RESPIRATORY AND CIRCULATORY CHANGES DURING ACCLIMATIZATION TO HIGH ALTITUDE

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The studies of decreased barometric pressure made by Paul Bert (1) during the latter half of the nineteenth century may properly be considered as the beginning of modern knowledge of, and interest in, the effects of oxygen lack upon the human body. During the same period the rapid development of mountaineering as a sport produced a new occupational disease—altitude sickness, or seroche as it was called in the Andes. At the turn of the last century Moss0 (2) was defending acapnia as the cause of mountain sickness, against Haldane and Priestley (3), who regarded acapnia as the result rather than the cause of the illness. About this time it was observed that residents at high altitude experienced none of the unpleasant symptoms developed by visitors recently arrived, and a process of acclimatization to high altitude was postulated.

In the famous controversy which raged for more than a quarter of a century, stimulating two scientific mountain expeditions and innumerable laboratory studies, Haldane and Priestley (3) contended that acclimatization was due, in part at least, to active oxygen secretion from alveolus to blood, whereas Barcroft (4) maintained that oxygen secretion never occurred, and argued that acclimatization consisted of a series of respiratory and circulatory changes. Our modern knowledge indicates that Barcroft’s concept, fully discussed by him in 1934 (5) and recently summarized by Van Liere (6) is correct. The Pike’s Peak expedition of 1913 (7) which remained for five weeks at 14,100 feet, demonstrated a fall in the “alkaline reserve” of the blood, as previously suspected by Galleotti (8), and confirmed the earlier observations by Viault (9) of the increase in circulating red blood cells. The Pike’s Peak investigators mistakenly believed that they had proven the occurrence of oxygen secretion by the lung. A thorough analysis of the process of acclimatization was made by the 1922 expedition to Peru (10). Barcroft, the leader of this expedition, considered the three major factors to be: increased pulmonary ventilation, polycythemia and a shift to the left of the oxyhemoglobin dissociation curve. The International High Altitude Expedition of 1936 greatly expanded the original studies and added detailed analyses of electrolyte balance, blood pH, and the characteristics of hemoglobin (11, 12). Most of these mountain studies were carried out between 13,000 and 18,000 feet.

In the meantime mountaineers, climbing solely for sport and unable to perform

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complex measurements, ascended to 28,000 feet on Mt. Everest in 1924 (14) and on numerous occasions spent weeks above 22,000 feet (13, 15). Their contribution to our knowledge of acclimatization may be summarized as follows: a gradual ascent is necessary to provide complete acclimatization; secondly, at extreme altitudes, deterioration may be as rapid as is acclimatization (although cold, fatigue, and inadequate food and shelter influence this effect); thirdly, acclimatized man can perform heavy work as high as 25,000 feet, an altitude which rapidly causes unconsciousness in unacclimatized man; and finally, additional oxygen does not fully restore the acclimatized man to his sea level condition (14).

All of these high altitude expeditions had one common defect: the subjects were also the observers, and since oxygen lack notoriously dulls cerebral function, their observations of their own and their companions’ condition were open to question. Ideally, only the subjects should be exposed to oxygen lack, while the observers should be unaffected, a condition attainable only by use of a low pressure altitude chamber. Brief studies of this type were made by Hasselbalch and Lindhard (16), Haldane et al. (17) and Barcroft (5), but their work was necessarily limited in time and scope. Only the extensive development of altitude chambers and the availability of trained personnel attendant upon the altitude training programs of the last war, made possible the prolonged study of acclimatization which is reported here.

In the course of this study a wide variety of data were collected. The present report, however, deals only with those data required for an analysis of the oxygen transport system and some closely related adaptations.

**EXPERIMENTAL DESIGN.** From a number of volunteers were selected four subjects found to be physically sound and psychologically stable.

- **McNutt:** Age 27, height 175 cm., weight 69 kgm., surface area 1.82 sq. m. College graduate (physiology), excellent and well trained athlete, non-smoker.
- **Morris:** Age 19, height 180 cm., weight 69 kgm., surface area 1.86 sq. m. High school graduate, moderate athlete, smokes one package cigarettes daily.
- **Hertel:** Age 23, height 174 cm., weight 66 kgm., surface area 1.79 sq. m. High school graduate, moderate athlete, smokes one package cigarettes daily.
- **Wilkins:** Age 20, height 171 cm., weight 62 kgm., surface area 1.72 sq. m. High school graduate, moderate athlete, smokes one package cigarettes daily.

A rectangular altitude chamber measuring 10 by 12 by 7 feet was fitted with conveniences necessary to make living conditions as comfortable as possible. By means of a communicating lock, in which pressure could be equalized with either the main chamber or the outside, observers wearing oxygen equipment could enter the chamber at will without themselves experiencing anoxia. The pressure within the chamber was accurately controlled by manually operated valves, adjustment of which permitted continuous ventilation of the chamber at a rate of 20–30 cubic feet per minute. A Pauling (18) oxygen analyzer, installed within the chamber, was read several times each day and checked at least once daily by analysis of a sample of the chamber air by the Haldane technic. The pressure was carefully determined by a mercury barometer which agreed almost precisely with two previously calibrated aircraft altimeters, and at no time did
the analysis of chamber air show significant accumulation either of additional oxygen or of carbon dioxide.

