Teaching the physiology of adaptation to hypoxic stress with the aid of a classic paper on high altitude by Houston and Riley

Etain A. Tansey
School of Medicine and Dentistry, Queen’s University Belfast, Belfast, Northern Ireland

Submitted 6 February 2007; accepted in final form 19 December 2007

Tansey EA. Teaching the physiology of adaptation to hypoxic stress with the aid of a classic paper on high altitude by Houston and Riley. Adv Physiol Educ 32: 11–17, 2008; doi:10.1152/advan.00005.2007.—Many pathological conditions exist where tissues exhibit hypoxia or low oxygen tension. Hypoxic hypoxia arises when there is a reduction in the amount of oxygen entering the blood and occurs in healthy people at high altitude. In 1946, research sponsored by the United States Navy led to the collection and subsequent publication of masses of data demonstrating the physiological consequences and adaptations of ascent to high altitude. This article describes how a figure from a 1947 paper from the American Physiological Society Legacy collection (Houston CS, Riley RL. Respiratory and circulatory changes during ascent to high altitude. Am J Physiol 149: 565–588) may be used to allow students to review their understanding of some of the generalized effects of hypoxia on the body. In particular, this figure summarizes some of the adaptive responses that take place in the oxygen transport system as a consequence of prolonged hypoxia.

hypoxia; oxygen transport system; education

The advent of World War II meant that research into aviation medicine intensified, and, as a consequence, altitude physiology benefited hugely. In 1946, the United States Navy sponsored research into the physiology of altitude acclimatization. The study was to become known as Operation Everest (OP EV I), and its principle investigators were C. S. Houston and R. L. Riley. The study’s aim was to assess the physiological changes that take place during a slow ascent to 29,000 ft. Some of the derived data discussed in the present article were published in a classic paper from the American Physiological Society Legacy collection (4).

Humans and High Altitude

The innate human desire to conquer the world’s highest peaks, including Mt. Everest (8,848 m), together with an interest in the deleterious effects that oxygen deprivation can have on the body, have led to many important expeditions throughout time. The 20th century saw some of the most significant. In 1909, the Duke of Abruzzi led an expedition to the Karakoram and reached a height of 7,500 m; Haldane, in 1911, led an expedition to Pike’s Peak, CO (4,300 m) to study the effect of low barometric pressure; and, in 1924, Norton climbed to within 300 m of the summit of Everest without supplementary oxygen. Despite these achievements, for much of the first half of the 20th century, many investigators believed that, because of the extremely low Po2, to summit Mt. Everest without supplementary oxygen was an impossibility. Experiments in the 1930s and 1940s in low barometric pressure chambers and in the field seemed to confirm earlier conclusions. Houston and Riley’s experiment of 1946 was the first postwar long-term acclimatization study to investigate the human response to high altitude. In their hypobaric chamber, the “summit” measurements for alveolar PO2 were extremely low, as low in one case as 21 mmHg. Unfortunately, this was an erroneous measurement; the investigators used the United States Standard Atmosphere1 to calculate summit barometric pressure, which led to an underestimation of this pressure and, hence, alveolar PO2. It was not until 1981 that the actual barometric pressure was directly measured at Everest and found to be 252 Torr (1 Torr = 1 mmHg), 17 Torr higher than the value used in 1946. This difference most likely explains why Mt. Everest can be climbed without supplementary oxygen. Therefore, in 1946, it was thought that maximal oxygen uptake on Everest would be so low as to only support basal metabolism, if at all, and would certainly not be sufficient to allow climbing the mountain too.

Nevertheless, in 1953, Everest was summited for the first time by Hilary and Norgay, but with the aid of supplementary oxygen. This achievement further excited interest in altitude physiology, and, in 1960–1961, Pugh led the Himalayan Scientific and Mountaineering Expedition (9). Measurements of maximal oxygen consumption were made using a bicycle ergometer up to an altitude of 7,440 m (the highest exercise test recorded at that time), and alveolar gas samples were collected at an altitude of 7,830 m. The results demonstrated the extraordinary low Po2 humans can tolerate allowing for sufficient acclimatization, but suggested that if humans could ascend to the summit of Mt. Everest, it would be almost at the limits of human tolerance.

