 response

In Chapter II it was shown that the respiratory response to CO_2 was markedly increased in man on going first to altitude in that both the intercept of the CO_2 response line (B) was lowered and its slope (D) was increased. But Chiodi (1957) found that in long term Andean residents this increase in CO_2 sensitivity was largely lost and that the slope of the CO_2 response line approached sea level values or even became lower although the intercept was similar. We therefore expected to find a definite difference in the parameter D between our groups.

In our preliminary studies there was a small but definite difference in the slope of the CO_2 response line between our groups using a high oxygen mixture only. When we later carried out fuller experiments using various oxygen mixtures we found that the Sherpas more often showed the well-known "cross-over" effect on high oxygen described by Cunningham, Patrick and Lloyd (1964). That is while the lower Po_2 lines converge to a single point on the CO_2 axis, the line for high oxygen crosses over this fan to a lower intercept. So that on changing from a Po_2 of say 100 to 200 at low CO_2 values the ventilation rises, while at high CO_2 values the ventilation may remain unchanged or fall slightly. This is well seen in experiment H-N3 (Fig. 4.1). Sometimes this paradoxical effect of

high oxygen continues up to high CO_2 values in which case the response line is found to lie entirely to the left of that for a lower Po_2. This was found in four experiments on Sherpas, e.g. experiment P-N2 and H-N4 (Fig. 4.1) and in experiments on Sherpa P at sea level. This effect is presumably due to a reduction in cerebral blood flow with high Pao_2 resulting in a higher tissue Pco_2. Why this effect should be more marked in Sherpas is not clear. It may merely happen at lower O_2 values, i.e. between Po_2 100 to 200 whereas Cunningham et al. found it to occur mainly above Po_2 210 in lowlanders at sea level. However, in calculating D from the full experiments the effect of such cross-over is eliminated and our conclusion is that with respect to CO_2 parameters there is very little difference between our two groups. This is in accord with the results of Severinghaus, Bainton and Carcelen (1966) in Andean residents.

But it may well be that Sherpas respond differently from Andean natives. Chiodi (1957) reported in the same paper the finding that his subjects had higher resting P_Aco_2 and lower P_Ao_2 than acclimatized lowlanders, and when plotted on the O_2-CO_2 diagram of Rahn and Otis (1949) clustered around the line for unacclimatized man. We found that the alveolar gas tensions for our two groups were less divergent though there was a significant difference (mean P_Aco_2 for lowlanders was 25.9 $\pm$ 0.60 mm Hg; for Sherpas 28.6 $\pm$ 0.42 mm Hg; $P < 0.002$) and both fell close to the line for acclimatized man.

It is interesting that on descending to sea level the one Sherpa subject studied had very low values for both D and B, which at 1.3 l/min/mm Hg and 25.1 mm Hg are well below the normal value given by Cunningham

et al. (1964) of 3.9 + 1.4 and 37.7 + 2.8 respectively. But Sørensen, Severinghaus, Cruz, Whayne and Carcelen (1964) did not find low values in Andean high altitude natives resident at sea level.

The averaged results from both expeditions for D in ml/min/mm Hg/kg are:

at sea level		and at altitude	
Sherpa	25	lowlanders (4,880 m)	73
Indian lowlander	29	Sherpas (4,880 m)	72
European lowlander	52	Lowlanders (5,800 m)	107

Hypoxic response

There has been considerable debate about the effect of acclimatization on the ventilatory response to hypoxia in both newcomers and in residents at high altitude.

Earlier work has mainly centered on observing the reduction in ventilation on breathing oxygen enriched mixtures (including Haldane and Priestly, 1935; Chapin, 1954; and Chiodi, 1957). The results showed a wide range of variation. This method is theoretically unsatisfactory as a measure of hypoxic sensitivity, since any reduction in ventilation results in a rise of $Paco_2$ and the new steady state level of ventilation is due as much to sensitivity to CO_2 as to hypoxia. The single breath of oxygen technique of Dejours, et al. (1959) overcomes this and has been used at altitude. Ceretelli (quoted by Dejours, 1963) used it on one subject, a lowlander well acclimatized to 5,000 m and showed a very definite response. Lefrancois, Gautier, and Pasquis (1967) more recently reported results on natives to high altitude and showed that their response to a single breath of oxygen is about half that of lowlanders. But Chiodi (1963) found the single breath method to be no improvement over continuous inhalation.

Since the work of Nielsen and Smith (1951), Cormack, Cunningham and Gee (1957) and Lloyd et al. (1958), we have come to think of hypoxia acting on the CO_2 feed back system by enhancing its sensitivity. Therefore, the most satisfactory way of measuring the hypoxic response is to plot the CO_2 response at various levels of hypoxia. The increasing slope of the CO_2 response lines thus found is a measure of the hypoxic stimulus, parameter A. On the previous expedition (Chapter II) we found no significant change in the oxygen parameters A and C between lowlanders at sea level and when acclimatized to altitude though there was a suggestion of some slight increase in A. (Three subjects showed an increase and one a decrease.)

Now we find a very definite difference between Sherpas and lowlanders at altitude. The lowlanders data though a little meager agrees well with results from the previous expedition and with values given by Cunningham et al. (1964).

The parameter A is found to be consistently much reduced in Sherpas. This result is in accord with Severinghaus et al. (1966) though in their results the CO_2 response lines were too close together to permit the calculation of parameters (Severinghaus, personal communication) such as we found in experiment P-N4 (Fig. 1).

The relative lack of hypoxic sensitivity is not related to differences in hematocrit as might be inferred from the work of Severinghaus et al. (1966), since in our subjects hemoglobin values were the same for our two groups at altitude (Sherpas, 19.0 gm per cent; lowlanders, 19.3 gm per cent).

In the study on muscular work (Chapter V) we found that whereas in lowlanders the addition of oxygen to the inspired air during exercise

resulted in a marked reduction in ventilation; the same increase in P_IO_2 in Sherpas had a small effect on ventilation. Conversely, a further reduction of P_IO_2 in the lowland subject resulted in a great increase in ventilation; in the Sherpas it produced only a slight rise.

Severinghaus and Carcelen (1964) showed that the acid-base situation in cerebrospinal fluid of Andean residents did not differ from that of newly arrived lowlanders. They argued, therefore, that the lower ventilation found in these residents must be due to reduced peripheral chemoreceptor drive (assuming the CO_2 drive to be mediated through H^+ concentration in CSF). Our findings in this respect were similar except that our lowland subjects actually had slightly higher CSF pH values (mean: lowlanders, 7.363; Sherpas, 7.328) (Chapter VI) suggesting a greater respiratory drive in Sherpas due to CSF H^+ concentration and, therefore, even less due to peripheral chemoreceptors.

Dr. Lahiri collected some data on breath-holding during the two expeditions (unpublished) which also demonstrated this relative insensitivity in Sherpas to respiratory stimuli. Taking his own maximum voluntary apnoea time at various altitudes as 100 per cent, Sherpa P had times of 188 per cent at sea level, 160 per cent at 4,880 m and 140 per cent at 5,880 m.

Thus all these separate lines of evidence support the contention that residents at high altitude have a greatly reduced hypoxic ventilatory response.

High altitude residents at sea level

The one Sherpa studied at sea level retained his hypoxic insensitivity in the four experiments performed on him, and while this finding by itself

is of uncertain significance, it has since been supported by Sørensen, Severinghaus, Cruz, Whayne and Carcelen (1967) in Andean high altitude residents at sea level and later by Sørensen and Severinghaus (1967) in patients born with cyanotic heart disease whose condition had been corrected. Both these groups of people had been subject to chronic hypoxia from birth but had enjoyed normoxia for a number of years before being studied. They all showed a relative insensitivity to hypoxia. Conversely, people native to low altitude retained their hypoxic response even though they had been at altitude for years (Sorensen et al., 1967). The findings in the congenital heart disease group is of special interest as it makes it unlikely that this hypoxic insensitivity can be attributed to genetic causes.