After an initial three day observation period at sea level, the chamber pressure was reduced to simulate an ascent of 2000 feet per day up to 8000 feet, of 1000 feet per day to 15,000 feet, and of 500 feet per day thereafter (fig. 1). Up to 15,000 feet the daily ascents were made in the course of a few minutes; above this altitude the pressure was reduced over a two hour period during the evening. The subjects were usually told of the altitude, and all plans and results were freely discussed with them. Temperature was regulated between 65° and 75°F.

An observer was continuously on duty at a window to keep detailed notes of the subjects' condition. A complete kitchen under the direction of a trained dietitian was established to provide the subjects with the best available food, and they were permitted to choose their menus. A bicycle ergometer was available within the chamber and McNutt exercised regularly; the others worked only sporadically.

Every effort was made to provide the subjects with comfortable living conditions, appetizing meals, and moderate exercise, in a controlled environment of which the chief variable was the barometric pressure. They were obviously far better provided for than are mountaineers at comparable altitudes. In addition all of the studies and observations were made by trained observers who were unaffected by anoxia. This experimental design is obviously unattainable on mountain expeditions.

Each morning before the subjects arose an observer measured each man's resting pulse and blood pressure and collected a sample of alveolar air by the
Haldane-Priestley method; each man was then weighed. At eight-thirty, approximately one hour after breakfast, the resting arterial blood and respiratory studies described below were begun, followed shortly afterwards by the same studies during standard work. These studies were made on one subject each day. Either x-rays, or psychological tests were then made on all subjects, and before the noon meal an hour was made available for exercise and recreation. A short rest followed the meal, and the remainder of the afternoon was devoted to electrocardiographic work and measurement of pulse rate before, during, and after standard exercise on a twenty-inch step. Baths were given before supper which was usually followed by movies and a visit by a medical officer. Handwork, cards, books, and a radio supplemented their recreational facilities, and thanks to the whole-hearted cooperation of the entire team, the four volunteers remained in good health and spirits throughout the thirty-five day study.

Methods. The analysis of oxygen transfer from inspired air to tissue capillaries was based upon samples of arterial blood and expired air which were collected in the following manner. An indwelling needle was inserted into the brachial artery under local anesthesia, and a mouthpiece and nose clip were adjusted. After the subject had rested quietly for 10 or 15 minutes, samples of blood and expired air were collected simultaneously during a one minute period. Then, with the arterial needle still in place, the subject mounted a stationary bicycle and pedalled at 69 revolutions per minute in time to a metronome. At sea level the work load was not measured, but at altitude the load was so adjusted that the work was 2530 foot lbs. per minute except at altitudes above 20,000 feet where the work was reduced to 1490 foot lbs. per minute. Samples of arterial blood and expired air were again collected after the subject had been exercising for 7 minutes. In general, each man served as subject every fifth day and the two blood samples totaled 35 ml. The studies caused the men only slight discomfort, and after their first one or two experiences as subject, they were not apprehensive about the procedures.

Pulmonary ventilation, i.e., the minute volume of expired air at body temperature and pressure and saturated with water vapor (BTPS), was calculated from the inspiratory minute volume as measured in a Tissot spirometer. This value, corrected to dry volume at standard sea level temperature and pressure (STPD), was used in the calculation of carbon dioxide output and oxygen intake. The expired air was collected at altitude in a Douglas bag and brought to sea level for analysis for CO2 and O2 in the Haldane apparatus.

Arterial blood samples were drawn into iced syringes in which the dead space had been eliminated with heparin-fluoride solution. Carbon dioxide and oxygen pressures of the arterial blood were determined by the direct bubble method of Riley et al. (19).

Effective alveolar gas pressures were calculated by the method of Riley et al. (20), in which the effective alveolar pCO2 is considered to equal arterial pCO2, and effective alveolar pO2 =

\[
\text{tracheal } pO_2 \times \frac{\text{expired } %N_2}{\text{inspired } %N_2} - \frac{\text{arterial } pCO_2}{\text{R.Q.}}.
\]
To determine the oxyhemoglobin capacity 2 ml. of blood were exposed to 8 ml. of 85 per cent carbon monoxide in a 10 ml. syringe within 7 to 10 minutes after the blood was drawn. The syringe was then rotated for 3 minutes, the CO expelled, fresh CO introduced, and rotation continued for 3 minutes more. The gas was then completely expelled and the syringe sealed. This sample was then analyzed by the Scholander-Roughton technic (21) to obtain the CO capacity of the blood. The O₂ and CO contents of the blood as drawn were determined by the combined method of Scholander and Roughton (21). The O₂ capacity was then calculated from the CO capacity by subtracting the CO content (22).

When blood contains both O₂ and CO it is necessary to take both gases into consideration if pressure-saturation points are to be compared to standard oxyhemoglobin dissociation curves (22). Accordingly, total saturation

\[
\frac{(COHb) + (O_2Hb)}{(Hb) + (COHb) + (O_2Hb)} \times 100
\]

and total gas pressure (pO₂ + MpCO⁴), were calculated for each arterial blood sample. In these experiments, however, the CO content of the blood was uniformly so low that total saturation was but a fraction of 1 per cent higher than oxyhemoglobin saturation and total gas pressure was usually but 1 mm. Hg higher than O₂ pressure. Since these differences are of little significance the oxygen data alone will be used in the graphs and discussions appearing in this paper.

