The major health implications of ascent to high altitude

1: Acclimatisation to chronic hypoxia

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With increasing altitude, air pressure and oxygen availability fall. At altitudes above 2500 m, this begins to produce hypoxic effects upon human physiology. However, the body is capable of acclimatising itself to the effects of high altitude. Acclimatisation responses to the chronic hypoxia of altitude occur within differing time intervals (hours to months) and in different body systems. The acclimatisation process is entirely reversible and is soon lost with descent to sea level, with the acclimatisation effects lasting at least eight days.[1] There is considerable individual variation in the acclimatisation process, but few people are unable to acclimatise. Failure to acclimatise is found in both humans and animals; in cattle it is known as Brisket disease. In Han infants in Tibet it is most typically identified as subacute infantile mountain sickness.[2] In young Indian soldiers presenting with altitude-induced congestive heart failure it is known as adult subacute mountain sickness.[3]

Some climbers acclimatise more swiftly than others and both the slow and the rapid tend to repeat their time to acclimatise on subsequent altitude reexposures. Evidence suggests that periods spent in a hypobaric chamber before rapid ascent to high altitude may assist the acclimatisation process.[4] The acquired acclimatisation of the sea level resident, irrespective of the duration spent at high altitude, is quantitatively less complete than the natural acclimatisation of the native highlander. This is true when acclimatised lowlanders are compared with both Himalayan Sherpas and Andean Quechuan Indians.

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Synopsis

- The physiological consequences of hypobaric hypoxia are well known, but the concept of high altitude is still arbitrary, without standard terminology for different altitudes.
- Humans can acclimatise to the effects of high altitude (ie, beyond 2500 m). Acclimatisation is entirely reversible and soon lost on the return to sea level. Some people acclimatise more swiftly than others, but there are few who cannot completely acclimatise.
- Beyond 5800 m acclimatisation can only be partial, and beyond 8000 m no acclimatisation is possible.
- The normal physiological response to high altitude is an increase in ventilation, known as the hypoxic ventilatory response (HVR). The HVR shows individual variation. It usually commences at an altitude of 3000 m.
- HVR is dependent on peripheral chemoreceptor stimulation of the central respiratory centre in the medulla.
- Adaptation to high altitude in nature has involved the development of high-affinity haemoglobin molecules and is probably confined to animals and birds. Similar human adaptive change is unknown. High altitude sickness is almost unknown among the Sherpas of the Himalayas, but is well documented among Peruvian Quechuan Indians of the Andes.

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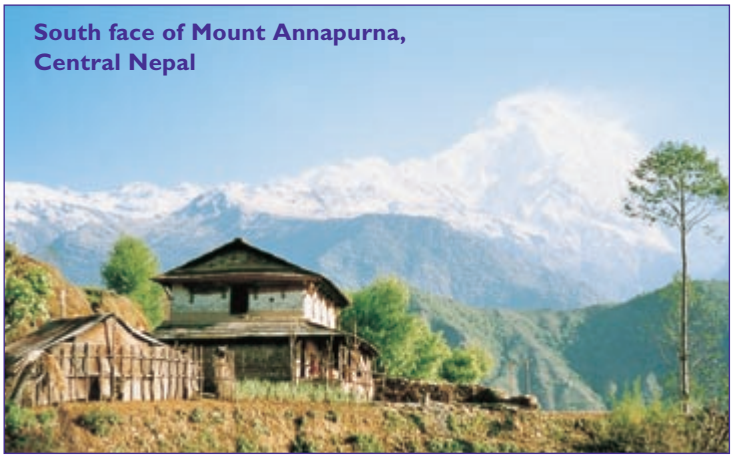
Completed acclimatisation up to an altitude of 5755 m is typified by the absence of acute mountain sickness (AMS), and perhaps with an improved sleep pattern. Above this height, the increasing effect of chronic hypoxia is associated with the appearance of an overall physiological deterioration. Above 8000 m no acclimatisation is possible. After lengthy stays at extreme altitude (above 5500 m) climbers notice a progressive lethargy and irritability associated with a loss of motivation and slower recovery from fatigue. Anorexia, deteriorating sleep pattern, nausea and weight loss accompany this syndrome. This condition of high altitude deterioration was first described by members of early Everest expeditions. The mechanism is unknown, but it is dependent on hypoxia. Dehydration, fluid depletion, fever and starvation all severely exacerbate the condition.