It was not until May 1978 that Messner and Habeler were the first to summit Mt. Everest without the aid of supplemental oxygen—an extremely arduous task. Messner, in his memorable account of the event, elucidates the fact that the climbers had very little in reserve: “I am nothing more than a single, narrow, gasping lung, floating over the mists and the summits” (6). As we now know, this feat could only be achieved because the summit of Mt. Everest is just short of the limit of human tolerance to oxygen deprivation. In 1981, the American Medical Research Expedition to Everest (AMREE), one of the most extensive high-altitude studies ever conducted, concluded that

1 The United States Standard Atmosphere hypothetically predicts average atmospheric pressure over the surface of the earth. It is typically used in aviation to assess aircraft performance and calibrate altimeters and in aircraft design. It is based on an assumed vertical distribution of factors that typically affect atmospheric pressure such as temperature and density. The United States Standard Atmosphere does not take into account that barometric pressure varies from this standard in response to changes in latitude. This omission led to Houston and Riley’s underestimation of summit barometric pressure at Everest.
maximal oxygen uptake on the summit of Everest would be just over 1 l/min, just sufficient to allow a climber to ascend to that altitude (14).

Critically, ascent to the summit of Mt. Everest may only be achieved through the profound increase in breathing that occurs on exposure to hypobaria, a process known as ventilatory acclimatization.

Ventilatory Acclimatization to High Altitude

The most significant factor determining the inspired Po2 at any given altitude is the barometric pressure since the inspired Po2 remains constant at ~21%. Low barometric pressure reduces the pressure gradient over which the diffusion of oxygen can take place so that humans ascending to high altitude must compensate for the lack of oxygen reaching the tissues. A rapid ascent to high altitude is likely to result in death; however, a slow ascent can be successful when accompanied by compensatory physiological adaptations. For example, a person taken directly from sea level to the summit of Mt. Everest would fall unconscious and die within minutes, yet the summit has been reached without supplemental oxygen.

In the push to conquer Mt. Everest, much was learned about the physiological adaptations necessary to defend the body against severe hypoxia. Of these many adaptations, some of which will be discussed further in the Discovery Learning part of this article, ventilatory acclimatization is the most important.

Mechanism of ventilatory acclimatization. A marked and immediate increase in pulmonary ventilation (hyperventilation) is evident on ascent to high altitude. At sea level, carbon dioxide is the main stimulus to ventilation. However, an arterial Po2 of <60 mmHg also acts as an important stimulus. The peripheral chemoreceptors sense the hypoxia and signal the respiratory center to increase the ventilatory rate and depth. Ventilation increases in proportion to the degree of hypoxemia detected by the peripheral chemoreceptors. The reflex response to hypoxic stimulation of peripheral chemoreceptors is known as the hypoxic ventilatory response (HVR). In humans, this response is almost solely due to the carotid body. In experimental animals, bilateral denervation of the carotid bodies results in an attenuation or abolition of ventilatory acclimatization (see Ref. 8). The HVR is variable among individuals and is partly genetically determined, and it seems likely that a strong HVR improves the tolerance to extreme altitude by increasing the magnitude of hyperventilation.

Hyperventilation leads to a decrease in the arterial PCO2. This is because as long as carbon dioxide production remains constant, the alveolar PCO2 is inversely related to the amount of alveolar ventilation. This drop in PCO2 results in the blood becoming more alkaline and corresponds with an increase in pH. A fall in carbon dioxide normally depresses breathing, which opposes the hyperventilation induced by a fall in oxygen. It was originally believed that restoration of the balance between acid and base (through the removal of HCO3 at the kidneys) would remove the alkaline inhibition of ventilation (acting at both central chemoreceptors in the brainstem and peripheral chemoreceptors in the carotid and aortic bodies) and allow the HVR to reach its maximum, that is, the respiratory center would be further stimulated and ventilation further improved. Ventilation does continue to increase over several weeks on exposure to high altitude; however, we now know that respiratory alkalosis persists despite the renal excretion of HCO3. More recent evidence suggests that the principle mechanism mediating ventilatory acclimatization is an increase in the sensitivity of the carotid chemoreceptor to prolonged hypoxia in the hours to days following the ascent to high altitude.