Parameter C

This parameter, the theoretical Po_2 at which CO_2 sensitivity becomes infinite is of uncertain significance. It does not necessarily measure the same biological function as A, since in noradrenaline infusion A is increased independently of C (Cunningham, Hey, Patrick and Lloyd, 1963). This value is also smaller in Sherpas at altitude and seems to remain low on coming down to sea level. Possibly it indicates an increased tolerance to extreme hypoxia. On one run at sea level in the Sherpa subject, due to an error in making up the gas mixture, a lower P_Io_2 than intended was given resulting in a P_Ao_2 of 26.5 mm Hg. The subject became uncomfortable with slight shivering by the time the mixture was switched off after six minutes but showed no irrational behavior or clouding of consciousness as is normally seen in unacclimatized subjects at P_Ao_2 35-40.

CONCLUSION

The important difference in ventilatory control between lowlanders and high altitude residents is the very low hypoxic sensitivity of the latter. We were unable to demonstrate any difference in CO_2 sensitivity between the two groups.

This hypoxic insensitivity persists at sea level apparently for years.

The question of its significance in oxygen supply and acid-base regulation will be discussed in Chapter VI.

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CHAPTER V

VENTILATION DURING EXERCISE IN SHERPAS

INTRODUCTION

One of the most obvious differences in response to altitude between Sherpas and even well-acclimatized lowlanders is the apparent freedom from dyspnoea of the Sherpas when climbing. The impression is that to do the same degree of work, they require less ventilation. In 1962 on one Sherpa examined, this was confirmed (Pugh et al., 1964). On the second School-House expedition in 1964 (Chapter I) we had the opportunity to examine this more fully as a companion study to the inhalation experiments at rest described in the previous chapter.

We also performed some experiments in which the subject inhaled oxygen-enriched or -reduced gas mixtures to determine the effect of reducing or increasing the hypoxic drive.

SUBJECTS

These were the same as in the companion study. Their characteristics are given in Table 4.1.

METHODS AND PROCEDURE

Measurements were begun not less than two hours after a light meal. Most exercise studies were done on a bicycle ergometer similar to that used on the previous expedition, made to our order in India. But in view of the fact that Sherpas are unaccustomed to bicycling, we also did some

studies during climbing up a slope of about 30 degrees with and without a 19 kg load, at various speeds. The Sherpas after considerable practice learned to bicycle with varying degrees of success. All four subjects could manage light and moderate work by the second month but only two could keep their feet on the pedals when working at maximum rate.

On the bicycle ergometer or on the test climbing slope the subjects breathed through a valve of low resistance, and the expired air was collected for a timed period in a light plastic Douglas bag of low O_2 and CO_2 permeability. The volume and temperature of the expired air and the ambient pressure were noted. In experiments with gas mixtures other than air, the subject breathed from a 1,000 liter bag. When end-tidal samples were collected, a Rahn-Otis sampler was attached to the breathing valve, and the sample was drawn at a rate of about 100 ml/min by water displacement over a series of Barcroft sampling tubes filled with mercury. These samples collected by mercury displacement were coincident with the expired air collection. End-tidal samples thus lost were taken into account in calculating the expired volume of air. For the recovery experiments, the subjects pedalled at the highest work rate they could accomplish. After 2.5 min, expired air was collected for a timed period of half a minute, at the end of which the subject stopped working but remained seated at the ergometer. Expired air was then collected for the following 5 min in one bag, and then for the subsequent 10 min in a second bag. Blood samples for the estimation of lactate were taken from the finger tip of the warm hand at 2-3 min, 9-10 min, and 15-16 min after stopping work. Prior to this type of experiment resting oxygen consumption on the bicycle was determined, and blood samples were collected for resting lactate.

Respiratory gas samples were analyzed using a Lloyd-Haldane gas analysis apparatus. Heart rates were recorded with a Cambridge Transrite 111 electrocardiograph, usually during the last half minute of work on the bicycle and often continuing for a few seconds after stopping. Blood pH was determined with an Astrup capillary microelectrode and Radiometer M4 pH meter at 37°C. Phosphate buffers of 6.840 and 7.384 at 37°C served as the primary standards and for testing electrode sensitivity over this range. Except for arterial blood, all samples for blood pH were obtained from the finger tip of the warmed hand. These samples are known to be similar in pH to arterial blood (Siggaard-Andersen et al., 1960). No correction for the effect of polycythemia in lowering plasma pH was made (Severinghaus, Stupfel and Bradley, 1956).

In one series of experiments involving the breathing of air and of pure oxygen by a Sherpa and a lowlander, arterial samples were collected anaerobically to determine the effects of oxygen inhalation on arterial saturation and arterial O_2 saturation and pH at rest and during exercise. Blood pH was determined immediately and blood gases were estimated within 2 hr of their collection by the volumetric method of Haldane (Cunningham, Shaw, Lahiri and Lloyd, 1961).

For lactate determinations, 0.1 ml blood samples were placed in 4.9 ml of normal saline, to which was added 5 ml of 10 per cent trichloroacetic acid. The samples were filtered, the filtrates were placed in air tight containers, and stored in the frozen state for shipment to Calcutta where they were analyzed by a modification of a method of Barker and Summerson (1941).

RESULTS

The data are presented in Tables 5.1-5.3 and shown graphically in Figs. 5.1-5.3.

Oxygen uptake and work

Fig. 5.1 shows steady-state relation between oxygen uptake (average of each subject) and work rate in Sherpas and lowlanders at 4,880 m and at sea level. This relation is linear and similar in Sherpas and lowlanders, and it is independent of altitude.

Oxygen uptake and pulmonary ventilation

Fig. 5.2 shows the relation of ventilation (BTPS) to oxygen uptake, both in climbing and ergometer experiments at high altitude. At a given work level, Sherpa subjects ventilated relatively less than the acclimatized lowlanders and their rate of increase was smaller, particularly in the higher range of oxygen uptake. The mean respiratory rates for a given work level were similar in both groups. The mean rate was 22 at rest and 30, 42, and 50, respectively for work levels of 475, 900, and 1,265 kg-m/min.

Ventilation in acute exposure to low and high Po_2 (Table 5.3)

On inhalation of sea level P_IO_2 at high altitude, pulmonary ventilation during exercise decreased considerably more in the lowlanders than in the Sherpa subjects. Ventilation in the lowlanders was reduced by 33 per cent on oxygen inhalation up to an oxygen uptake of 1 l/min, falling further at higher work rates; the greatest reduction amounting to 48 per cent. This progressive fall in ventilation possibly corresponds to the removal of increasing arterial hypoxaemia that occurs

TABLE 51. *Results of work experiments at 4,880 m*

Subj	No. of Observ	$\dot{V}_{BTPS}$, liters/min	$\dot{V}_{O_2}$, liters/min	R	Heart Rate, beats/min
		Rest, sitting on ergometer			
Lowlanders					
SL	2	10.6	0.227	0.77	99
JSM	1	11.6	0.270	0.84	72
		Work rate, 475 kg-m/min			
SL	8	59.9	1.205	0.97	140
JSM	4	44.2	1.144	0.94	113
		Work rate, 900 kg-m/min			
SL	7	87.5	1.673	1.09	166
JSM	4	86.5	1.959	0.99	141
		Work rate, 1,265 kg-m/min			
SL	5	98.4	1.797	1.20	165
JSM	4	148.0	2.566	1.14	146
		Rest, sitting on ergometer			
Sherpas					
PEN	2	12.9	0.288	0.97	67
PN	1	22.5	0.277	1.00	63
HN	1	13.6	0.296	1.02	69
LT	1	26.4	0.365	0.99	62
		Work rate, 475 kg-m/min			
PEN	7	42.4	1.134	0.95	138
PN	5	43.1	1.216	0.92	131
HN	7	47.7	1.352	0.92	139
LT	5	57.1	1.274	1.05	112
		Work rate, 900 kg-m/min			
PEN	7	76.0	1.831	1.06	176
PN	4	98.8	2.188	1.04	181
HN	7	77.1	2.148	1.06	172
LT	5	108.8	2.118	1.05	143
		Work rate, 1,265 kg-m/min			
PEN	2	109.4	2.550	1.08	198
PN	4	118.7	2.763	1.09	195
HN	1	116.3	2.713	1.07	154
LT	1				150