The high country

Mountains and high plateaus cover about a fifth of the Earth's surface and are home to over 300 million people, of whom at least 50% live above 2400 m. They are visited by trekkers, climbers, skiers, mountaineers, military personnel, mine and scientific workers. Mountain terrain, such as the Himalayan Ranges, with its two navigable passes, has long been of military significance.

The Chinese official, Tookim, was the first to document the dangers of high altitude.[9] Between 37 and 31 BC, he travelled the silk routes from Kashi in Chinese Turkestan to Kabul in Afghanistan, and described the passage through the Kilik Pass region (4827 m): "Next, one comes to Great Headache and Little Headache Mountains". The first awareness of the danger of high altitude among Western Europeans stems from the time of Francisco Pizarro and the Spanish *Conquistadores*, who defeated the Inca King, Atahualpa, in 1533. Following the conquest of the Inca Empire, a large scale search for gold commenced in and around the Inca capital of Cusco, in eastern Peru, situated at 3415 m. In 1590, de Acosta gave the first account of the European experience with the potentially fatal syndrome of acute mountain sickness (AMS), known in the Peruvian Andes as *soroch agudo*.



South face of Mount Annapurna, Central Nepal

High altitude defined

Intermediate or moderate altitude (1500 m to 2500 m)

The altitude range of many of the worldwide alpine sport resorts. Serious altitude-related illness rarely occurs at this elevation, but some susceptible persons may develop mild acute mountain sickness, and symptoms of pre-existing cardiopulmonary disease may be exacerbated.

High altitude (2500 m to 3500 m)

Rapid ascent beyond 2500 m commonly precipitates altitude illness.

Very high altitude (3500 m to 5800 m)

This is the zone where serious altitude illness occurs. These altitudes are associated with a drop in arterial oxygen saturation (SaO_2) below 90%, resulting in marked hypoxaemia on exertion. It is possible to become acclimatised to very high altitudes. The highest permanent human habitation recorded in the world is at an altitude of 5340 m at Aconquilcha, Chile.[10]

Extreme altitude (above 5800 m)

Climbing to altitudes above 5800 m is only attained by well-acclimatised mountaineers. At these extreme heights, acclimatisation becomes gradually overwhelmed by an overall failure of physiological function.

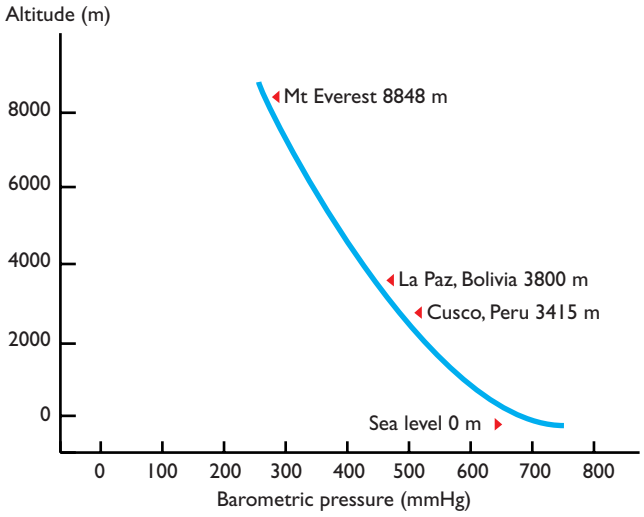
Mountain heights around the world

	Metres	Feet
Kosciusko (Australia)	2228	7310
Matterhorn (Switzerland–Italy)	4477	14688
Mont Blanc (France)	4810	15781
Vinson Massif (Antarctica)	5140	16864
Ararat (Turkey)	5165	16946
Kilimanjaro (Tanzania)	5895	19340
McKinley (Alaska)	6194	20320
Ojos del Salado (Chile–Argentina)	7084	23240
Annapurna (Nepal)	8078	26504
Dhaulagri (Nepal)	8172	26810
Kanchenjunga (Nepal–Sikkim)	8600	28115
K2 (Kashmir–Sinkiang)	8611	28250
Everest (Nepal)	8848	29028