The carbon dioxide content of arterial blood was determined on 0.5 ml. samples in the Van Slyke apparatus. The CO₂ content of fully oxygenated blood at a pCO₂ of 40 mm. Hg (T40), the CO₂ content of the serum, and the pH of the serum were calculated by the graphic methods contained in the Syllabus of Methods of the Fatigue Laboratory (23). For comparison the pH₄ was also determined with the glass electrode (22).

On two occasions cardiac output determinations were made by the dye injection method of Hamilton et al. (24), with modifications in the sampling technic.

The hematocrit was determined using Wintrobe tubes. Readings were taken after centrifuging the blood for 25 minutes at approximately 3000 r.p.m. Blood sugar was determined by the modified Folin-Malmros method (23). Plasma proteins were determined by the Kjeldahl method (25) and by the copper sulfate specific gravity method (23). The former values averaged about 0.4 gram per 100 ml. higher than the latter and are considered the more accurate. The plasma was also analyzed for non-protein nitrogen, lactic acid, and chloride (23). All analyses on plasma were very generously performed for us by Mr. Frank Consolazio at the Harvard Fatigue Laboratory.

RESULTS. The data are presented in tables 1–5 and in figure 2.

Pulmonary ventilation (table 1). In all four subjects the ventilation increased as the altitude increased, though there were marked individual variations. McNutt and Wilkins, for example, showed relatively little increase in ventilation, whereas Hert.:! and, to a lesser extent, Morris, showed a considerable increase.

₄ M is the relative affinity of CO for hemoglobin as compared to the affinity of O₂ for hemoglobin. Its value is approximately 210.
The effectiveness of a large volume of pulmonary ventilation in sustaining arterial oxygenation during exposure to reduced oxygen pressures (26) is dramatically illustrated by contrasting the resting studies on McNutt at 21,000 feet with those on Hertel at 22,000 feet. McNutt showed a relatively low ventilation (11 l./min.) which was associated with the extremely low alveolar $pO_2$ of 30 mm. Hg,

### TABLE 1

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<th>RESPIRATORY RATE</th>
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an arterial pO$_2$ of 29 mm. Hg, and an oxyhemoglobin saturation of 52 per cent. Hertel, although a thousand feet higher, by ventilating at the rate of 19 l./min.

TABLE 2

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maintained an effective alveolar pO$_2$ of 35 mm. and an oxyhemoglobin saturation of 66 per cent.
Pulmonary ventilation remained elevated for at least four days in the two subjects studied upon return to sea level, a confirmation of the observation made by Schneider (27).

Gas exchange. The values for CO₂ output, O₂ intake and R.Q. shown in table 1 remained nearly constant during rest at all altitudes, indicating that there was
no appreciable effect of altitude on over-all bodily metabolism. This observation is in agreement with the findings of D'Angelo (28) and of Lewis et al. (29).

<p>| TABLE 4 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| DATE | ARTERIAL CO₂ | CO₂ CONTENT (VOLUMES PER CENT) | SERUM CO₂ CONTENT (VOLUMES PER CENT) | pH₆ (HENDERSO- | pH₈ (GASS ELECTRODE) |
| PER CENT | FULLY OXYGENATED (pCO₂ = 40 MM. HO) | | | RANKSALCH) |</p>
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and Dill (30), though not with those of Cook (31). The constancy of the respiratory quotient shows that these values were determined primarily by metabolic
requirements and not by transient alterations in ventilation. This finding lends increased significance to the higher than normal values for ventilation, which are thus shown to be representative of a fairly steady state.
During the standard work of 2530 ft. lbs./min. performed between 9000 and 20,000 feet, the O₂ intake and CO₂ output were also remarkably constant.

Arterial and effective alveolar pCO₂ and pO₂ (table 2). The observed drop in arterial pCO₂ was an inevitable consequence of the sustained hyperventilation. In one instance (Hertel, 20,000 ft.) the arterial pCO₂ reached the low value of 16 mm., but in none of the subjects was there any sign of impending tetany despite pH values of 7.5 or higher.

Fig. 2. Composite chart of selected data from all four subjects.

The level of the effective alveolar pO₂ (20) was in general directly related to pulmonary ventilation, since the larger the respiratory minute volume, the more closely alveolar pO₂ approaches the pO₂ of inspired air (26).

Alveolar-arterial pO₂ gradient. In general the difference in pO₂ between alveolar air and arterial blood was less in the partially acclimatized subjects at altitude than it is in normal subjects at sea level (32). This is probably one of the physiological adaptations to low pO₂ in the inspired air and may be related to an increase in both ventilation and pulmonary circulation. In previous unpublished studies we have noted that the alveolar-arterial oxygen pressure gradient decreases with voluntary hyperventilation during anoxia. The occasional finding of arterial oxygen pressures which were higher than the corresponding effective alveolar
oxygen pressures must be considered technical error in one or both figures since under the conditions of these experiments the directly determined arterial pO$_2$ is only accurate to $\pm 3$ mm. Hg and the calculated effective alveolar pO$_2$ to $\pm 4$ mm. Hg.

In keeping with previous findings, the alveolar-arterial gradients were larger during exercise. The unusually large gradients found in the two subjects studied on return to sea level may be attributed in part to technical error (since the direct arterial pO$_2$ technic is less accurate for very high oxygen pressures), and in part to the increasing influence of venous admixture at high levels of oxygenation (32).