The proposed mechanisms include changes in neurotransmitter release and/or receptor numbers and changes in the density of Na+ and K+ channels at the carotid body. Other proposed mechanisms include plasticity in the carotid body, plasticity in the central nervous system, and an increase in the responsiveness of the respiratory center to carbon dioxide (for a recent review of proposed mechanisms, see Ref. 8). Ventilatory acclimatization is extremely important because it ensures that the PCO2 is higher in acclimatized individuals than in those who are unacclimatized for any given altitude.

Rate of ventilatory acclimatization. Within minutes of high altitude exposure, the increase in minute ventilation defends against a decrease in alveolar and arterial Po2. However, on arrival at high altitude, the increase in ventilation is incomplete. Immediate and complete ventilatory acclimatization would raise Po2 levels but deplete Po2 levels, thereby resulting in severe alkalosis. On the other hand, no ventilatory acclimatization would maintain the sea level Po2 and pH at the expense of Po2, thereby resulting in severe hypoxemia.

Ventilatory acclimatization at altitude is a time-dependent process. More time is required for full ventilatory acclimatization as the altitude and extent of hypoxia increase. At a moderately high altitude of 3,000 m, the acclimatization process may take 3–5 days, whereas for altitudes above 6,000 m, a period of at least 6 wk may be required. There is, however, marked variability in the time required for acclimatization between individuals.

After years of living at high altitude, further ventilatory changes take place. High-altitude natives have a blunted HVR (12) compared with acclimatized individuals. The mechanism for this decrease is unknown but may be due to other adaptive mechanisms that preserve Po2, for example, increased tissue capillarity, increased lung diffusion capacity, and increased numbers and density of mitochondria.

Oxygen Diffusion at High Altitude

Although the increased alveolar ventilation evident on ascent to high altitude provides an adequate alveolar Po2 for diffusion from the air to blood, the success of this transfer depends on a number of factors. The two most important factors that can interfere with pulmonary gas exchange are ventilation-perfusion mismatching and diffusion limitation. In the normal lung, at sea level, ventilation and perfusion are not perfectly matched. However, hypoxia is known to induce constriction of the pulmonary arteries, increasing pulmonary vascular resistance, and pulmonary artery pressure, thereby redirecting blood flow to better-ventilated areas of the lung. This leads to an increase in ventilation-perfusion matching. Nevertheless, there is an increased alveolar-arterial difference for oxygen at high altitude, which indicates that a diffusion limitation exists and persists. The diffusion limitation for oxygen (whereby oxygen does not come into equilibrium with the alveolar capillary blood) becomes more significant with increasing altitude (11). This is because 1) the decreased pressure gradient for oxygen from alveolar gas into arterial blood is insufficient to fully oxygenate the blood and 2) the
oxygenation is taking place close to or on the steep portion of the oxyhemoglobin dissociation curve where saturations rapidly fall. The rise in arterial \( P_2 \) on Everest’s summit is therefore slow: from 21 mmHg in mixed venous blood to a value of 28 mmHg in the arterial blood, with alveolar \( P_2 \) being \( \approx \) 35 mmHg. A large difference in \( P_2 \) (7 mmHg) between the arterial blood and alveolar gas therefore exists (15). Since the diffusion limitation is exacerbated by exercise, as the cardiac output increases, and there is insufficient time for equilibration of oxygen across the pulmonary capillaries, humans must limit their activity to survive at high altitude.