Background: Mount Rathang, Sikkim

Barometric pressure and altitude

The mean barometric pressure at sea level is 760 mmHg (1013 millibars) and falls as altitude increases. As the weight of upper atmospheric gases compresses the lower gas, this fall is not linear, the rate of decline in pressure decreasing as the altitude increases. At the Equator, the barometric pressure at high altitudes is higher than elsewhere on the globe,[11] a phenomenon related to the paradox of the coldest atmospheric air lying above the Equator. Everest is at latitude 28°N, where the summit pressure is considerably greater than at a hypothetical mountain of the same altitude near one of the poles.[12] The increase in barometric pressure of 17 mmHg brought about by this so-called equatorial bulge is enough to improve maximal oxygen uptake and thus make possible the ascent of Mt Everest without supplementary oxygen[13] (a feat accomplished for the first time on 8 May 1978 by Habeler and Messner[14]).



Barometric pressure falls as altitude increases

The proportion of oxygen in the atmosphere remains constant at 20.93% to an altitude of 110 000 m.[15] The reduction in barometric pressure with altitude results in a fall in the partial pressure of oxygen (pO_2). The ambient partial pressure of oxygen at sea level is 20.93% of 760 mmHg, or 159 mmHg. However, the effect of water vapour in inspired air is to reduce the partial pressure of oxygen by 12 mmHg to 147 mmHg. At 5800 m the barometric pressure is approximately 50% of that at sea level. At the summit of Mt Annapurna, 8078 m, in central Nepal, the barometric pressure is 275 mmHg, with a consequent ambient air pO_2 of 57.6 mmHg (ie, 36% of the sea level value).

Ventilatory changes of acclimatisation

Ventilation increases in response to hypobaric hypoxia and is known as the hypoxic ventilatory response (HVR). Individual differences exist in the HVR. Generally the response commences at a partial inspired air pressure of oxygen (PIO_2) of approximately 100 mmHg (an altitude of 3000 m).[5] The increase in tidal volume is usually greater than the increase in the respiratory rate.[6]

The initial HVR to hypobaric hypoxia is due to the stimulation of the peripheral arterial chemoreceptors situated in the carotid and aortic bodies. The chemoreceptors respond to arterial partial pressure of oxygen (PAO_2) and not to blood oxygen content. After a fall in PAO_2, there is an increase in carotid body transmitter substance, dopamine. This generates signals via the glossopharyngeal nerve to stimulate the central nervous system respiratory centre. The reversible enlargement of the carotid body (normal weight, about 10 mg) in acclimatising lowlanders is due to increased organ vascularity. In native highlanders, however, enlargement is due to cellular hyperplasia.[7] Denervation of the carotid bodies in animal studies leads to a failure of normal acclimatisation with resultant hypercapnoea.[8]

Thus the HVR is triggered by the carotid body, and leads to increased carbon dioxide exhalation with a consequent fall in arterial carbon dioxide tension and a rise in arterial pH. This respiratory alkalosis is slowly corrected by renal excretion of the excess bicarbonate and a return of normal arterial pH. The increased urinary bicarbonate excretion is stimulated by the decreased intracellular partial pressure of oxygen within renal tubular cells. The initial hypocapnoea secondary to the HVR somewhat limits the initial increase in ventilation; however, with renal compensation, ventilation continues to further increase during the first week at a given altitude.