TABLE 51. *Results of work experiments at 4,880 m*

Subj	No. of Observ	$\dot{V}_{BTPS}$, liters/min	$\dot{V}_{O_2}$, liters/min	R	Heart Rate, beats/min
		Rest, sitting on ergometer			
Lowlanders					
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JSM	1	11.6	0.270	0.84	72
		Work rate, 475 kg-m/min			
SL	8	59.9	1.205	0.97	140
JSM	4	44.2	1.144	0.94	113
		Work rate, 900 kg-m/min			
SL	7	87.5	1.673	1.09	166
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LT	1	26.4	0.365	0.99	62
		Work rate, 475 kg-m/min			
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PN	5	43.1	1.216	0.92	131
HN	7	47.7	1.352	0.92	139
LT	5	57.1	1.274	1.05	112
		Work rate, 900 kg-m/min			
PEN	7	76.0	1.831	1.06	176
PN	4	98.8	2.188	1.04	181
HN	7	77.1	2.148	1.06	172
LT	5	108.8	2.118	1.05	143
		Work rate, 1,265 kg-m/min			
PEN	2	109.4	2.550	1.08	198
PN	4	118.7	2.763	1.09	195
HN	1	116.3	2.713	1.07	154
LT	1				150

Table 5.2. Results of climbing experiments on a mountain slope at 4880 m. P_B 422 - 4 mm Hg.

Subject:		$\dot{V}$ STPD	$\dot{V}$ BTPS	V_{O_2}	
		l/min			
Moderate rate					
Lowlander	JSM	16.6	37.3	0.882	0.87
Sherpa	PEN	12.8	29.6	0.802	0.90
	BN	17.6	40.5	1.188	0.93
Moderate rate with load on back (19 kg)					
Lowlander	JSM	23.0	53.0	1.316	0.91
Sherpa	PEN	12.8	29.2	0.856	0.87
		17.6	40.6	1.126	0.95
	HN	23.1	53.3	1.510	0.95
Maximum rate of climb with load (19 kg)					
Lowlander	JSM	39.5	90.1	1.663	1.04
Sherpa	PEN	35.8	82.7	1.637	1.22
	HN	42.7	98.6	2.280	1.160

TABLE 5.3 *Blood pH, heart rate, and respiratory data of acclimatized lowlanders and Sherpa highlanders breathing different oxygen mixtures at 4,880 m measured in a single session*

Subj	Tracheal P_{O_2}, 79 mm Hg						Tracheal P_{O_2}, 150 mm Hg					
	$\dot{V}_{BTPS}$, liters/min	$\dot{V}_{O_2}$, liters/min	P_{ACO_2}, mm Hg	P_{AO_2}, mm Hg	Blood pH	Heart Rate, beats/min	$\dot{V}_{BTPS}$, liters/min	$\dot{V}_{O_2}$, liters/min	P_{ACO_2}, mm Hg	P_{AO_2}, mm Hg	Blood pH	Heart Rate, beats/min
Sherpas												
					Work rate, 475 kg-m/min							
PEN (2)	27.6	0.823	29.3	45.2	7.373	138	24.7		29.4	107	7.360	135
PN (1)	45.6	1.245	28.2	48.9	7.395	131	43.6	1.216	27.1	125	7.390	126
HN (2)	40.3	1.209	27.0	49.2	7.397	147	43.0	1.352	29.3	109	7.420	127
LT (1)	52.2	0.856	21.3	53.7	7.383	89	46.2		21.5	131		82
					Work rate, 900 kg-m/min							
PEN (2)	69.8	1.781	27.9	49.4	7.356	182	61.2	1.831	30.4	105	7.353	161
PN (2)	102.8	2.431	27.5	51.0	7.359	177	83.0	2.188	28.8	118	7.356	156
HN (2)	76.5	1.920	27.0	52.2	7.375	162	71.3	2.148	31.2	114	7.378	142
LT (1)	85.2	1.907	21.3	55.4		130	72.6	2.118	25.6	116		110
					Work rate, 1,265 kg-m/min							
PEN (1)	98.4	2.599	30.1	53.7		198	84.6	2.600	31.8	113		159
PN (2)	116.0	2.795	27.9	55.7	7.257	195	110.5	2.763	27.0	116	7.252	160
HN (1)			24.5	57.8	7.338	172	79.3		28.2	112	7.330	150
LT (1)					7.360	147	102.5		25.1	126	7.323	135
Lowlanders												
					Work rate, 475 kg-m/min							
SL (1)			23.8	54.5	7.401	140	33.5	1.130	28.1		7.366	141
JSM (2)	45.9		25.6	51.8	7.410	123	35.2	1.000	29.7	126	7.396	122
					Work rate, 900 kg-m/min							
SL (1)			23.5	56.5	7.325	164	39.0	1.673	32.1	120	7.265	161
JSM (2)	81.3		24.5	53.4	8.448	144	54.6	1.959	31.0	127	7.397	140
					Work rate, 1,265 kg-m/min							
SL (3)	101.3	1.883	24.9	57.3	7.288	166	73.0	1.949	32.1		7.259	189
JSM (1)	96.4		25.7	52.4	7.436	144	74.5	2.566	32.2	131	7.388	163

Subj	Tracheal P_{O_2}, 57 mm Hg											
	$\dot{V}_{BTPS}$, liters/min	$\dot{V}_{O_2}$, liters/min	P_{ACO_2}, mm Hg	P_{AO_2}, mm Hg	Blood pH	Heart Rate, beat/min	$\dot{V}_{BTPS}$, liters/min	$\dot{V}_{O_2}$, liters/min	P_{ACO_2}, mm Hg	P_{AO_2}, mm Hg	Blood pH	Heart Rate, beats/min
	Work rate, 475 kg-m/min						*Work rate, 900 kg-m/min*					
Sherpa *PN*	59.2		26.9	38.5		129	80.1		26.9	42.6		165
Lowlander *JSM*	82.8					116	114.0		19.8	46.5		94

Number of observations on each subject are given in parentheses.

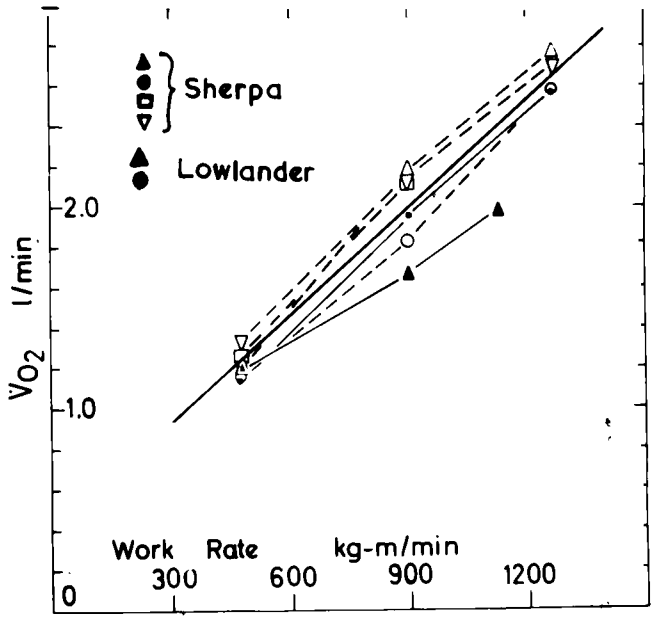

FIG. 5.1. Relation of O_2 consumption to work rate. Symbols for individual subjects are joined by broken lines. The heavy line indicates the sea level relationship.

