# 10.3.6 Diseases of high terrestrial altitudes 1701

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10.3.6 Diseases of high terrestrial altitudes 1701 resemble the structure of cell membranes, and they can be patched into cell membrane defects including those caused by electroporation. On the one hand they might offer a therapeutic restorative for damaged membranes, and on the other a radio- labelled polaxamer might be used for imaging the extent of damage. The mechanisms of the psychological disability and remote in- jury are beginning to be elucidated. Victims are frequently written off as malingering or simply depressed, when a more extensive syndrome exists. Expert evaluation is highly desirable, especially if litigation or compensation is involved. The useful duration of monitoring of otherwise asymptomatic people has not been determined. A pressing need is the formulation of the psychological syndrome into a Diagnostic and Statistical Manual (DSM) formulation. FURTHER READING Andrews CJ (2006). Further documentation of remote effects of elec- trical injury, with comments on the place of neuropsychological testing and functional scanning. IEEE Trans Biomed Eng, 53, 2102–13. Andrews CJ, et al. (1992). Lightning injuries: electrical, medical and legal aspects. CRC Press, Boca Raton, FL. Andrews CJ, Reisner AD (2017). The neuropsychological conse- quences of lightning and electrical injury: review and hypotheses for causation. Neural Regen Res, 12, 677–86. Cherington M, Cooper MA (eds) (1995). Seminars in Neurology,
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565–9. 10.3.6 Diseases of high
terrestrial altitudes Tyler Albert, Erik R. Swenson, Andrew J. Pollard, Buddha Basnyat, and David R. Murdoch ESSENTIALS Ascent to altitudes above 2500 m leads to exposure to hypobaric hypoxia. This affects performance on first arrival at high altitude and disturbs sleep, but physiological changes occur over time to defend arterial and tissue oxygenation and allow the individual to adjust. This process of acclima- tization includes (1) an increase in the rate and depth of breathing; and (2) an increase in red cell mass, and in red cell 2,3-diphosphoglycerate. Acclimatization is no longer fully possible at extreme altitude (>5800 m) and the exposed individual will gradually deteriorate. Altitude illness results from a failure to adjust to hypobaric hypoxia at altitude. Risk is increased by ascent to higher altitudes, by more rapid gain in altitude, and (in some people) genetic predisposition; the condition may be avoided in most cases by slow, graded ascent. Clinical presentation occurs soon after arriving at a new altitude, most often manifest as one of three conditions: Acute mountain sickness A common condition that presents with nonspecific symptoms, including headache and anorexia. The victim is likely to be apathetic, but clinical examination is generally unremarkable. Mild cases usu- ally resolve with rest and avoidance of further ascent. Those whose symptoms fail to resolve (or worsen) should descend immediately. Treatment with acetazolamide (which can also be used as prophy- laxis) or dexamethasone is often given in severe cases. High-altitude cerebral oedema An uncommon condition that typically presents with worsening symptoms of acute mountain sickness and ataxia, with progressive neurological symptoms including behavioural changes, confusion, and impairment of consciousness. Papilloedema and focal neuro- logical signs may be present. Treatment is urgent, with the most im- portant measure being descent. Oxygen or simulated descent using a portable hyperbaric chamber can be helpful. Dexamethasone is widely recommended (and can be used as prophylaxis). High- altitude pulmonary oedema A relatively uncommon condition with significant mortality that typ- ically presents with dyspnoea and cough. Signs include low-grade fever, tachycardia, tachypnoea, basal crepitations, and (in late dis- ease) cyanosis. Treatment is urgent, with the most important measure being descent. Oxygen should be given if available. Simulated des- cent using a portable hyperbaric chamber can be helpful. Nifedipine reduces pulmonary artery pressure, relieves symptoms, and is usually given (and can be used as prophylaxis). Chronic mountain sickness and other medical problems Chronic mountain sickness (Monge's disease) is a disease of adults who reside for prolonged periods at high altitude and develop polycythaemia and eventually cor pulmonale. Symptoms appear to

