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High-altitude medicine

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Pulmonary physicians sometimes regard high-altitude medicine as a niche area, and perhaps this opinion is understandable in countries such as the UK, where the highest mountain, Ben Nevis, has the modest altitude of 1344 m. However, 140 million people live at altitudes exceeding 2500 m,[1] and many diseases are associated with the hypoxia that is the inevitable effect of people going high.

A distinction exists between diseases affecting people who live near sea level (lowlanders) and visit high altitude, and those who live permanently at high altitude (highlanders). The largest populations of highlanders are in the South American Andes, the Tibetan Plateau, and parts of Ethiopia.

Millions of lowlanders go to high altitude for recreation every year as walkers, skiers, or mountaineers. The commonest disease affecting lowlanders at altitude is acute mountain sickness. This sickness is characterised by headache, fatigue, dizziness, palpitations, insomnia, loss of appetite, and nausea.[2] It is caused by hypoxia and usually resolves after a couple of days. The incidence of the sickness can be reduced by taking 250 mg or 500 mg of acetazolamide on the morning of ascent.[2]

Figure: **Christopher Pizzo taking samples of his alveolar gas while sitting on the summit of Mount Everest during the 1981 American Medical Research Expedition to Everest**

Two other diseases of lowlanders are more serious and can be life threatening. High-altitude pulmonary oedema is uncommon, but the risk increases with altitude.[3] The disease usually develops 2 or 3 days after ascent, and exercise is an aggravating factor. The pathogenesis was initially thought to be left heart failure, but this theory was ruled out when normal pulmonary artery wedge pressures were reported.[4] A strong correlation exists between high-altitude pulmonary oedema and pulmonary hypertension caused by hypoxic pulmonary vasoconstriction, and the vasoconstriction is now believed to be uneven, with the result that some pulmonary capillaries are exposed to such a high pressure that their walls are damaged.[4] This damage explains why the oedema fluid has a very high protein concentration. The disease should be treated by immediate descent. The vasodilator nifedipine is also helpful.[4]

The most serious high-altitude disease of lowlanders is high-altitude cerebral oedema, which is fortunately rare and, again, worsens with increasing altitude.[4] It is characterised by headache, ataxia, clouding of consciousness, and coma, and death can occur rapidly in untreated cases. Again, treatment is by immediate descent. Dexamethasone is useful. If descent is impossible, both high-altitude pulmonary and cerebral oedema can be treated temporarily with a portable hyperbaric bag.

Highlanders sometimes develop chronic mountain sickness.[5] The prevalence is greater in the South American Andes than in Asia or Africa. The most obvious feature is excessive erythrocytosis; a haemoglobin concentration of 210 g/L in men and 190 g/L in women is taken as diagnostic. Associated symptoms include

headache, fatigue, and dizziness, and cyanosis is often striking. Unfortunately, the only effective treatment in most cases is descent, but often this descent is impossible because of economic factors, such as the patient not being able to obtain work at a low altitude. Venesection gives temporary relief. The sickness is improved in some patients by acetazolamide 250 mg or 500 mg daily.[6]

Another disease affecting highlanders is high-altitude pulmonary hypertension.[5] Its physiological basis is excessive hypoxic pulmonary vasoconstriction. High-altitude pulmonary hypertension in adults results in a form of right heart failure with dyspnoea, dependent oedema, and right ventricular enlargement. The disorder is also seen in infants born at high altitude, particularly Han Chinese who, in general, do not tolerate high altitude well.

Many important advances have been made in high-altitude biology. One of the most interesting is the discovery of the different genetic makeup of Tibetans compared with the Han Chinese.[7] The frequency of a particular genetic change in *EPAS1* is much higher in Tibetans than in the Han Chinese. *EPAS1* encodes the transcription factor HIF2α. HIF acts as a master switch that upregulates a series of genes controlling responses to hypoxia. Other genes implicated include *EGLN1* and *PPARA*, which are associated with haemoglobin concentration. Some evidence exists that these genetic changes occurred within the past 3000 years, which is very fast in evolutionary terms.

A remarkable feature of the Tibetan phenotype is that haemoglobin concentration is not increased at high altitude, but is instead similar to that of lowlanders.[8] This observation at first seems counterintuitive because, for many years, an increased haemoglobin concentration has been argued to be valuable because it assists oxygen delivery to tissues under hypoxic conditions. However, excessive polycythaemia is now appreciated to be a factor in chronic mountain sickness. Strikingly, the two main populations in the world that have successfully adapted to high altitude—the Tibetans and the Andeans—have very different phenotypes and, particularly, the Andeans have very high haemoglobin concentrations.[8]

Coincidentally, the highest point in the world, the summit of Mount Everest (8848 m), seems to be very close to the limit of human tolerance to hypoxia. Less than 300 climbers have reached the Everest summit without supplementary oxygen, whereas nearly 7000 have done so with oxygen. Alveolar gas samples collected on the summit (figure) have shown an extraordinarily low partial pressure of carbon dioxide in alveolar gas of 0·93–1·1 kPa (normal 5·3 kPa).[9] This low figure can be attributed to the enormous increase in ventilation that occurs at extreme altitude. This increased ventilation is accompanied by an extreme degree of respiratory alkalosis, with an arterial blood pH of more than 7·7. Hyperventilation maintains the alveolar partial pressure of oxygen at viable levels, but the arterial value is very low. Direct sampling of arterial blood taken near the summit has shown an arterial partial pressure of oxygen of about 4·0 kPa.[10] The fact that someone can tolerate such extreme derangement of normal physiology in this adverse environment and live to tell the tale is amazing.

High-altitude medicine is a rapidly expanding discipline. Research on genetic changes in the Tibetans and Andeans is moving at a frenetic pace. Another burgeoning area is efforts to find strategies to help the increasing numbers of lowlanders who now need to work at high altitude, such as in mines. Fortunately, the 140 million people who reside permanently at high altitude are, at last, receiving the attention that they deserve.

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