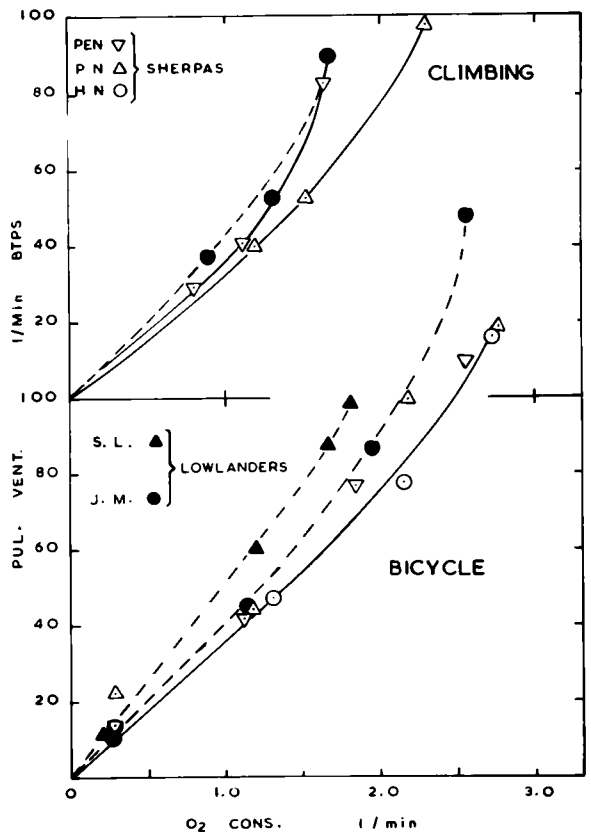

FIG. 5.2. Relation of ventilation to O_2 consumption in lowlanders (closed symbols) and Sherpas (open symbols) during two types of exercise.

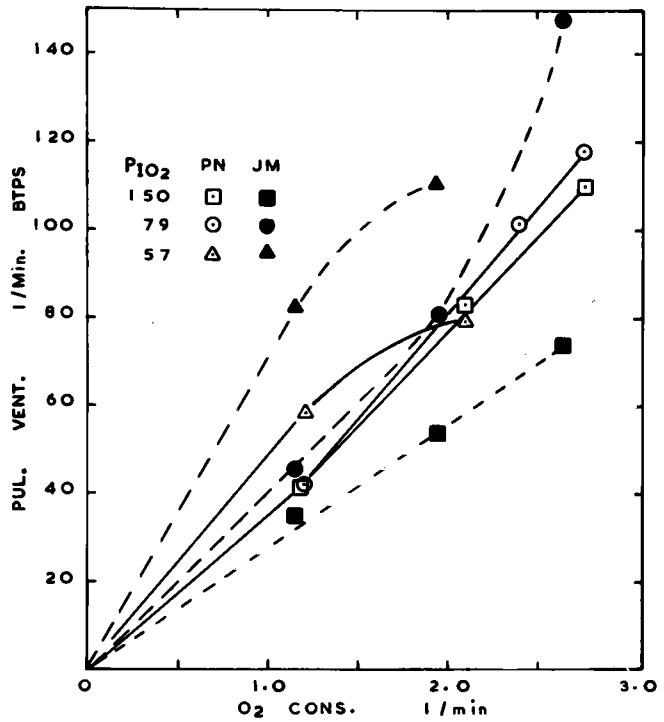

FIG. 5.3. The effect of changing the inspired Po_2 on the relation of ventilation to O_2 consumption in a lowlander, (closed symbols) and a Sherpa (open symbols).

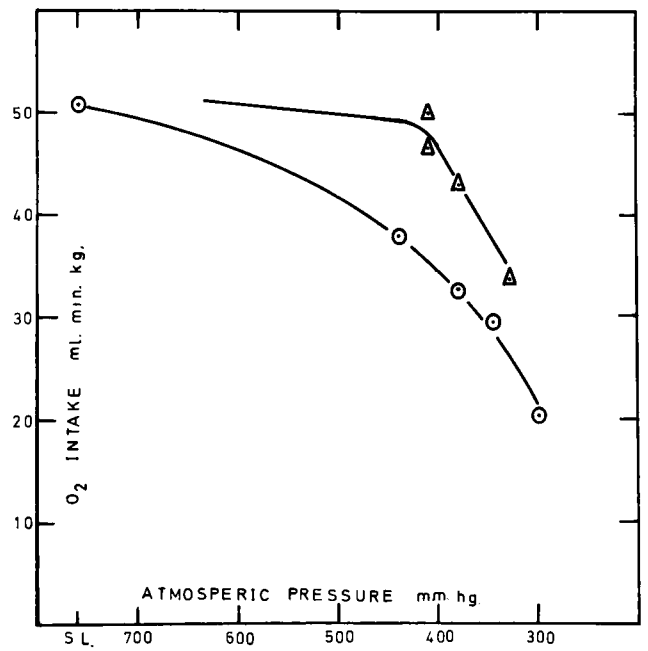

FIG 5.4. Relation of maximum O_2 intake to atmospheric pressure; the lower line lowlanders, (from data in chapter 3 and fig 3.5); the upper line Sherpas. The end Sherpa point is that of a subject acclimatised to 4,880m acutely exposed to PIO_2 57mmHg.

at the higher work load. In Sherpas, however, oxygen often increased ventilation at rest and produced only little change at a low work rate. A fall was appreciable only beyond an oxygen uptake of 1 l/min where fall in arterial oxygen saturation is known to increase progressively on air (West, Lahiri, Gill, Milledge, Pugh and Ward, 1962 and Banchero, Sine, Penaloza, Cruz, Gambo and Marticorena, 1966). The greatest reduction in ventilation was only 14 per cent, and this value did not change for oxygen uptake values in excess of 2 l/min. Subjectively, the lowlanders felt great relief from breathing sea level $P_{I}o_2$ but the Sherpa subjects did not seem to derive the same benefit. On acute exposure at 4,880 m to a tracheal Po_2 of 57 mm Hg, ventilation in lowlander J.S.M. increased greatly while Sherpa P.N. showed only a small increase. Both subjects showed extreme exhaustion at 900 kg-m/min, but the Sherpa subject was able to continue for 6 min while J.S.M. stopped after 3 min. Fig. 5.3 shows the effect on ventilation of increasing and decreasing $P_{I}o_2$ in these two subjects.

The respiratory exchange ratio was higher in the Sherpas, and there was a smaller increase with exercise than in the lowlanders at altitude.

Submaximal work and oxygen debt

These results are given in Table 5.4. The Sherpa's O_2 debt and blood lactate for a given work rate were somewhat smaller than those of the lowlanders. The rate of recovery to the basal state with respect to ventilation, O_2 debt, and lactate did not appear appreciably different. Resting blood lactate in both groups was higher than the normal sea level value, which is in conformity with published reports (Asmussen, von Dobeln and Nielsen, 1948, and Klausen, 1966) on acclimatized lowlanders.

Table 5.4. Oxygen uptake and blood lactate concentration at rest, during last half minute of 3-min exercise period, and after exercise at 4,880 m.

Subject	Oxygen uptake, liters/min				Blood lactate, mg/100 ml			
	Rest	Work	After work		Rest	Min after work		
			First 5 min	Next 10 min		2-3	9-10	15-16
Sherpas								
P.E.N.	0.267	2.599	0.782	0.325	16.1	73.2	49.5	45.4
P.N.	0.277	2.794	0.585	0.375	20.7	67.3	62.8	39.8
H.N.	0.296	1.486	0.638	0.223	17.8	48.5	49.4	33.3
L.T.	0.265	1.690	0.370	0.215	21.9	50.2	38.8	30.8
Lowlanders								
S.L.	0.227	1.850	0.764	0.396	23.7	92.6	103.2	68.4
J.S.M.	0.290	2.363	0.533	0.368	24.5	73.8	61.2	46.8

Exercise and acid-base

In Table 5.4 are also shown the results of pH and P_Aco_2 measurements. It will be seen that in Sherpas increasing exercise results in reductions in pH while P_Aco_2 remained unchanged. One lowlander, J.S.M., has a rise in pH while the other, S.L. had a fall. Both had a reduction in P_Aco_2.

DISCUSSION

Our findings confirmed the impression that at altitude Sherpas do not hyperventilate on exercise as much as lowlanders. This effect is not very marked at light and moderate work rates (O_2 intake less than 1.5 l/min). However, at an oxygen intake of 2 liters the Sherpas ventilate

at only about 80 per cent of the lowlander's value, while at an oxygen intake of 2.5 l/min (the lowlander's maximum work rate) the figure is only 70 per cent or less.