 resolve with descent, but treatment with venesection has been at- tempted in those who remain at altitude. High-altitude pulmonary hypertension has been described in both infants and adults, pre- dominantly native lowlanders who ascend to and reside at high alti- tude: this also appears to resolve on descent. Pre-existing medical conditions are mostly little affected by as- cent to altitude, but people particularly likely to be affected by hypoxia/ altitude include those with (1) coronary ischaemia and a strongly positive exercise treadmill test; (2) sickle cell disease or trait; (3) chronic pulmonary disease, especially pre-existing pulmonary hypertension from any cause. Introduction High-altitude regions of the world, once considered remote and ac- cessible to only a few individuals, are in fact home to over 200 million people living permanently above 2500 m in Asia, South America, and North America. In South America, miners and astronomers work for long durations at altitudes over 4500 m, while an equal number of tourists spend time at these altitudes in such activities as trekking, skiing, and pilgrimages. Anyone at these altitudes is sus- ceptible to high-altitude illnesses which, if not recognized and ap- propriately treated, can spoil the experience of alpine environments, impair work ability, and in the worst scenarios cause death. The high-altitude environment Although the percentage of oxygen in ambient air remains con- stant at 21%, barometric pressure decreases with increasing altitude, leading to a corresponding fall in partial pressure of oxygen (Po2) (Fig. 10.3.6.1). At 2500 m the barometric pressure and inspired Po2 are about 75% those of sea level values. At 5000 m, which is close to the maximum for permanent human habitation, Po2 is about half of the sea-level value. On the summit of Mount Everest (8848 m), Po2 is about one-third of the sea-level value. In human physiology, the definitions of high altitude in Box 10.3.6.1 are commonly used. In addition to hypoxia, several other characteristics of the high- altitude environment are important to understand. Temperature decreases approximately 1°C for every 150 m rise in altitude, irrespective of latitude, so that high-altitude areas are considerably colder. Ultraviolet penetration increases by approximately 12% for each 1000 m altitude gain, increasing the risk of sunburn, ultraviolet kera- titis, and other sun-related problems. The low humidity at high altitude contributes greatly to fluid loss and dehydration, as does the increased solar radiation, which might be very much exaggerated by reflection from snow. While air quality is generally superior in mountainous areas, heavily populated areas in valleys that are prone to inversions can be associated with unhealthy concentrations of irritating gases and particulates. Effects of hypobaric hypoxia A reduction in exercise capacity is a major effect of ascent to high altitudes. Maximal oxygen consumption decreases by approxi- mately 10% for each 1000-m gain in altitude above 1500 m, and this does not recover appreciably with acclimatization. Reduced max- imal oxygen consumption occurs by a reduction in mitochondrial Po2, interfering with the function of the electron transport chain and adenosine triphosphate synthesis, or through central inhibition in the brain to prevent injurious tissue hypoxia. Genetic factors are partly responsible for individual variations in exercise performance at high altitudes. For example, Tibetans, a population having resided at high altitude for more than 25 000 years, have a variant of the gene encoding a transcription factor (hypoxia inducible factor -2, HIF-2), and mountaineers who perform well at high altitudes have a higher expression of an angiotensin-converting enzyme gene variant. Sleep can also be disturbed at high altitude. There is difficulty getting to sleep, frequent arousals, less rapid eye movement (REM) time, and a decrease in slow-wave sleep. Periodic breathing, char- acterized by episodes of hyperpnoea followed by apnoea, is rela- tively common among travellers over 2500 m. It is thought to result from instability of the respiratory control system through enhanced hypoxic drive or response to CO2, and can be minimized by the use of acetazolamide. Hypoxaemia during apnoeic episodes during periodic breathing likely accounts for many of the arousals from sleep that are experienced at high altitude. 800 700 600 500 400 300 200 0 Barometric pressure (mmHg) Barometric pressure falls as altitude increases Altitude (m) Mont Blanc 4807 m Mount Everest 8848 m 8000 10000 6000 4000 2000 Fig. 10.3.6.1 Change in barometric pressure with altitude. © Pollard, Andrew J. and Murdoch, David R., The High Altitude Medicine Handbook (3e). Oxford: Radcliffe Medical Press Ltd; 2003. Reproduced with the permission of the copyright holder. Box 10.3.6.1 Altitude—definitions Intermediate altitude (1500–2500 m) Physiological changes due to hypobaric hypoxia (such as reduced exer- cise performance, increased ventilation, increased haematopoiesis) are detectable, but arterial oxygen saturation remains above 90%. Acute altitude illness is unlikely. High altitude (2500–3500 m) Acute altitude illness is common following rapid ascent to this altitude. Very high altitude (3500–5800 m)

Arterial oxygen saturation falls below 90%. Acute altitude illness is common and marked hypoxaemia can occur during exercise and sleep. Extreme altitude (>5800 m) Further acclimatization cannot be achieved, progressive physiological deterioration occurs, and survival cannot be maintained permanently. Marked hypoxaemia occurs at rest.