In high-altitude natives, however, pulmonary gas exchange under hypoxic conditions is surprisingly efficient. High-altitude natives have a low alveolar-arterial difference for oxygen (which preserves arterial \( P_2 \) and saturation) that can never be matched by hyperventilation alone. This is because high-altitude natives have an increased diffusing capacity at rest and during exercise (10). The increased diffusing capacity is probably due to the native’s larger lung volume, greatly increased pulmonary capillary blood volume, and increased pulmonary arterial pressure.

**Operation Everest in Context**

Studies that took place during the first half of the 20th century elucidated many of the mechanisms of acclimatization that we know to be true today, even before any successful ascent of Everest took place. Houston and Riley recount much of this in the Introduction of their paper. Barcroft, as early as 1922, had concluded, based on his own work and that of his predecessors, that the three major factors in the process of altitude acclimatization were 1) increased pulmonary ventilation, 2) polycythemia, and 3) a leftward shift of the oxyhemoglobin dissociation curve (1). All three factors still remain important steps in the acclimatization process. In 1936, the International High Altitude Expedition (2) investigated the changes in blood chemistry that take place at high altitude, and those results provided much of our present knowledge on the subject. Houston and Riley’s 1946 paper looked at the changes that take place in various components of the oxygen transport system on ascent to high altitude (22,000 ft) and the rate of those changes. Four male volunteers were recruited and remained in a low-pressure chamber for 35 days. After an initial 3-day observation period at sea level, volunteers were subjected to barometric pressures so as to simulate an ascent of 2,000 ft/day up to 8,000 ft, followed by 1,000 ft/day up to 15,000 ft, and then 500 ft/day thereafter up to 22,000 ft (6,706 m). The end barometric pressure was \( \approx \) 320 Torr. The data obtained from this classic experiment by Houston and Riley, only some of which are described here, were an important addition to the research on high-altitude physiology in the 1940s and added greatly to the evidence that acclimatization consists of a series of integrated responses that take time to develop and aim to protect the body against severe oxygen deprivation.

The study was conducted in a decompression or hypobaric chamber. The use of such a chamber in the experimental design was crucial because the ascent rates could be exactly calculated to give a gradual fall in barometric pressure over the duration of the experiment. Measurements were made on a day-to-day basis, and there were no variabilities in exposure time at any given altitude between subjects. This is often difficult to ensure in experiments run in the field. The controlled ascent rates meant that the mechanisms and time periods for acclimatization of the oxygen transport system could be analyzed better than ever before.

**The Use of Decompression Chambers in Altitude Physiology**

Much of what we now know concerning high-altitude physiology is a direct result of both studies undertaken in the field and, importantly, those conducted in decompression chambers under conditions of simulated high altitude. Some important chamber studies include the work of Paul Bert (1833–1886), a respiratory physiologist who provided us with the basis of much of what we know today about the physiological effects of high altitude, and that of Angelo Mosso, who, in 1894, built the first high-altitude physiological research station (La Capanna Margherita) at 4,570 m on one of the peaks of the Monte Rosa in the Italian Alps. Toward the end of World War I, decompression chambers were often used for the training of pilots and the testing of aviation equipment. World War II saw advances in these chambers, and Houston and Riley’s study benefited from these advances.

**Advantages and disadvantages of using decompression chambers.** The use of decompression chambers is advantageous for a number of reasons. For example, one can avoid the adverse environmental conditions associated with high altitude (decreased temperature, lower humidity, and increased exposure to ultraviolet radiation) and concentrate on studying the physiological effects of hypoxia alone. Fluid and food type consumed can be closely monitored and regulated. Decompression chambers can importantly minimize logistical difficulties, circumventing the need for the construction of laboratories at high altitude, where complicated measurements and invasive studies are difficult to carry out on the mountainside. Also, chamber studies are, for the most part, thought to be cheaper than expeditions to high altitude. Houston and Riley favored the use of a low-pressure chamber because of their particular concern that their subjects be studied by observers who were not themselves exposed to hypoxic conditions, which might have led to errors in measurement. Disadvantages of using decompression chambers include the isolation and anxiety that may be felt as a consequence of confinement; in the case of Houston and Riley’s experiment, the chamber measured just \( 10 \times 12 \times 7 \) ft, and, remarkably, the men stayed in the chamber for 35 days.