The greater efficiency of Sherpas is even more marked when maximum oxygen intake is considered. Fig. 5.4 shows the same graph of subjects as was used in Chapter III; we see the maximum oxygen intake (per kg weight) declining with altitude. The data from the second expedition is added together with the one Sherpa studied in 1961. It will be seen that at the altitude of our 1964 station (4,880 m) the two Sherpas who were able to achieve maximum work rate on the bicycle ergometer had maximum oxygen intake of 46.5 and 50.0 ml/min/kg, while the lowlanders had values of 37 (J.S.M.) and 30 (S.L.). The former value lies on the line of the graph from the previous expedition. Thus, at this altitude Sherpas have a maximum oxygen intake which is normal for lowlanders at sea level (Asmussen, 1965). It should be noted however that Balke (1965) found lower values in Andean high altitude residents, 36.5 ml/min/kg, the same as for lowlanders. Elsner, Bolstad and Forno (1964) found similar results.

The last Sherpa point in Fig. 5.4 is that of Sherpa P.N. acclimatized to 4,880 m and accutely exposed to a P_IO_2 of 57 mm Hg. The line shown for Sherpas is, of course, very tentative because of the rather meager data.

This relative hypoventilation in people resident at high altitude has been reported from the Andes by Balke (1964) and by Hurtado, Velasquez, Ranafarje, Lozano, Chavez, Aste-Salazar, Raynaforje, Sanchez and Munoz (1956), and therefore it would seem to be common to man resident at high altitude. But Grover, Reeves, Grover and Leather (1967) found no difference in ventilation at exercise between residents and new-comers at Leadville,

Colorado, altitude 3,100 m. Their findings are hard to explain, especially when closer scrutiny of their data shows that in both groups the ventilatory equivalent was well above that predicted from Fig. 3.4 and their P_Aco_2 lower than expected from the literature (Rahn and Otis, 1949). It is possible that the degree of hypoxia at Leadville was insufficient to produce the changes resulting in hypoventilation or that racial or genetic factors present in Himilayan and Andean high altitude residents is absent from the Caucasian subjects as suggested by these authors. Clearly more studies are required in different races and at intermediate altitudes.

Hypoxic insensitivity

We consider that the principle cause of hypoventilation in the Sherpas is due to their relative insensitivity to hypoxia, as demonstrated in the previous chapter. In the experiments where the P_Io_2 was raised to sea level values or lowered, the effect on ventilation in Sherpas was quite different from that seen in lowlanders (Table 5.3 and Fig. 5.3). The change in ventilatory equivalent (ΔVE) on changing from ambient P_Io_2 (79 mm Hg) to sea level P_Io_2 is an average of 3 in Sherpas and about 12 in lowlanders (J.S.M.). In the one experiment in which the P_Io_2 was lowered, the Sherpa did respond by an increase in ventilation, but less so than the lowlander, ΔVE = 13 in the Sherpa and 17 in the lowlander. The changes in P_Aco_2 reflect and confirm this change in ventilation.

Acid-base differences in exercise

The differences in the reaction of the blood to the response to exercise is shown in Table 5.5, where the arterial pH of a representative lowlander and Sherpa are compared at various work rates.

Table 5.5. pH and P_{50} in a representative lowlander and Sherpa during exercise at 4,880 m.

Work Rate kg-m/min	Lowlander J.S.M.		Sherpa P.E.N.	
	pH	P_{50} mm Hg	pH	P_{50} mm Hg
Rest	7.424	26.8	7.403	27.6
475	7.410	27.2	7.373	28.3
900	7.448	26.2	7.356	28.8
1265	7.436	26.5	7.318	29.7

It will be seen that whereas the Sherpa's reaction becomes more acid with increasing exercise, the lowlander's blood becomes slightly more alkaline. The difference is presumably due to the respiratory alkalosis of hyperventilation in the lowlander countering the metabolic acidosis of anaerobic metabolism, while in the Sherpas P_Aco_2 is unchanged so that metabolic acidosis is unopposed.

What is the effect of this difference in pH on the oxygen transport systems of the two groups? In Table 5.5 is shown the calculated position of the oxygen dissociation curve expressed as the Po_2 when 50 per cent of the hemoglobin is saturated (P_{50}), assuming there is no difference in the type of hemoglobin between Sherpas and lowlanders. At rest both groups are a little below the normal value of 28 mm Hg, the lowlander being lower than the Sherpa, i.e. the curve is shifted slightly to the left of normal. The P_{50} for the lowlander remains unchanged as work rate is increased, but

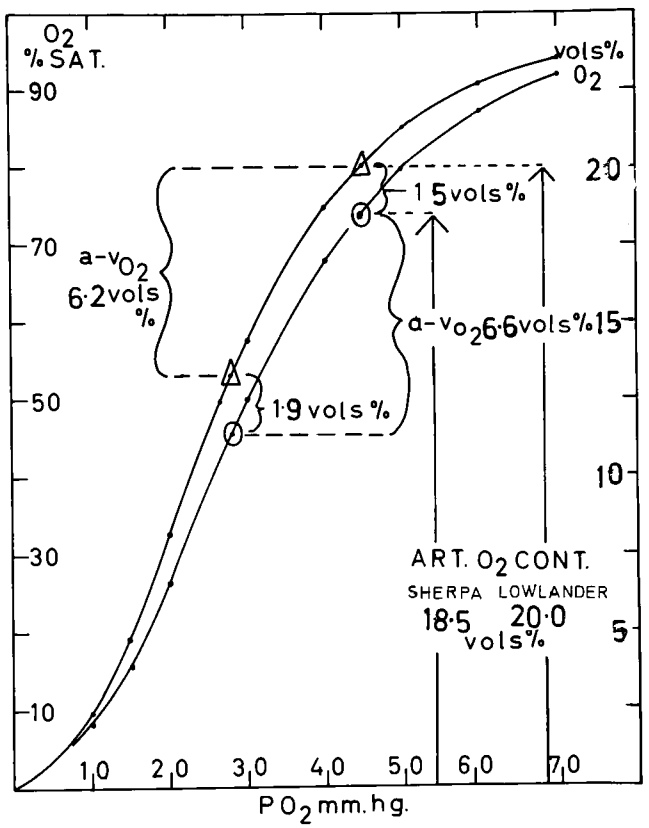

FIG. 5.5. Oxygen dissociation curves calculated for blood of a lowlander (JSM) P50=26.5, and a Sherpa (PEN) P50=29.7 at maximum work rate at 4,880m altitude. Venous points ignore Bohr effect.

for the Sherpa it increases progressively until it reaches 29.7 mm Hg, i.e. a shift to the right of the dissociation curve (Fig. 5.5). These calculations and the curves in Fig. 5.5 were made from the Severinghaus blood gas calculator (Severinghaus, 1966). So at rest the two curves are very close, but at maximum work rate they are separated by 3.2 mm Hg at P_{50}. This means that assuming the same Pao_2 of 45 mm Hg the lowlander's blood is saturated by 6.0 per cent more than the Sherpa's blood or 1.5 vols per cent with an O_2 capacity of 25 vols per cent, the normal value for both Sherpas and lowlanders at this altitude (Fig. 5.5).

The effect on the tissue oxygen supply depends upon the position on the dissociation curve of the venous point, which in turn depends upon the blood flow and metabolism, or the oxygen extraction of the particular tissue. In the case of low extraction organs such as kidney and even the brain, the Sherpa may not be at a disadvantage. For these organs the venous point is on the steep part of the dissociation curve at Po_2 25-35 mm Hg where for a given P_vo_2 a much greater amount of oxygen will be unloaded; e.g. at Po_2 28 mm Hg the two curves are separated by 7.5 per cent saturation or 1.9 vols per cent, giving 0.4 vols per cent more O_2 for the same a-v Po_2 difference (ignoring the Bohr effect). But in the case of high extraction organs such as heart and especially working muscles which can apparently extract O_2 to almost zero Po_2, lowlander's blood will be able to deliver more O_2 than Sherpas. This situation holds for any Pvo_2 less than about 20 mm Hg.