Fig. 3. Oxygen pressure saturation points determined on arterial blood, superimposed on standard oxyhemoglobin dissociation curves for pH 7.4 and 7.6.

**Oxyhemoglobin dissociation** (table 3, fig. 3). The oxyhemoglobin saturation decreased with increasing altitude as did the arterial pO$_2$, although the decrease was less marked than that of pO$_2$ because of the shape of the oxyhemoglobin dissociation curve.

The scatter of the experimental points around the standard curve for pH = 7.4 (12, 33) may be in part technical error but is significantly related to two biochemical factors. First, the individual pressure-saturation points correspond to arterial samples of different pH$_a$ values and accordingly would not be expected to fall along the curve for any single pH$_a$ value. Second, many individual points show a definite "shift to the right"; i.e., they fall to the right of the point to be expected for the pH$_a$, pO$_2$, and saturation determined. This finding indicates an altered affinity of hemoglobin for oxygen at a given pH$_a$ and is presumably an adaptation related to the prolonged alkalosis and hypoxia to which the subjects...
were exposed. It is comparable to the changes found in 1935 by Keys et al. in studies of natives and temporary residents at high altitudes in Peru (34).

**Oxyhemoglobin capacity and content.** The oxyhemoglobin capacity increased throughout the entire period at altitude to values which were high in comparison to sea level values, but which were not as high as those found in fully acclimatized subjects (35). Although total blood volume was not determined the constancy of the serum protein values indicates that the increase in capacity was probably due to an actual increase in hemoglobin rather than to hemoconcentration from fluid loss. Since these measurements were made after the subjects had been above sea level for 4–5 days, this observation does not conflict with the work of Asmussen and Nielsen (36) who found that the increase in hemoglobin which occurs during the first days at high altitude is due to hemoconcentration and not to an absolute increase in circulating red blood cells.

The oxygen content of the arterial blood remained almost constant from sea level up to 20,000 feet due to the fact that the increase in oxygen capacity compensated for the fall in oxygen saturation.

**Alkaline reserve, pH, and acid-base balance** (table 4). The CO₂ content of fully oxygenated blood at a pCO₂ of 40 mm. Hg (T40), which is a measure of the alkaline reserve, fell progressively with increasing altitude to approximately 75 per cent of the sea level value.

The values for pH, increased during the early part of the experiment and then leveled off at about 7.51. The highest single figure was 7.59, determined by glass electrode for Hertel at rest at 20,000 feet. The high pH, was associated with a very low pCO₂ (16 mm. Hg). These values are not to be considered as the normal response to altitude since the subject was apprehensive over the cardiac output procedure and was obviously over-breathing. These extreme changes in acid-base balance were not associated with signs of tetany.

Since pH, varies according to the Henderson-Hasselbalch formula,

\[
pH_\text{a} = pK' + \log \frac{\text{BHCO}_3}{0.0301p\text{CO}_2}
\]

restoration of the pH, in the presence of low pCO₂, devolves upon the BHCO₃. Although bicarbonate concentrations are not listed separately in the tables, they are practically the same as serum CO₂ content. Like T40, serum CO₂ content showed a progressive fall to approximately 75 per cent of the sea level value.

In figure 4 the Henderson-Hasselbalch relationships for the resting bloods are plotted on triangular co-ordinates. The directly determined arterial pCO₂ values

6 In the report of the 1922 Peruvian expedition (10) a "shift to the left" of the oxyhemoglobin dissociation curve was described. Possibly this finding resulted from Barcroft's use of pH, values significantly lower than those found by later investigators using more accurate methods. An error in this direction would cause an apparent shift to the left of the dissociation curve.

6 Total serum CO₂ content includes both bicarbonate and dissolved CO₂, but the ratio of concentrations is normally about 20:1. Dissolved CO₂, which varies with pCO₂, thus makes a relatively insignificant contribution to total serum CO₂ while bicarbonate makes the major contribution.
and the directly determined glass electrode pH values were used. Normal sea level points determined before the experiment was started appear in the upper left hand part of the chart. As the altitude increased the points moved down and to the right, then down between the pHi 7.5 and pHi 7.6 lines. If arterial pCO₂ is considered fixed by the obligatory hyperventilation at altitude, the distribution of the points shows the degree to which the lowering of plasma bicarbo-

![Diagram of acid-base relationships plotted on triangular co-ordinates. Data obtained from resting bloods on all four subjects. The shaded points were obtained after return to sea level.]

Fig. 4. Acid-base relationships plotted on triangular co-ordinates. Data obtained from resting bloods on all four subjects. The shaded points were obtained after return to sea level.

...bicarbonate limited the rise in pHi. The two points determined after return to sea level (cross hatched) showed normal pHi values, but BHCO₃ and pCO₂ were still low by sea level standards.

In this experiment there was little change in the concentration of negative ions other than bicarbonate: chloride, although slightly elevated, showed a definite change from the sea level value in only one subject; protein showed no change; lactate showed a slight rise above the sea level value in three of the four subjects. Bicarbonate decreased approximately 4.5 m.-eq./l. which is probably more than the increase in other negative ions. If the sum of all negative ions including bi-
carbonate decreased slightly, a corresponding decrease in positive ion concentration must also have occurred in order to restore ionic equilibrium. Although our data are not complete enough to establish these changes with certainty, they are consistent with the findings of Dill et al. (12).