OP EV I was one of the first studies to recognize the advantages of using hypobaric chambers for long-term acclimatization studies. In fact, this first simulated climb to the summit of Mt. Everest was so groundbreaking that it was repeated again in 1985, in a study known as Operation Everest II (OP EV II), and again in 1997, in a study known as Operation Everest III (OP EV III). The fact that this 1946 study directly led to further research using hypobaric chambers demonstrates its importance in the history of high altitude research and is a fitting tribute to the ingenuity and foresight of these scientists.
Fig. 1. Adaptive physiological changes that occur on an ascent to high altitude. This annotated graph from Houston and Riley’s classic paper shows a composite chart of selected data from all 4 subjects. After an initial 3-day observation period at sea level (SL), volunteers were subjected to barometric pressures so as to simulate an ascent of 2,000 ft/day up to 8,000 ft, followed by 1,000 ft/day up to 15,000 ft, and then 500 ft/day thereafter up to 22,000 ft. The alveolar PO2 obtained on the mountain was consistently significantly higher than those obtained in the chamber for the same altitude. The results from the AMREE study would suggest that subjects were sufficiently acclimatized at both moderate and high altitudes, and these results are consistent with those from the British 40th Anniversary Everest Expedition. It seems likely, therefore, that the ascent rate in OP EV I subjects was too fast, and, as such, steady-state conditions were not attained at each ascent level.

Second, the introduction of the United States Standard Atmosphere to predict the summit barometric pressure of Everest was used erroneously by Houston and Riley. The use of the Standard Atmosphere meant that the predicted pressures at high altitudes were usually much too low. This would, of course, affect physiological responses.

Third, in their paper, the investigators imply that the physiological responses to high altitude might restore PO2 back toward sea level. However, we now know that hypobaric hypoxia can never fully be compensated for.

Fourth, the mechanism involved in ventilatory acclimatization and the time-dependent manner of acclimatization, although not completely understood, have been better clarified since 1947 (see Ventilatory Acclimatization to High Altitude).

Fifth, there are now a number of proposed reasons for the maintained increase in ventilation that is observed in individuals having returned to sea level (see the answer to question 10 in the APPENDIX).

Sixth, changes in acid-base balance are better understood; we now know that pH, although approaching normal with acclimatization, never achieves sea level values.

Finally, OP EV I examined the data from only four subjects, and the resting arterial blood and ventilatory studies were made on one subject each day so that each man served as a subject every 5th day. There are large individual variations in the physiological response to hypobaric conditions, and larger
subject numbers providing data with means ± SD would better elucidate the response pattern.

**Using This Classic Paper by Houston and Riley in Discovery Learning**

A general study of altitude physiology provides a useful opportunity for the application of the principles of respiratory, cardiovascular, and blood physiology. These systems all play a role in the slowly developing responses that occur during prolonged exposure to hypoxia, and hypoxia, in turn, impacts on all systems within the body. Figure 1, an annotated figure from classic paper of Houston and Riley, is a concise chart depicting the adaptive changes that occur to the oxygen transport system in particular. Figure 1 displays traces of selected data obtained from all four subjects. There are many different ways of using Fig. 1 in the classroom, and many different lines of questioning that would be valid. The tutorial set out below is just one suggestion.

Figure 1, together with the Discovery Learning questions shown in Table 1, could be assigned to students for use in a discussion concerning the physiological effects of generalized hypoxia, concentrating on the functioning of the lungs and blood transport system as well as acid-base balance. Figure 1 could also serve as a useful aid in the revision of basic systems physiology by undergraduate students.

The lesson consists of a series of questions related to the responses observed in Fig. 1.

In a standard tutorial class size of ∼12–16 students, a simple and effective method of introducing the task could be to divide the class into 4 groups (3–4 students/group). **Group 1** could present the answers to questions 1–3, **Group 2** could present the answers to questions 4 and 5, **Group 3** could present the answers to questions 6 and 7, and **Group 4** could present the answers to questions 8–10. The class as a whole could then prepare answers to questions 11 and 12.