10.3.6 Diseases of high terrestrial altitudes 1703 Neuropsychological changes at high altitude are often quite subtle, although various changes in mental performance have been docu- mented. Attention span, short-term memory, arithmetic ability, and decision-making can all be impaired at altitudes over 4000 m. Acclimatization Acclimatization is the process of gradual adjustment to high alti- tude hypoxia. In general, it is a physiological process involving a series of adjustments that occur in both the short term (minutes to hours) and long term (days to weeks). These changes enhance oxygen delivery to cells and efficiency of oxygen use. In contrast, ‘altitude adaptation’ refers to physiological changes that occur over longer time periods (decades and generations) and confer advan- tages for life at high altitude. Acclimatization reduces the impact of high-altitude hypoxia, but is insufficient to fully return the body to its sea-level normoxic capacities. The principal steps involved in high altitude acclimatization can be summarized as follows: Ventilation Hyperventilation is the most important feature of acclimatiza- tion and serves to defend alveolar Po2 and thus arterial and tissue Po2. Increases in the rate and depth of breathing, termed the hyp- oxic ventilatory response, are mediated by hypoxic stimulation of peripheral chemoreceptors located mainly in the carotid bodies. Hyperventilation increases alveolar Po2 in the face of decreased in- spired Po2, while also reducing alveolar Pco2 leading to a respira- tory alkalosis. Although initially the alkalosis limits the full hypoxic ventilatory response, eventually it is somewhat compensated for by increased urinary bicarbonate excretion over several days and subse- quently followed by a further increase in ventilation over the course of several weeks, reflecting an increase in intrinsic hypoxic sensitivity of the peripheral chemoreceptors. The degree of hyperventilation in response to high-altitude hypoxia can be profound and, with exercise, it may be what subjectively causes a person to have to stop. Alveolar ventilation increases approximately fivefold on the summit of Mount Everest, where inspired Po2 is less than one-third of its sea-level value and arterial Pco2 values as low as 10 mmHg at rest have been recorded. Blood Although erythropoietin secretion is increased within 2 h of ascent to high altitude, it takes many days to weeks for an increase in red cell mass to occur. This ultimately increases the oxygen-carrying capacity of the blood and permits greater oxygen transport to tis- sues. The shift in the oxyhaemoglobin dissociation curve to the right, which occurs on ascent and is due to an increase in red cell 2,3-diphosphoglycerate, which favours unloading of oxygen in the tissues. However, this particular adjustment is offset by the shift to the left caused by the respiratory alkalosis mentioned previously, leaving the P50 essentially unchanged. Circulation Although there is an abrupt increase in cardiac output on ascent to high altitude, there follows a progressive decrease in stroke volume and maximal cardiac output is reduced at all levels of exercise, including maximal exercise. Although there is no evidence for insuf- ficient myocardial oxygenation, there is disagreement about whether the myocardium is depressed by hypoxia. There is an immediate redistribution of blood flow: coronary and cutaneous flow both fall, cerebral and retinal flow increase, and renal flow decreases initially although returns to normal with acclimatization. Fluid balance Central blood volume increases with ascent to high altitude due to peripheral venous constriction. This, in turn, can suppress anti- diuretic hormone and aldosterone to induce a diuresis along with an independent action of peripheral chemoreceptors stimulated by hypoxia to reduce renal sodium and water reabsorption. Extreme