During the 1981 American Medical Research Expedition to Everest, Winslow et al noted that at extreme altitudes the metabolic compensatory mechanisms for the respiratory alkalosis proceeded slowly. While the mechanism is unclear, it may relate to an associated dehydration, in spite of adequate fluid intake, due to the large insensible loss of fluids secondary to hyperventilation. A defect in body fluid regulation was suggested following the observation that plasma arginine–vasopressin concentrations remained unchanged from levels recorded at sea level.[16]

The carotid chemoreceptors are sensitive also to acidosis and hypercapnoea. The main sensor for changes in the partial pressure of carbon dioxide is a paired region beneath the floor of the fourth ventricle in the medulla, the central medullary chemoreceptor. Increased acidity and levels of carbon dioxide in the cerebrospinal fluid stimulate the central medullary chemoreceptor. On the initial exposure to high altitude, carotid body stimulation leads to a reduction in the partial pressure of carbon dioxide in cerebrospinal fluid. The relative alkalinity of the cerebrospinal fluid forms part of the

general respiratory alkalosis and tends to inhibit respiration via its effect on the medullary hydrogen ion receptors. Therefore, the powerful hypoxic peripheral chemoreceptor response is partly offset by the alkaline inhibition of the central medullary chemoreceptors.

It is by the inhibition of the enzyme carbonic anhydrase, with the resultant retention of hydrogen ions and the development of an intracellular acidosis, including the cells of the medullary chemoreceptors, that acetazolamide acts as a central respiratory stimulant rather than as a stimulant of the peripheral chemoreceptors. This central action is in addition to the drug's renal effect of promoting urinary bicarbonate loss, whereby the drug assists in correcting the respiratory alkalosis associated with hypobaric hypoxic hyperventilation. Acetazolamide therefore creates a transient artificial respiratory acclimatization.

Circulatory changes of acclimatisation

Acute hypoxia causes an increase in both cardiac output and heart rate, at rest and with exercise. The increases are greater the higher the altitude. Except at extreme altitudes, above 4500 m, resting heart rates return to sea-level recordings in the acclimatised individual. Likewise, acute hypoxia in man causes little change to mean arterial pressure at altitudes below 4500 m.

Grover et al studied lowlanders at an altitude of 3100 m and noted a diminution of coronary blood flow of 32% and an increased oxygen extraction of the myocardium of some 28%.[17] A study by Moret showed coronary blood flow to be lowered in permanent highlanders in La Paz (3800 m) and Cerro de Pasco (4330 m), with levels falling from a mean of 72 mL/min/100 g LV, sea-level, to 55 mL/min/100 g LV in La Paz.[18] Nevertheless, there is little clinical evidence of myocardial ischaemia among people living at high altitude.[19]

Pulmonary hypertension is also observed in the acclimatised lowlanders at high altitude, as well as in most high altitude native residents. In persons subject to acute hypoxia, this can be reversed with oxygen administration. In highlanders, however, oxygen therapy has little effect in lowering the increased pulmonary vascular resistance. In one study, the mean pulmonary arterial pressure increased from 12 mmHg at sea level to 18 mmHg at 4540 m after one year's residency.[20]

The mechanism of hypoxic pulmonary vasoconstriction is unclear. Recent investigations of the endothelial derived relaxing factor, nitric oxide (NO), synthesised from L-arginine by the endothelial cell, suggests a role for NO in the vasoconstrictive process. In isolated pulmonary artery rings, NO synthase inhibitors augment hypoxic pulmonary vasoconstriction,[21] whereas, in humans, inhaled NO reduces hypoxic pulmonary vasoconstriction.[22]

In established pulmonary hypertension of the native highlander, tissue examination of pulmonary arterioles (55 µm diameter) reveals smooth muscle development between a duplicated elastic lamina, resembling the muscular state of the fetal pulmonary vasculature. It is unclear whether the smooth muscle cells develop from pre-existing muscle cells or as a result of an infiltration of primitive mesenchymal cells, but it is likely that they are responsible for secreting the new internal elastic lamina in the same way that smooth muscle cells produce the elastic laminae in the developing aorta.[23]