Table 1. Questions related to Fig. 1 for use in discovery learning

<table>
<thead>
<tr>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What do we refer when using the term “acclimatization”?</td>
</tr>
<tr>
<td>2. Describe the ventilatory response to high altitude of a subject at rest</td>
</tr>
<tr>
<td>3. How does this response affect the partial pressure of blood gases?</td>
</tr>
<tr>
<td>4. Describe the shape of the curve depicting the saturation of hemoglobin</td>
</tr>
<tr>
<td>with oxygen in Fig. 1. Compare and contrast this curve with that for PCO2</td>
</tr>
<tr>
<td>5. Oxyhemoglobin capacity values increased steadily from sea level</td>
</tr>
<tr>
<td>throughout the period at high altitude. Why might this be?</td>
</tr>
<tr>
<td>6. Why do the data for oxyhemoglobin content remain almost constant</td>
</tr>
<tr>
<td>from sea level?</td>
</tr>
<tr>
<td>7. Describe the acid-base changes associated with respiratory</td>
</tr>
<tr>
<td>acclimatization to altitude.</td>
</tr>
<tr>
<td>8. Describe the significance of the low carbon dioxide content of fully</td>
</tr>
<tr>
<td>oxygenated blood at a PCO2 of 40 mmHg, given that this a measure of the</td>
</tr>
<tr>
<td>alkaline reserve.</td>
</tr>
<tr>
<td>9. After subjects breathe at altitude for a few days, the quantity of 2,3-</td>
</tr>
<tr>
<td>diphosphoglycerate in the blood increases considerably. What may be the</td>
</tr>
<tr>
<td>significance of this increase?</td>
</tr>
<tr>
<td>10. Minute ventilation was reduced when subjects returned to sea level</td>
</tr>
<tr>
<td>but did not return to normal values immediately. What might be the reason</td>
</tr>
<tr>
<td>for this?</td>
</tr>
<tr>
<td>11. Summarize the physiological adaptations to high altitude evidenced in</td>
</tr>
<tr>
<td>this study and discuss how these adaptations are advantageous.</td>
</tr>
<tr>
<td>12. Can you see any potential benefits of the physiological adaptations</td>
</tr>
<tr>
<td>discussed on the return of an individual to sea level?</td>
</tr>
</tbody>
</table>

Teacher’s notes related to the questions shown in Table 1 are in the **APPENDIX**.

In conclusion, Fig. 1 demonstrates clearly and concisely how acclimatization to high altitude consists of a series of integrated adaptations or responses, designed so as to restore tissue oxygenation in the face of hypoxic hypoxia. Acclimatization requires changes in all body systems involved in the uptake of oxygen into the body, the transport of that oxygen to the tissues, and the unloading of that oxygen at the tissues. With the use of Fig. 1 together with the Discovery Learning questions provided, the educational value of the dataset can be exploited in this simply designed tutorial or revision class. Assuming the students have a good basic knowledge of respiratory physiology and that the questions are available prior to class, this tutorial should not require a time commitment of >1 h.

**Relevance of Scientific Investigation Into the Physiology of High Altitude Today**

One of the primary reasons why investigations into altitude physiology began and continue today is because, increasingly, more and more people are choosing to visit high-altitude locations. Lowlanders, that is, sea-level residents, are travelling to high altitude for recreational purposes including skiing, trekking, and climbing. It is also important to remember that many people live and work at high altitude, for example, mining in the Peruvian Andes, and telescopes are increasingly being positioned at high altitude. In addition, investigations at high altitude can be beneficial to understanding the pathophysiology of diseases where hypoxia is a characteristic. The most recent expedition to the summit of Everest took place in May 2007. The 2007 Everest Medical Research Expedition (Caudwell Xtreme Everest) took the first ever arterial blood sample at 8,400 m (not on the summit for safety reasons), and the world’s highest research laboratory was built at 8,000 m. The researchers are hoping the results will benefit intensive care patients, in particular, those suffering from diseases of the heart and lungs and severe infections preventing adequate amounts of oxygen reaching the cells. It is clear, therefore, that even now much is yet to be learned from observing the physiological responses of healthy humans to the hypoxia of high altitude.