The observed hypoventilation in Sherpas due to hypoxic insensitivity and its effect on arterial pH and O_2 dissociation curve would seem to be disadvantageous in terms of oxygen supply to the tissues, especially to

the working muscles. We must therefore look to other mechanisms for the explanation of the Sherpa's greater efficiency at high altitude. Degraph, Grover, Hammond, Miller and Johnson (1965) have shown highlanders to have twice the membrane component of diffusing capacity found in lowlanders. This is probably of great importance on heavy exercise since we found lowlanders at altitude develop increasingly wide A-a O_2 gradients due to diffusion limitations and their arterial O_2 saturation falls to the low 40 per cent levels (West, et al., 1962). Another factor in tissue oxygen supply is cardiac output. We found that the heart rate and cardiac output in lowlanders was limited to a lower maximum than at sea level (Pugh et al., 1964; Pugh, 1964) whereas we found no such limitation to heart rate in Sherpas (Lahiri, Milledge, Chattopadhyay, Battacharya and Sinha, 1967). There may also be further differences such as a richer capillary network which gives highlanders an advantage especially in heavy work, about which we have little data.

CONCLUSION

These exercise studies show a definite relative hypoventilation in Sherpas compared with acclimatized lowlanders at the same altitude. The experiments in which $P_{I}O_2$ was raised or lowered confirm the results of the resting studies discussed in the previous chapter that Sherpas have a markedly reduced respiratory hypoxic sensitivity.

This hypoventilation in Sherpas results in a lower arterial pH at rest which becomes lower still on exercise, whereas in lowlanders the arterial pH tends to rise slightly. Thus the H^+ stimulus to breathing is actually considerably greater in the Sherpa at exercise. This pH difference therefore to some extent masks the difference in respiratory response between the two groups and makes us underestimate it.

These differences in themselves would tend to reduce oxygen supply to the tissues because: 1) the lower ventilation results in reduced P_Ao_2 and Pao_2 and 2) the lower arterial pH shifts the oxygen dissociation curve to the right thus reducing still further the arterial O_2 saturation and content. These findings do not explain the Sherpa's efficiency compared with lowlanders at altitude.

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C H A P T E R V I

BLOOD AND CSF ACID-BASE BALANCE IN MAN AT HIGH ALTITUDE

In considering the effect of altitude on the control of breathing in the previous chapters, we have shown in some detail the changes in ventilation resulting from CO_2 inhalation and hypoxia and from exercise at various altitudes. In this way we have measured the effect of altitude on the control mechanism, and the differences in the setting of this mechanism as a whole between highlanders and lowlanders.

In this chapter we consider the factors underlying this setting of the control mechanism. The most important factor is thought to be the acid-base state of the environment of the central respiratory center or of receptor sites close to it. Therefore, we collected data on blood and CSF on the second expedition (1964) and in Peru (1968). In this chapter this data is considered.

In Chapter II we showed that there was a correlation between shift to the left of the CO_2 response curve (reduction in B) and the reduction in plasma HCO_3^- (Fig. 2.6). However, there was a discrepancy between our results and those from experiments on metabolic acidosis (Cunningham, Shaw, Lahiri and Lloyd, 1961). This was presumably due to the difference in CSF response to metabolic and respiratory acidosis. It was therefore obvious that to gain insight into the mechanism of the change in respiratory control we needed to know not only the acid-base status of the blood, but also that of the CSF.

On the second expedition (1964) we sampled arterial and capillary blood, and CSF from lowlanders and Sherpas at 4,880 m (16,000 ft).

In 1968 as part of a study on cerebral metabolism we measured arterial and CSF pH, CO_2 and arterial and jugular venous Po_2 and O_2 content on Andean high altitude natives at 4,330 m (14,300 ft) in Peru.

SUBJECTS

The physical characteristics of the subjects in the 1964 expedition have been given in Table 4.1. Two of the lowlanders had only been at the physiological camp for 24 hours when measurements were taken; their CSF values were similar to the other lowlanders, but their blood values were different and they could not be considered fully acclimatized. Therefore, for the purposes of comparison with acclimatized Sherpas, their results have been excluded. In 1968 we studied 16 subjects, all born and resident at 4,300 m.

METHODS

All sampling of CSF, blood and alveolar gas was done at least 2 hours after a light breakfast. Lumbar CSF which gives a good estimation of cisternal CSF in steady state (Bradley and Semple, 1962; Fisher and Christianson, 1963) was used in all of our CSF estimations. Prior to lumbar puncture the subject lay comfortably on his right side on a bed in a separate tent. After about 10 min the subject delivered Haldane-and-Priestly end-expiratory samples which were collected in Barcroft tubes by displacement of mercury and stored under positive pressure until analyzed. Within 10 min of alveolar sampling lumbar CSF was drawn anaerobically. For this the space between second and third lumbar was anesthetized with 1 cc of 1 per cent lignocaine. A short 20-gauge needle was placed deeply in the interspinous ligaments through which a 26-gauge spinal needle was

driven slowly until spinal fluid started flowing after the removal of the stylet. A 10 ml syringe whose plunger was sealed with mineral oil was connected to the needle and about a ml of CSF was collected for filling the dead space. Excess fluid was rejected, and the syringe reconnected to the needle and about 8 ml CSF collected completely anaerobically. Its pH was measured immediately with a Radiometer pH meter M_4 and an Astrup capillary micro-electrode. Temperature at the electrodes was around 37°C and the final values were corrected to 37°C using the factor of -0.004 pH unit per degree as found by Mitchell (in Severinghaus et al., 1963) and verified by us. This measurement showed a drift with the first reading, and eventually 3-4 samples were taken into the microelectrode for a stable pH value. Phosphate buffers of pH 6.840 and 7.384 were used as the standards and for determining the sensitivity of the electrodes.

The remaining sample was kept anaerobic in an ice bath for other measurements. Total CO_2 in 1 ml samples was measured in a modified Haldane blood-gas analysis apparatus as described by Cunningham et al. (1961) for blood. For lactate measurement later in Calcutta 0.1 ml CSF was diluted to 10 ml in a final concentration of 5 per cent trichloroacetic acid. Lactate was determined by a modification of the method of Barker and Summerson (1941). A 4-5 ml sample was used for the construction of a three-point CO_2 dissociation curve. The remaining CSF, if any, was sealed in a 10 ml plastic bottle and frozen for later use for Na^+ and K^+ estimation by flame photometry in Calcutta. For CO_2 dissociation the usual tonometric method was employed using 1.5 ml samples. At the end of 12 minutes equilibration at 37°C with CO_2 the total pressure above atmospheric was noted. CSF was then sampled directly from the tonometer anaerobically into the capillary microelectrode and pH was measured as before. The

tonometer gas was collected at the same temperature for CO_2 analysis. On several occasions the total CO_2 of the tonometer CSF sample was measured. All respiratory gas analysis was done with the Lloyd-Haldane gas analyzer.

Most of the blood pH measurements were made on capillary blood from the finger tip of the warmed hand. In a few instances blood was obtained by arterial puncture and its pH and whole blood total CO_2 were measured as for CSF. Temperature correction for blood pH at 37°C was made according to Severinghaus, Stumpfel and Bradley (1956).

All CSF and blood measurements were made on a Sherpa and a lowlander in pairs. This was planned deliberately to minimize the relative error between the two groups in measurements of pH under conditions which could not be controlled rigorously.

The methods used in Peru in 1968 were similar except that all blood samples were by arterial puncture and the equipment used was a Beckman 160 physiological gas analyzer, a Radiometer Po_2 electrode and a Bradley pH electrode. A working phosphate buffer, pH 6.950 was used. This was checked on alternate days with freshly opened Radiometer precision phosphate buffer, pH 6.841 and 7.383. The working buffer solution did not change over the two weeks at Cerro-de-Pasco. The blood and CSF were analyzed for total CO_2, and the blood for total O_2 by the Van Slyke method. The Pco_2 results reported are those calculated from the total CO_2 and pH. Since a direct Pco_2 measurement in CSF is likely to be inaccurate, it was not attempted. In calculating the Pco_2 of blood the nomogram of Van Slyke was used to obtain plasma $[HCO_3^-]$ and from this and the pH, the Pco_2 was calculated using the Henderson-Hasselbalch equation, and a pK' of 6.130 in CSF and 6.100 for blood was used.

RESULTS

The results are given in Tables 6.1 to 6.4.