Cardiac output and arterio-venous oxygen difference. Of the two cardiac output determinations which were performed, the one on McNutt at 20,000 feet was the more satisfactory since the subject was not far from a basal state and the technical aspects of the dye injection and multiple arterial sampling went smoothly. The value obtained was 9.8 l./min., which, with an oxygen intake of 329 ml./min., indicates an arterio-venous oxygen difference of 3.35 vols. per cent. Since the arterial oxyhemoglobin content was 14.95 vols. per cent, the mixed venous blood must have contained 14.95 - 3.35 or 11.6 vols. per cent. The oxyhemoglobin saturations of arterial and mixed venous blood were 64 and 49 per cent respectively. The arterio-venous difference was thus 15 per cent in saturation or 8 mm. Hg in oxygen pressure (as read from the oxyhemoglobin dissociation curve).

The cardiac output determination on Hertel at 20,000 feet (less satisfactory because the subject was excited) showed the minute volume of blood flow to be 10.8 l./min. The calculated arterio-venous difference was therefore 1.8 vols. per cent in saturation and 9 mm. Hg in oxygen pressure. Since Hertel's level of oxygenation was higher than that of McNutt, his arterio-venous difference, although lower in per cent saturation, was actually larger in terms of oxygen pressure. If the normal resting cardiac output is considered to be 5 l./m. at sea level, the figure for McNutt was almost twice, and that for Hertel more than three times normal.

Effect of exercise. The work load at sea level was different for each individual and unfortunately these data cannot be compared with the data collected during the standard work at altitude.

The work performed at altitude required an oxygen intake of slightly more than three times the resting rate and was associated with an increase in pulmonary ventilation to three or four times the resting rate (table 1). As was the case at rest, oxygen consumption during standard work was not significantly changed as the altitude increased. The highest ventilation during work was Hertel's at 19,500 feet, which reached 69 l./m. BTPS at a respiratory rate of 36 per minute. The highest pulse recorded during work was 142 for Morris at 15,000 feet.

The arterial pO2 during work at sea level remained the same as, or actually increased above, the resting level, but at altitude the arterial pO2 during work was usually several millimeters Hg below the resting level. At altitude the alveolar-arterial oxygen pressure gradient was larger during work than while at rest, in keeping with earlier experience (32). Oxyhemoglobin content usually remained constant and oxyhemoglobin capacity increased slightly with the net result that oxyhemoglobin saturation usually dropped during exercise. CO2 content dropped probably because of the increase in lactate ion. At the level of work studied there was no evidence of the decrease in lactic acid production or

7 The determinations were made by Dr. John W. Remington.
tolerance at altitude found by Edwards (37). The pH usually, though not invariably, decreased slightly during work.

Discussion. The data recorded in this paper fit into the concept advanced by Barcroft (5) that acclimatization to high altitude consists of a series of integrated adaptations which tend to restore tissue oxygen pressure toward normal sea level values in spite of lowered oxygen pressure in the atmosphere. Since at any given altitude the \( P_{O_2} \) of the inspired air is fixed, tissue \( P_{O_2} \) can be restored toward normal only by diminishing the drop in \( P_{O_2} \) between inspired air and tissues. Accordingly, in order to analyze the changes occurring in the oxygen transport system as a result of acclimatization, we shall examine the \( P_{O_2} \) gradients which occur at successive stages along the route of oxygen transport.

From the data at hand we can compare the \( P_{O_2} \) gradients from inspired air to alveolar air, and from alveolar air to arterial blood in acclimatized and unacclimatized individuals. On theoretical grounds we should like to continue the analysis to include the \( P_{O_2} \) gradients from arterial blood to capillary blood, and from capillary blood to tissue cells. Unfortunately the gradient from capillary blood to tissue cells is beyond hope of quantitative approximation from the data at hand, but the arterial-capillary \( P_{O_2} \) gradient can be estimated with enough accuracy to be very helpful in evaluating the relative importance of certain circulatory adaptations to high altitude.

In order to obtain a single figure for the \( P_{O_2} \) gradient between arterial blood and capillary blood it is necessary to assign an average or mean value to a function which is in fact constantly changing. The arterial \( P_{O_2} \) is the same for all the capillaries of the body and is readily determined by direct analysis; the capillary \( P_{O_2} \), however, varies widely, and it is this end of the gradient for which a theoretical average value must be obtained. The concept of a mean capillary \( P_{O_2} \) was first introduced by Bohr (38), who estimated this value for blood in the pulmonary capillaries by a graphic integration method. Barcroft (5) expanded the idea and applied it to the capillaries of the greater circulation. Houston (39) has recently shown graphically how this expanded concept can be used to evaluate the relative importance of factors involved in acclimatization to high altitude.