**APPENDIX**

**Teacher’s Notes Related to the Questions Shown in Table 1**

**Question 1.** The term acclimatization refers to the physiological responses or adaptations that take place when one ascends to high altitude. Acclimatization, of which ventilatory acclimatization is the most important feature, greatly improves the tolerance of human beings to hypobaric environments but does not abolish the effects of hypoxia.

**Question 2.** There was a fold increase in minute ventilation in this study from sea level to 22,000 ft, although it must be noted that there were marked individual variations consistent with differing HVRs, particularly at higher altitudes. Houston and Riley were able to use these data to demonstrate the effectiveness of a large increase in pulmonary ventilation in sustaining arterial PCO2. One subject, at 21,000 ft, exhibited relatively low ventilation (11 l/min), which was associated with an extremely low alveolar PO2 of 30 mmHg, arterial PO2 of 29 mmHg, and oxyhemoglobin saturation of 52 %. Another subject, although at an altitude 1,000 ft higher than the first, ventilating at a rate of 19 l/min, maintained an alveolar PO2 of 35 mmHg and oxyhemoglobin saturation of 66 %. On the summit of Mt. Everest, the
alveolar ventilation is increased approximately fivefold, which maintains the alveolar PO$_2$ near 35 mmHg (15). This value is just sufficient to keep the climber alive. In fact, there is no further decline in alveolar PO$_2$ once an altitude of $\sim$7,000 m has been exceeded; it remains at $\sim$35 mmHg. This can only be achieved by increasing ventilation as the climber ascends.

**Question 3.** The decreased inspired PO$_2$ at high altitude is in part minimized by ongoing ventilatory acclimatization, i.e., hyperventilation, which increases the PO$_2$ in the pulmonary alveoli (and, as a result, arterial PO$_2$). In Figure 1, arterial PO$_2$ falls to a value of 35 mmHg at 22,000 ft, which is consistent with the AMREE study. Hyperventilation leads to a decrease in the PCO$_2$. In this study, one subject at an altitude of 20,000 ft showed an arterial PCO$_2$ of $\sim$16 mmHg. In fact, on the summit of Mt Everest, the PCO$_2$ is $\sim$7.5 mmHg, if not lower ($\sim$40 mmHg at sea level) (15). This drop indicates the extreme hyperventilation that can occur.

**Question 4.** The curve depicting the saturation of hemoglobin with oxygen in Fig. 1 demonstrates a gradual descent, which is much less marked than that of PO$_2$. This is because of shape of the oxyhemoglobin dissociation curve. The curve is relatively flat up to a PO$_2$ of $\sim$50–60 mmHg that oxygen desaturation will be relatively rapid. This is where the curve becomes much steeper and the affinity of hemoglobin for oxygen becomes much more sensitive to changes in PO$_2$. For example, in Fig. 1, the arterial PO$_2$ decreases to 60 mmHg at an altitude of $\sim$9,000 ft. This decrease in alveolar PO$_2$ results in arterial hemoglobin being $\sim$89% saturated with oxygen, only 8% below the normal saturation of 97%. However, at an altitude of 22,000 ft, the PO$_2$ has fallen to $\sim$30 mmHg, which results in a decrease in arterial hemoglobin saturation of $\sim$60%.