Lowlanders and Sherpas, 1964

The numbers of subjects in 1964 are small, but the results are consistent (Tables 6.1 and 6.2). Lowlanders even after a stay of two to six weeks do not completely correct their respiratory alkalosis and their arterial blood pH remains slightly elevated (mean, 7.439). The CSF pH of lowlanders is also elevated (mean, 7.383; normal about 7.32). It is perhaps worth noting that the highest blood and CSF pH values were on subject A.B. (30 days at 4,880 m) who was unable to acclimatize and was eventually forced to go down to base camp. The Sherpas on the other hand had normal blood pH (mean, 7.399) and CSF pH (mean, 7.328) at 4,880 m.

In Sherpas the arterial Pco_2 was 2 mm Hg higher than that of the lowlanders, reflecting their slightly lower ventilation; the CSF Pco_2 is also 3 mm Hg higher. Both groups have a normal arterial-CSF Pco_2 gradient of about 9 mm Hg.

The plasma $[HCO_3^-]$ is similar in the two groups (Sherpas, mean 17.1 mEq/l, lowlanders, mean 17.4 mEq/l), showing the well known reduction with acclimatization. In CSF there is a difference of 0.7 mEq/l: Sherpas, mean 19.1 mEq/l; lowlanders, mean 19.8 mEq/l. That is, Sherpas have a slight cerebral acidosis as compared with lowlanders.

Andean subjects (Tables 6.3 and 6.4)

In Andean natives at 4,330 m (14,300 ft) we find normal arterial pH values (mean 7.412 $\pm$ 0.013). Compared with Sherpas and lowlanders at 4,880 m we find less reduction in plasma $[HCO_3^-]$ (mean 21.2 $\pm$ 1.0 mEq/l)

TABLE 6.1. Arterial blood data in Sherpas and lowlanders at 4,880 m.

Subject	pH	HCO_3^- mEq/l	Pco_2 mm Hg	Lactate mM /l	Hb g %
Sherpas					
P.E.N.	7.403	17.3	28.2	1.80	20.9
P.N.	7.387	17.3	29.3	2.31	16.9
L.T.	7.408	16.9	27.2	2.30	17.8
H.N.	7.400	17.7	28.9	1.98	20.4
Mean	7.399	17.1	28.4	2.09	19.0
Lowlanders					
J.S.M.	7.424	17.1	26.6	2.98	19.7
A.B.	7.465	18.6	26.1	2.78	18.1
S.L.	7.429	16.5	25.6	2.76	20.4
Mean	7.439	17.4	26.1	2.84	19.4

TABLE 6.2. CSF data on Sherpas and lowlanders at 4,880 m.

Subject	pH	HCO_3^- mEq/l	P_{CO_2} mm Hg	Lactate mM/l
Sherpas				
P.E.N.	7.330	19.0	37.5	3.14
P.N.	7.311	19.0	39.1	2.91
L.T.	7.344	19.2	36.6	2.92
Mean	7.328	19.1	37.7	2.98
Lowlanders				
J.S.M. 1.	7.370	19.6	35.2	3.18
2.	7.362	19.8	36.2	--
A.B.	7.417	20.1	32.4	3.10
Mean	7.383	19.8	34.6	3.14

TABLE 6.3. Blood data of Andean high altitude natives at 4,300 m.

Subject	pH	HCO_3^- mEq/l	Pco_2 mm Hg	Haematocrit %
D.N.F.	7.397	20.2	33.5	61.5
L.A.	7.405	21.9	35.6	64.0
J.G.	7.403	20.6	33.6	51.0
F.S.	7.398	23.2	38.3	67.0
E.R.	7.413	19.9	31.8	50.5
T.P.	7.422	21.6	33.6	60.5
P.V.	7.432	21.3	32.4	58.0
M.S.	7.421	21.0	33.5	50.5
Mean	7.412 ± 0.013	21.2 ± 1.0	34.0 ± 2.0	57.9 ± 6.5

TABLE 6.4. CSF data of Andean high altitude natives at 4,300 m.

Subject	pH	HCO_3^- mEq/l	Pco_2 mm Hg
D.N.F.	7.296	20.7	44.6
L.A.	7.311	21.7	45.4
J.G.	7.285	20.2	44.7
F.S.	7.276	23.0	52.0
E.R.	7.299	20.8	44.5
T.P.	7.268	21.5	49.5
P.V.	7.314	22.6	46.9
M.S.	7.281	22.0	49.2
Mean	7.291 ± .016	21.6 ± 1.0	47.1 ± 2.8

and $Paco_2$ (mean 34.0 ± 2.0 mm Hg). This is explained, at least in part, by the altitude difference.

The CSF results show a pH definitely lower than normal (mean pH 7.291 ± 0.016). The $[HCO_3^-]$ is similar to arterial values (mean 21.6 ± 1.0 mEq/1). Mean Pco_2 was 47.1 ± 2.8 which gives an arterial CSF gradient of 13.1 mm Hg.

Lactate in lowlanders and Sherpas, 1964

The blood lactates were significantly different between Sherpas (mean 2.09 mEq/1) and lowlanders (mean 2.84 mEq/1). CSF lactate values showed no significant difference (lowlanders, mean 3.14 mEq/1, Sherpas, mean 2.89 mEq/1). This means that there was a greater blood-CSF gradient in Sherpas (0.89 mEq/1) than lowlanders (0.30 mEq/1).

DISCUSSION

Respiratory acclimatization

The changes which bring about the alteration in control of breathing known as respiratory acclimatization must come to a focus at the central chemoreceptors which are believed to lie near the ventro-lateral surface of the medulla (Mitchell, Loeschke, Massion and Severinghaus, 1963). Functionally, the receptor cells seem to respond to hydrogen ion concentration somewhere on the gradient between CSF and blood, i.e. brain extracellular fluid (Mitchell et al., 1963; Pappenheimer, Fencl, Heisey and Held, 1965). The $[HCO_3^-]$ in this fluid provides the "setting" of the chemostat in terms of Pco_2 according to the Henderson-Hasselbalch equation.

At sea level the CSF pH is approximately 7.32 and $[HCO_3^-]$ 24.4 mEq/1 and the Pco_2 49 mm Hg. If the HCO_3^- is reduced to 19.1 mEq/1 (as in our

Sherpa subjects at altitude) the same $[H^+]$ is obtained only if the CSF Pco_2 is reduced to 38 mm Hg by hyperventilation. At any higher Pco_2, the H^+ will be greater, thus providing an increased stimulus to breathing and an increased ventilation. This happens when an acclimatized subject inhales a CO_2 gas mixture and the CO_2 response curve from such an experiment originates from a lower Pco_2 i.e. is shifted to the left. This is the clearest way of demonstrating respiratory acclimatization. Thus a reduction of CSF $[HCO_3^-]$ (or more accurately brain extracellular $[HCO_3^-]$) is necessary for respiratory acclimatization.

What then is the mechanism of this reduction in CSF $[HCO_3^-]$? It used to be assumed that hyperventilation was initiated by hypoxic stimulation of the peripheral chemoreceptors. This would cause a respiratory alkalosis, stimulating the kidneys to excrete an alkaline urine, resulting in a reduction in blood $[HCO_3^-]$ and passively of CSF HCO_3^-.

This mechanism was found to be inadequate because: 1) The arterial pH becomes progressively more alkaline during the early stages of acclimatization (Nielsen and Smith, 1952 - appendix to paper); and 2) Kellogg in 1963 showed that the time course for the change in blood pH and the shift in the CO_2 response curve were quite different, the latter being much more rapid, so that after the first few days, the Pco_2 was 14 mm Hg lower, while the arterial pH was 0.05 units higher than sea level values. He suggested that the chemical environment of the respiratory center was changed by some other, as yet unidentified, mechanism -- possibly active transport.

In 1963 Severinghaus, Mitchell, Richardson and Singer reported results of acid-base measurements on blood and CSF in man at altitude which they thought could best be explained by active transport of either HCO_3^- or H^+

across the blood-brain barrier. This hypothesis was developed by Mitchell, Carmen, Severinghaus, Richardson, Singer and Shnider (1965) and has received support from Pappenhiemer et al. (1965) and Fencl, Miller and Pappenheimer (1966). This is further discussed later.