The mean capillary \( P_{O_2} \) may be defined as that oxygen pressure which, if it prevailed throughout the entire length of all the capillaries of the body, would not alter the quantity of oxygen diffusing from capillaries to tissues from the quantity diffusing under actual physiological conditions. The method for calculating mean capillary \( P_{O_2} \) is a modification of Bohr's graphic integration procedure\(^8\) and depends upon the basic principle that the rate at which oxygen diffuses across a membrane (in this case the capillary wall and tissue fluids) is directly proportional to the \( P_{O_2} \) gradient between the two sides of the membrane. In calculating this value the necessary data are the arterial \( P_{O_2} \), the mixed venous \( P_{O_2} \), and the mean

\[
\text{Mean capillary } P_{O_2} = \text{Venous } P_{O_2} + \frac{\text{Arterial } P_{O_2} - \text{Venous } P_{O_2}}{3}
\]

\(^8\) During moderate and severe anoxia the results obtained by the lengthy integration procedure are almost identical to those obtained by the simple approximation suggested by Barcroft.
tissue pO₂. The arterial pO₂ is determined from the brachial artery sample. The mixed venous pO₂ refers to the blood entering the right heart which is a mixture of venous blood from all parts of the body. In the analysis which follows, mixed venous pO₂ is calculated from the cardiac output and the oxygen consumption according to the Fick relationship. Mean tissue pO₂ has been arbitrarily considered to lie half way between zero and mixed venous pO₂. At high altitude this arbitrary choice introduces no significant error in the calculation of mean capillary pO₂. For sea level conditions (arterial pO₂ of 95 mm. Hg and mixed venous pO₂ of 35 mm. Hg), the exact value of mean tissue pO₂ is a more important factor: mean capillary pO₂ will vary by 7 mm. Hg if mean tissue pO₂ ranges from 1 mm. to 34 mm. For an assumed mean tissue pO₂ of 17 mm. (midway between zero and mixed venous pO₂) the mean capillary pO₂ is 47 mm.

Let us proceed to an examination of the pO₂ gradients occurring at each stage in the oxygen transport system before and after acclimatization. In the following analysis we shall use data on Hertel at sea level and on McNutt at 20,000 feet

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<th>ALVEOLAR pO₂, MM. HG</th>
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* At 37 degrees C. and complete saturation with water vapor, and corrected for the difference in volume between inspired and expired air.

because the most satisfactory determinations were obtained in these two instances. The data are summarized in table 6.

The drop in pO₂ between inspired air and alvoclar air was 26 mm. Hg less at altitude than at sea level (26 mm. instead of 52 mm.). The mechanism by which this diminution was accomplished was increased ventilation (Barcroft's first step). For normal individuals doubling the ventilation approximately halves the pO₂ gradient between inspired air and alvoclar air (26); in this case the ventilation increased from 6 to 13 l./min. and the gradient was halved.

The pO₂ gradient between alvoclar air and arterial blood was 3 mm. less at 20,000 feet than at sea level (2 mm. instead of 5 mm.). At 20,000 feet this gradient was due almost entirely to the diffusion resistance of the pulmonary membrane, and the diffusion constant of the lung, as calculated by the method of Lilienthal et al. (32), is found to be 70. For sea level conditions the alvoclar-
arterial \( pO_2 \) gradient must be differently interpreted, and on this account the
determinations which were adequate for calculating the diffusion constant at
altitude were insufficient at sea level. Previous studies have shown, however,
that the diffusion constant ranges between 20 and 30 under normal conditions.
The increased value at altitude probably resulted from increased perfusion of
alveolar capillaries and increased alveolar ventilation. Both of these factors
increase the effective diffusing surface in the lung and would therefore be expected
to diminish diffusion resistance and increase the diffusion constant of the lung.

| TABLE 7 |
|------------------------|------------------------|------------------------|
| **ARTERIO-VENOUS DIFFERENCE** | **ART. \( pO_2 \)** | **MEAN CAP. \( pO_2 \)** |
| ml. \( O_2 \)/l. blood | mm. Hg | mm. Hg |
| 96% Arterial \( O_2 \)Hb Saturation (Hertel—Sea level) | 272 | 54 | 60 | 95 | 47 | 48 |
| 64% Arterial \( O_2 \)Hb Saturation (McNutt—20,000 ft.) | | | | | | |
| A. Assumed: cardiac output and \( O_2 \)Hb capacity as for Hertel at sea level | 320* | 66 | 36 | 17 | 36 | 26 | 10 |
| B. Cardiac output as found: \( O_2 \)Hb capacity as for Hertel at sea level | 329 | 34 | 18 | 10 | 36 | 31 | 5 |
| C. Cardiac output and \( O_2 \)Hb capacity as found | 329 | 34 | 15 | 8 | 36 | 32 | 4 |

A. Illustration of the effect of the shape of the oxyhemoglobin dissociation curve upon the gradient between arterial \( pO_2 \) and mean capillary \( pO_2 \).
B. Illustration of the additional effect of an increase in cardiac output.
C. Illustration of the additional effect of an increase in \( O_2 \)Hb capacity.

* For purposes of isolating the factors under A, B, and C it would have been desirable for the oxygen consumption of McNutt (329 ml./min.) to be the same as that of Hertel (272 ml./min.). However, the effect upon the gradient between arterial \( pO_2 \) and mean cap. \( pO_2 \) is minor.