Haematological changes of acclimatisation

Ninety-seven per cent of oxygen is carried in the red cell and only 3% in plasma. The tissue availability of oxygen depends on the ease with which it is released from the haeme group of the haemoglobin molecule. Binding of oxygen imposes chemical and mechanical stresses that break electrostatic bonds in the globin units of deoxyhaemoglobin. This leads to a *relaxed* (R) conformation in which the remaining binding sites become more exposed and have an affinity for oxygen about 500 times as high as when the molecule is in the *tense* (T) conformation.[24]

Conformational changes lead to assistance among binding sites, so that the binding of one oxygen molecule to deoxyhaemoglobin increases the oxygen affinity of the remaining binding sites on the same haemoglobin molecule.[25] The binding or oxygen–haemoglobin dissociation curve, first described by Bohr in 1904, assumes a sigmoid shape, reflecting the transition from low to high affinity as more binding sites become occupied.[26] Exclusive anaerobic glycolysis generates 2,3-diphosphoglycerate within erthrocytes. The molecule is transported to the core of the deoxy form of the haemoglobin molecule, binding itself between the two beta chains. This action stabilises the T conformation of deoxyhaemoglobin and favours oxygen release.

The hypoxia-induced rise in deoxyhaemoglobin leads to an increase in 2,3-diphosphoglycerate and oxygen availability.[27] In addition to high altitude residency, chronic lung disease and cyanotic heart disease are similarly associated with increased levels of 2,3-diphosphoglycerate. Conversely, other organophosphates and anions such as chloride compete with 2,3-diphosphoglycerate for deoxyhaemoglobin binding and their presence reduces the regulatory effect of 2,3-diphosphoglycerate on oxygen affinity.[28]

The effect of the rise in red cell 2,3-diphosphoglycerate is to decrease the affinity of haemoglobin for oxygen. This effect is also induced by an increase in the partial pressure of carbon dioxide, hydrogen ion concentration and body temperature. This temperature effect is advantageous by allowing oxygen release during prolonged heavy exertion.

Klocke demonstrated that the primary cause for the increased 2,3-diphosphoglycerate at altitude was due to the increase in plasma pH above that at sea level due to the hypobaric hypoxia-induced respiratory alkalosis.[29] Alkalosis inhibits 2,3-diphosphoglycerate diphosphatase, the enzyme responsible for the breakdown of 2,3-diphosphoglycerate. Slight elevations in 2,3-diphosphoglycerate are seen within the first few hours of exposure to moderate altitudes. At extreme altitude the oxygen-dissociation curve shifts progressively leftwards as a result of respiratory alkalosis. The effect of respiratory alkalosis ablates the small tendency for the rightward shift induced by the associated increased erythrocytic 2,3-diphosphoglycerate concentration.

Adding hydrogen ion or carbon dioxide to blood reduces the oxygen-binding affinity of haemoglobin (the Bohr effect), whereas oxygenation of haemoglobin reduces its affinity for carbon dioxide (the Haldane effect). These effects arise from interactions among oxygen, hydrogen ion and carbon dioxide bound to different sites on haemoglobin.[30]

A specific function of haemoglobin is to scavenge nitric oxide. This is achieved by two mechanisms. High-affinity ferrous binding sites exist on haeme (with a NO affinity some 8000 times greater than the affinity for oxygen) as well as on a residue on the globin chain, where NO binds in the form of S-nitrosothiol. As haemoglobin binds oxygen in the lungs, its binding affinity for S-nitrosol is increased; as peripheral oxygen release proceeds, the affinity for S-nitrosothiol reduces and NO is released into tissues, thereby protecting NO from being scavenged by the haeme binding site. The released NO in hypoxic tissues leads to vasodilation and a fall in regional vascular resistance, with an improvement in the matching of regional oxygen requirements to blood flow.