The mechanism of acclimatization then would be: Hypoxia → peripheral chemoreceptor stimulation → $P_{CO_2}\downarrow$ in blood and CSF → active transport of HCO_3^- out or H^+ into CSF under the influence of some pH regulating mechanism.

RESULTS OF PRESENT WORK

Blood

The acid-base balance of the arterial blood in our subjects at high altitude showed the well known respiratory alkalosis with compensatory metabolic acidosis. In lowlanders at 4,880 m this compensation is incomplete and a further reduction of 1.5 mEq/l $[HCO_3^-]$ would be required to bring the pH to 7.40. This slightly increased pH is in accordance with other workers (Kellogg, 1963; Pauli, Vorburger and Reuben, 1962; and Severinghaus et al., 1963). High altitude natives on the other hand seem to compensate completely. Hurtado and Aste-Salazar (1948) and Chiodi (1957) also found this same difference between residents and new-comers to high altitude.

Cerebrospinal fluid

Our results can best be compared with those of Severinghaus et al. (1963) and Severinghaus and Carcelen (1964).

Lowlanders. The alkalosis that results from a reduction in P_{CO_2} on going to altitude is more rapidly corrected in the CSF than in the arterial blood.

In dogs Michel (1963) showed a fall in CSF HCO_3^- of over 5 mEq/l within the first hour of hyperventilation. Severinghaus et al. (1963) found the CSF pH to be almost normal by the second day at altitude (their first sampling), while the arterial pH was still raised (7.485). There was little further change on either blood or CSF by the eighth day. They interpreted their results as suggesting a mechanism which regulated CSF pH by active transport of HCO_3^- out of the CSF against the gradient, into blood.

Our results, at a higher altitude, with lower CSF Pco_2 showed a more alkaline CSF pH. This is evidence against very close regulation of CSF pH to sea level values.

Sherpas and Andean natives. Severinghaus and Carcelen (1964) found the mean CSF in Andean natives at 4,300 m to be 7.336. In the same population and at similar altitude, we found the mean CSF pH to be 7.291 $\pm$ 0.016. We have no satisfactory evidence for this discrepancy, though they mention some alteration in the pH of their buffer during transportation and possibly the discrepancy may be partly due to this cause.

The difference between our results in Sherpas at 4,880 m (pH 7.328) and Andean natives at 4,330 m (pH 7.291) is presumably due to the difference in Pco_2, 37.7 and 47.1 mm Hg respectively, resulting in part from difference in altitude. The Sherpas are normally resident at about 4,000 m and so we studied them at almost 900 m above their place of residence. They may have undergone a degree of acclimatization analagous to lowlanders resulting in a shift of CSF pH towards the alkaline side.

In our Andean subjects the arterial CSF P_{CO_2} gradient was greater than normal (13 mm Hg). As part of the study of cerebral metabolism we measured cerebral arterial-venous O_2 difference and were surprised to find a high value of 7.89 vols per cent indicating a low cerebral blood flow. The CSF P_{CO_2} is in equilibrium with cerebral venous blood, and so the large arterial-CSF gradient is presumably due to this low cerebral blood flow. We have no data on cerebral blood flow in our Sherpa or lowland subjects but there may be important differences in cerebral blood flow response to hypoxia in these three groups, since in lowlanders at an altitude of 3,810 m Severinghaus, Chiodi, Eger, Brandstater and Hornbein (1966) found cerebral blood flow to be increased 24 per cent at 6-12 hours and 13 per cent at 3-5 days after arrival.

CSF pH regulation

The rather wide range of CSF pH values we have found is evidence against any mechanism which accurately regulates CSF pH by active transport of HCO_3^- or H^+ across the blood-brain barrier. The mechanism of any such homeostatic system must require a signal in a form of a disturbance of the homeostasis. In hyperventilation the signal would be a slight rise in pH due to respiratory alkalosis. This would cause the active transport of HCO_3^- out of the CSF against the concentration gradient. If the system were perfectly efficient, the signal necessary would be immeasurably small and the pH would be restored exactly to normal values. If the system were less than perfect, the CSF pH would remain alkaline. But in no way could the system pump out HCO_3^- to a point where the pH was lower than normal since before then the signal would be reversed, and HCO_3^- would be retained. Therefore, the low pH found in Andean natives is the strongest evidence against such a mechanism.

Our findings suggest a hypothesis that CSF pH is primarily reduced by some means other than hyperventilation, and that hyperventilation is secondary, a result of this resetting of the central chemostat. Three other pieces of evidence also support the hypothesis that acclimatization is not primarily the result of hyperventilation:

1) Natives to high altitude who have very little or no hypoxic sensitivity nevertheless acclimatize to about the same extent as lowlanders in terms of CSF HCO_3^- and shift of the CO_2 response curve (Severinghaus, Bainton and Carcelen, 1966; and the present work, Chapter IV).

2) Eger, Kellogg, Mines, Lima-Ostos, Morrill and Kent (1968) have shown a greater shift in the CO_2 response curve in human subjects hyperventilating for 8 hours with hypoxia compared with similar hyperventilation without hypoxia.

3) Sørensen and Mines (1968) have shown that goats with their carotid bodies denervated so that acute hypoxia depressed ventilation, nevertheless shifted their hyperoxic CO_2 response curve at altitude to the same extent as normal goats.

These all indicate that hypoxia has an effect on respiratory acclimatization apart from any effect through the peripheral chemoreceptor. The findings could be explained if the reduction of CSF HCO_3^- was a primary effect of hypoxia. This primary effect of hypoxia in lowering CSF HCO_3^- could be via the metabolites of anaerobic metabolism, e.g., lactic and pyruvic acid.

Anaerobic glycolysis, the basis for acclimatization

Severinghaus et al. (1963) considered the effect of the rise in lactic acid on CSF HCO_3^- but thought it unimportant. Taking their sea

observed. In this way the highlander has a greater central respiratory drive that largely masks the lack of peripheral drive and accounts for his respiratory acclimatization.

It is suggested therefore, that the major cause for the reduction in CSF $[HCO_3^-]$ in respiratory acclimatization is a metabolic acidosis from continuing anaerobic metabolism in the brain. The major role of the peripheral chemoreceptors would seem to be that of counteracting the central depression caused by hypoxia which is seen in animals with peripheral chemoreceptor denervation.

level value, our subjects in 1964 showed a rise in CSF lactate of 1.8 mEq/l. The HCO_3^- reduction due to a reduction of 15 mm Hg Pco_2 would be 0.3 mEq/l which together accounts for 2.1 mEq/l out of a total HCO_3^- reduction of 4.9 mEq/l in lowlanders and 5.6 mEq/l in Sherpas.

It may be that the lactate level found in the CSF does not reflect the extent of acidosis actually resulting from anaerobic metabolism. This could be either because H^+ is more diffusible than the lactate ion, or because the H^+ is pumped out of the cell in the same way, or even by the same mechanism as Na^+ is pumped. Thus although the measured rise in CSF lactate may be small, the increase in H^+ which combines with HCO_3^- may well be of the order of 4-6 mEq/l.

Such an explanation would be in agreement with our findings and those of other workers. The observed rapid reduction in CSF HCO_3^- on going to altitude would be due to diffusion or pumping of H^+ out of cells as metabolism changed to a degree of anaerobic glycolysis in the face of hypoxia. Hyperventilation results in similar changes due to a reduction in cerebral blood flow causing tissue hypoxia.

The differences in CSF pH between lowlanders and highlanders could then be accounted for by the differences in peripheral chemoreceptor response that we have shown (Chapter IV). In lowlanders the strong hypoxic ventilatory response further lowers Pco_2 resulting in a slight alkalosis in the CSF (and blood) and a reduction in central respiratory drive, while the highlanders with a weaker hypoxic response, have a slightly higher CSF Pco_2. For the same reason, the highlander also has a lower Po_2 and possibly a lower cerebral blood flow, which results in a greater cerebral lactic acid production giving a slightly lower CSF $[HCO_3^-]$. The higher Pco_2 and lower $[HCO_3^-]$ result in the lower CSF pH

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