The estimated drop between arterial \( pO_2 \) and mean capillary \( pO_2 \) was 48 mm. at sea level but only 4 mm. at altitude. In table 7 this gradient is subdivided to show the part played by each of the three major factors involved. The factor most largely responsible for the smaller gradient at altitude as compared to sea level is directly related to the characteristics of hemoglobin (table 7, A). The use of the mean capillary \( pO_2 \) makes possible a more accurate estimation of the physiological significance of this factor than has previously been possible. The shape of the oxyhemoglobin dissociation curve is such that at sea level (high \( pO_2 \))
a relatively large pressure drop is required for a given decrease in saturation (fig. 5). For the steeper portion of the curve at high altitude, however, the same decrease in saturation is accomplished by a much smaller drop in pO₂. In the illustrative figure, a decrease of 25 per cent in saturation is seen to require a pO₂ drop at sea level more than four times as great as that required at altitude. Mean capillary pO₂ lies between arterial and venous pO₂, and factors which reduce the arterio-venous difference in pO₂ likewise reduce the gradient between arterial

![Graph showing oxyhemoglobin dissociation curve for pH 7.4 and pressure gradients in oxygen transport system.](http://ajplegacy.physiology.org/)
put (Barcroft's step three) which occurred at altitude (table 7, B). If arterial 
\text{Po}_2 and oxygen consumption are fixed, the increased cardiac output, by decreasing 
A-V difference, raises the venous \text{Po}_2, thereby raising mean capillary \text{Po}_2. The net result of the increase in cardiac output was therefore a further lowering 
of the gradient between arterial \text{Po}_2 and mean capillary \text{Po}_2 of 5 mm. In the few 
measurements previously reported (40, 41) the cardiac output was found to return 
neaily to normal as acclimatization progressed.

The third and least important factor was the increase in the oxygen carrying 
power of the blood (Barcroft's step two), attendant upon the polycythemic 
response to altitude. Although this adaptation is commonly considered a major 
factor in acclimatization, it may be seen from table 7, C, that an increase in 
capacity from 18.5 to 23.5 vols. per cent further reduced the \text{Po}_2 gradient by only 
1 mm. (from 5 to 4 mm.). Even if the oxyhemoglobin capacity had increased to 
26 vols. per cent, the gradient would have been reduced by only 2 mm. This 
interesting observation indicates (as was suggested in 1928 by Campbell (42) 
and found in 1932 by Hurtado (43)) that polycythemia is not essential for 
acclimatization, but is in fact only one small element in the remarkably flexible 
adaptive process.

The three stages which we have analyzed in the oxygen transport system are 
summarized in figure 6. When the data at altitude are compared to those at sea 
level, it is clear that the most marked reduction in \text{Po}_2 gradient occurred between 
arterial and mean capillary blood, a reduction due primarily to the inherent and 
virtually unchangeable characteristics of hemoglobin. Increase in pulmonary 
ventilation, the most rapidly and easily accomplished adaptation to altitude, 
caused the next most marked reduction in gradient (inspiratory \text{Po}_2 to alveolar 
\text{Po}_2). The changes in cardiac output, in the oxygen capacity of the blood, and 
in the diffusion characteristics of the "pulmonary membrane" were quantitatively 
less effective. All of the changes taken together sustained tissue oxygenation at 
a remarkably high level, by lowering the gradient between inspired \text{Po}_2 and mean 
capillary \text{Po}_2 from 105 mm. at sea level to 32 mm. at 20,000 feet in the example 
shown. In spite of this striking change, mean capillary \text{Po}_2 was 15 mm. lower 
at 20,000 feet than at sea level (32 instead of 47 mm.), indicating that compensation 
was not complete. It is not surprising, therefore, that signs of tissue anoxia 
in all four subjects were easily detected by the normal observers, even though 
the subjects felt well and considered themselves in good condition.

Although there were evidences of tissue anoxia, the oxygen consumption during 
rest and during standard work remained the same at altitude as at sea level. In 
other words, there was no evidence that cellular metabolism decreased as a part 
of the acclimatization process. It thus appears that cellular function was im-
paired by low \text{Po}_2 even though the amount of oxygen used by the cells remained 
normal.

The efficiency of cellular metabolism at a given \text{Po}_2 involves the various en-
zyme systems, and it is conceivable that substances such as cytochrome C may be 
capable of restoring cellular function toward normal even at low oxygen pressures.

The same pulmonary and circulatory factors which help to sustain tissue \text{Po}_2
cause a decrease in tissue $pCO_2$. The effects upon $pO_2$ and $pCO_2$ are opposite, but the mechanisms involved are the same: the partial pressure of the gas in the tissues is made to approach the partial pressure of that gas in the inspired air. While there may be direct effects of low $pCO_2$ upon cellular metabolism, we shall consider $pCO_2$ only in relation to the pH of the blood.

At sea level the maintenance of a stable pH is facilitated by the rapid adjustment of $pCO_2$ which is accomplished by changes in pulmonary ventilation. At high altitude, however, the anoxic stimulus to ventilation is so urgent that $pCO_2$ is invariably low. It is no longer a labile factor available as a buffer against change in pH; on the contrary, it is the cause of the rise in pH or respiratory alkalosis which was a prominent feature in our acclimatizing subjects.

In contrast to $pCO_2$ which is controlled by pulmonary ventilation, BHCO$_3$ is dependent upon the concentration of those positive ions remaining uncovered by other negative ions. If available base, or alkaline reserve, increases, CO$_2$, which is always available in abundance, balances it in the form of bicarbonate, thus restoring ionic equilibrium. If the alkaline reserve decreases, the bicarbonate ion is immediately lowered by rapid elimination through the lungs in the form of CO$_2$. The bicarbonate concentration is thus governed by the other serum electrolytes (chloride, protein, lactate, total base, etc.). Changes in bicarbonate and in the other electrolytes may be considered secondary factors in acclimatization; indirectly they are adaptations to low $pCO_2$.