In response to tissue hypoxia, due either to hypoxia or anaemia, the glycoprotein, erythropoietin, is secreted from the renal juxtaglomerular apparatus, with a little of the total plasma level contributed by liver synthesis. The rise in serum erythropoietin commences within three hours of hypoxic exposure and reaches maximum by 48 hours. Thereafter the level declines again, returning to normal by three weeks.[31] The secondary reduction in erythropoietin synthesis relates to the gradual rise in the partial pressure of oxygen following the HVR and other acclimatisation mechanisms. Within certain limits, the rate of rise in haemoglobin levels relates to the severity of the hypobaric hypoxic stimulus; above 3500 m, haemoglobin levels rise more steeply than at lower altitudes.

The change in red cell mass is slow and the rise in haemoglobin is one of the slower components of acclimatisation. The haemoglobin increase observed in the first two days is due to the decreased plasma volume resulting from extravascular fluid shifts rather than increased red cell mass. The 120-day erythrocyte lifespan remains the same at altitude as at sea-level.[32] Daily erythropoiesis is about 30% greater at altitude than at sea-level.[33] Haemoglobin levels decline after descent and reach normal sea-level values after about six weeks.[34]

With acclimatisation, both plasma volume and red cell mass are increased, resulting in an increased total blood volume. Increasing haemoglobin results in increased viscosity in a curvilinear relationship, such that haemoglobin levels above 180 g/L cause sharp rises in viscosity. Very high levels of haemoglobin are seen in those with subacute mountain sickness and levels above 220 g/L are considered diagnostic of chronic mountain sickness *(*Monge's disease).

Subjects with haemoglobin variants that have an abnormally high affinity for oxygen are usually symptom-free, but exhibit a secondary erythrocytosis even at sea-level, indicating that a physiologically important oxygen deficit exists. Such an increased oxygen affinity may be most advantageous for altitude acclimatisation. Subjects with haemoglobin Andrew–Minneapolis ("human llamas") maintain normal arterial oxygen saturation at an altitude of 3100 m, have smaller heart rate increases and no increased plasma erythropoietin.[35] Llama, alpaca, yaks and certain migratory geese all have high-affinity haemoglobins. Whether highland human populations have undergone similar adaptive changes is controversial, as high altitude sickness is almost unknown among Sherpas but is well documented among Peruvian Quechuan Indians.[36]

Nocturnal periodic breathing and acclimatisation

Lowlanders at altitude develop sleep dysrhythmia with the appearance of nocturnal periodic breathing associated with periods of apnoea. Native highlanders show no such sleep disturbances. At sea level, the initiation of sleep involves a dreamless, restful period in which the eyes are quiescent. This slow wave sleep has four stages. Ninety minutes later, a second form of sleep emerges characterised by rapid horozontal eye movements, termed rapid eye movement (REM) sleep. REM sleep is associated with dreaming and lasts from 5 to 20 minutes. Paradoxically, during REM sleep the EEG resembles wakefulness, but the subject is more difficult to arouse. The two forms of sleep cycle every 90 minutes throughout the night.

At altitude, sleep is fragmented with increased wakefulness, reduced quality and a significant decrease in REM sleep. Altitude acclimatisation results in an abatement of the sleep disturbances. In addition, there is the complication of nocturnal periodic breathing: 8–10 seconds of apnoea, with associated oxygen desaturation, is followed by inspirations of increasing depth and frequency much like Cheyne–Stokes respiration. These apnoeic periods are of central nervous origin. Nocturnal periodic breathing is uncommon during REM-type sleep. Travellers may awaken in panic following the apnoeic spells due to feelings of suffocation. Nocturnal periodic breathing has been reported to occur at altitudes as low as 2440 m.

Evidence suggests that climbers with a high HVR, who acclimatise faster and thereby have less symptomatic acute mountain sickness, have more periodic breathing. A single nocturnal dose of 250 mg of acetazolamide has been shown to significantly decrease the time spent in periodic breath-

ing as well as improve oxygen saturations. The mode of action of acetazolamide is not completely understood. As a low oxygen tension is basic to the development and maintainance of periodic breathing, acetazolamide may stimulate ventilation by inducing metabolic acidosis.

In the next article of this two-part series, the major health implications of ascending to high altitude will be reviewed.

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