**Question 5.** An increase in the oxyhemoglobin capacity could be due to hemoconcentration from fluid loss after the initial few days at altitude, probably caused by dehydration (fluid loss can be significant because of the large ventilation of cold dry air) and diuresis or may be a result of a true increase in hemoglobin. Houston and Riley made their measurements after the subjects had been 4–5 days above sea level, thereby minimizing the effect hemoconcentration would have on the oxyhemoglobin capacity. The fact that serum protein concentrations remained unaltered during this study would also indicate that the increased hemoglobin levels and not hemoconcentration are responsible. This increase in hemoglobin is due to polycythemia caused by the hormone erythropoietin (EPO), which is released primarily by the kidneys in response to hypoxia. EPO stimulates the production of red blood cells in the bone marrow. This is a slow process that may require several weeks to reach a steady output level, after which time allowing the kidneys to retain HCO$_3^-$, which is not lower than 3% lower than normal, thereby raising the HCO$_3^-$ concentration in the blood. This process continues at high altitude due to the fact that the production of lactic acid would not be well tolerated.

Note that the hemoglobin carbon dioxide content is now normally expressed in units of ml/100 ml or ml/dl.

**Question 9.** 2,3-Diphosphoglycerate (2,3-DPG) binds to and stabilizes deoxyhemoglobin and lowers the affinity of hemoglobin for oxygen. This means that it is harder for oxygen to bind hemoglobin, and, as a result, oxygen is unloaded in the tissue capillaries due to a rightward shift in the oxyhemoglobin dissociation curve. However, above $\sim$4,500 m, because of only partially compensated respiratory alkalosis, the increased PCO$_2$ causes a leftward shift of the oxyhemoglobin curve, increasing the affinity of hemoglobin for oxygen and thereby enhancing the loading of oxygen at the pulmonary capillary. This leftward shift overcomes the rightward shift induced by 2,3-DPG. It seems likely that because the diffusion limitation in the lung increases with increasing altitude, the benefits of loading oxygen at the pulmonary capillaries outweigh the disadvantage of unloading at the tissues. The shifts in the oxyhemoglobin curve caused by 2,3-DPG and alkalosis seem to optimize oxygen transport under conditions of moderately high to high altitude, respectively.

**Question 10.** Once ventilatory acclimatization takes place, hyperventilation persists for several days after a return to sea level. In the results presented here, the increase in ventilation remained for at least 4 days in the two subjects studied upon the return to sea level even though the hypoxic stimulus to the respiratory center was relieved. The reason for this is unclear but could be partly due to a number of factors: a reduction in alkali reserve that occurred in response to the initial respiratory alkalosis (because the cerebrospinal fluid has a low HCO$_3^-$ concentration, its buffering capacity is diminished and even a small increase in PCO$_2$ yields an acidosis); a hypoxia-induced increase in carotid body activity, which remains for a period; or a resetting of the normal arterial PCO$_2$ “set point” during altitude acclimatization.

**Question 11.** The following are the primary physiological adaptations to high altitude evidenced in this study as well as how they are advantageous:

- **Hyperventilation:** increases PO$_2$
- **Polycythemia:** increases the oxygen-carrying capacity of blood
- **Partial renal compensation for respiratory alkalosis:** removes inhibition of low carbon dioxide on hyperventilation and left shifts the oxyhemoglobin curve, thereby enhancing the loading of oxygen at the pulmonary capillary (altitudes $>4,500$ m)
- **2,3-DPG production:** right shifts oxyhemoglobin curve (altitudes $<4,500$ m)

**Question 12.** Altitude exposure can act as a natural (and legal) form of blood doping. It is equivalent to using injections of EPO, which is illegal. Polycythemia leads to an increase in the blood capacity to transport oxygen, which could be beneficial to athletes on the return
to sea level. It seems that best results occur when athletes adopt a “live high, train low” regime (5). However, any adaptations to high altitude and physical training at high altitude appear to be lost within weeks of the return to sea level, and because authorities now test hematocrit levels and ban those above 50%, it may not be as advantageous as first thought.

ACKNOWLEDGMENTS

The author particularly acknowledges Dr. Stuart Warmington (Trinity College Dublin) for invaluable advice, help, and support in the preparation of this manuscript. The author also thanks Dr. Sean Roe, Dr. Laura Montgomery, and Prof. William Wallace (Queen’s University Belfast).

REFERENCES