Since the reduction in bicarbonate which occurs during acclimatization can proceed no faster than the accompanying changes in electrolyte concentration and since electrolyte concentration depends upon the rate of excretion by the kidneys, it appears that kidney function sets the pace in restoring pH to normal. At sea level the task of buffering the blood against change in pH is divided between the lungs and the kidneys, but at high altitude the obligatory increase in ventilation causes the lungs to hinder rather than to help in restoring pH toward normal. Accordingly the buffering function falls more heavily upon the kidneys, and it is on this account that restoration of pH values toward normal takes a prolonged period of time. The subjects of this experiment still showed high pH values after one month of exposure to increasing altitude.

On return to sea level the anoxic stimulus to ventilation is immediately relieved, the lungs resume their accustomed rôle in the buffering mechanism, and pH returns to normal. The acclimatized subject still has a low BHCO$_3$, however, and in order to maintain a normal BHCO$_3$/H$_2$CO$_3$ ratio the H$_2$CO$_3$ must remain low. But low H$_2$CO$_3$ depends upon low $pCO_2$ which in turn requires a high minute volume of ventilation. Accordingly, increased pulmonary ventilation continues until the kidneys have made electrolyte adjustments which permit BHCO$_3$ to return to its normal sea level value. These readjustments again require a considerable period of time.

Although the data collected in this experiment do not permit an analysis of the control of breathing during oxygen deficiency, they are consistent in all major respects with the findings of Bjurstedt in dogs (44). As the altitude increased the subjects showed varying degrees of hyperventilation with respiratory alkalo-
sis. For at least the early part of their period of residence at high altitude ventilation was probably sustained largely by chemoreflex drive from the carotid body. The chemosensitive cells of the respiratory center in the brain, which respond to increased acidity, were probably inactive due to missing stimulation. On return to sea level the anoxic stimulus to chemoreflex drive was immediately relieved, but control was promptly taken over by the respiratory center. Of this there can be little doubt because hyperventilation was maintained, in the absence of anoxia, during a transition period of at least four days during which reduction in ventilation would have occasioned acidosis.

Exercise at sea level, by increasing oxygen consumption, tends to lower tissue pO₂. This tendency is combated by increased ventilation (which raises alveolar pO₂), by an increase in the diffusion constant of the lung (which minimizes the drop in oxygen pressure between the alveoli and the arterial blood), and by an increase in cardiac output and in the oxygen carrying capacity of the blood (which minimizes the gradient between arterial pO₂ and mean capillary pO₂). During exercise at sea level tissue pO₂ is thus prevented from falling by mechanisms comparable to those by which tissue pO₂ is restored toward the normal during rest at high altitude. Exercise at high altitude imposes a double stress which can be met only by extremely vigorous ventilatory and circulatory responses.

The characteristics of hemoglobin and the minute volume of ventilation have been shown to be of preponderant importance in the process of acclimatization to high altitude. Since the benefits related to hemoglobin dissociation are available to the unacclimatized man, one may well ask why voluntary hyperventilation might not sustain the unacclimatized individual at high altitude. Many workers have shown this to be possible, and in additional studies at this laboratory a subject remained in good condition by this means for four hours above 20,000 feet. Arterial pO₂ and pCO₂ values were similar to those of the acclimatized subjects, but there was no tendency for the increased breathing to become automatic. Quite the contrary, every breath required conscious effort and attention. This subject lacked the adaptations to low pCO₂ which made adequate automatic breathing possible for the acclimatized subject.

**SUMMARY AND CONCLUSIONS**

Detailed studies of the respiratory and circulatory changes which occur during the process of acclimatization to oxygen lack were made on four men exposed to gradually increasing simulated altitude during one month in a low pressure chamber.

The data obtained strengthen the concept that acclimatization consists of a series of integrated adaptations which tend to restore the oxygen pressure of the tissues toward normal sea level values despite the lowered pO₂ of the atmosphere. The transfer of oxygen from inspired air to tissue cells can be conveniently divided into several stages which together comprise the oxygen transport system. A theoretical mean value for the capillary oxygen pressure has been intro-
duced to make possible a more quantitative evaluation of circulatory factors than heretofore possible.

The reduction in the $pO_2$ gradient between inspired air and mean capillary blood was due mostly to the shape of the oxyhemoglobin dissociation curve and to an increase in pulmonary ventilation; increase in cardiac output, increase in the diffusion constant of the lung, and increase in oxyhemoglobin capacity were less important factors.

The same pulmonary and circulatory changes which caused an increase in $pO_2$ necessarily caused a decrease in $pCO_2$, and an initial effect of the decrease in $pCO_2$ was an increase in the alkalinity of the blood. Further changes occurred, as acclimatization progressed, to counteract this respiratory alkalosis. The fall in blood bicarbonate reflected the extent of these changes which included a net increase in the other negative ions and probably a net decrease in the positive ions. These changes comprised secondary factors in acclimatization.

There was no evidence that cellular metabolism decreased as part of the acclimatization process, since the oxygen consumption remained the same at altitude as at sea level, both during rest and during standard work. Since clinical evidence indicated that the subjects were moderately anoxic, it appears that cellular function was impaired by low $pO_2$, even though the amount of oxygen used by the cells remained normal.

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