altitudes Acclimatization in adults seems to be possible up to about 5500 m. Above this height, there is a fine balance between adjustment to high altitude and deterioration as a result of chronic hypoxia. The term 'high-altitude deterioration' refers to the general deterior- ation in physical condition that occurs after lengthy stays at extreme altitudes. Typical features include progressive weight loss (fat and muscle), worsening appetite, poor sleep, and increased lethargy. The most extreme altitudes, such as the summit of Mount Everest, are very close to the limit of human tolerance to hypoxia. Indeed, early estimates indicated that all available oxygen on the summit of Mount Everest would be required for basal oxygen uptake, with none left for physical exertion. Alveolar gas samples taken near the summit of Everest (8400 m; barometric pressure, 36.3 kPa) show an inspired $Po_2$ = 6.27 kPa, and alveolar $Po_2$ = 4.00 kPa. Mean arterial gas values at this altitude were: $Po_2$ 3.3 kPa; $Pco_2$ 1.8 kPa; pH 7.5; oxygen saturation 54%. Consequently, it is extraordinary that some humans are able to climb to this height without using supplemen- tary oxygen. Missing in our efforts to fully describe acclimatization and the profound altitudes that some individuals can attain are pro- found changes at the levels of the microcirculation and cellular me- tabolism. Many of these might involve the hundreds of genes that are up- and down-regulated by gene transcription factors called hypoxia inducible factors 1 and 2 (HIF). Several reports have suggested mild, possibly permanent, defects in cognition in climbers who have as- cended to extreme high altitudes. Illnesses due to altitude Until high-altitude acclimatization has occurred, lack of physio- logical compensation for hypobaric hypoxia can manifest as altitude illness. Acute mountain sickness, high-altitude pulmonary oedema, and high-altitude cerebral oedema are recognized distinct clinical syndromes of altitude illness. Acute mountain sickness is both the most common and the quickest to develop, and while it often pre- cedes high-altitude pulmonary oedema or high-altitude cerebral oe- dema, either can occur in its absence. Development of altitude illness usually occurs after a rapid ascent, although there is considerable variation in susceptibility between in- dividuals. Genetic factors are likely to be important in determining susceptibility, but several other factors are contributory and are dis- cussed in the following paragraphs. Acute mountain sickness Incidence rates of acute mountain sickness vary with the absolute altitude gained and the speed of ascent. Some 30–50% of those who ascend to 4500 m on a standard trek in the Himalayas develop acute mountain sickness. Its incidence is greater at higher altitudes and

 with greater gains in altitude, and might be precipitated by physical exertion, although this remains controversial. Some people have a history of recurrent acute mountain sickness, suggesting individual susceptibility. Typically, symptoms of acute mountain sickness begin 6–12 h after ascent to altitudes over 2500 m. The familiar features are nonspecific symptoms that are readily confused with many other illnesses and include: • headache • nausea • vomiting • fatigue • anorexia • dizziness • sleep disturbance For practical purposes, people ascending to altitude with unex- plained symptoms that include the above mentioned should be as- sumed to have acute mountain sickness. The headache is typically worse at night, upon lying down, and with a Valsalva manoeuvre. Anorexia is often pronounced. Clinical examination is typically un- remarkable, although it might reveal some peripheral oedema. There might be tachycardia and elevated core temperature. Typically, the person with acute mountain sickness is apathetic and withdrawn, often seeking solitude (see Fig. 10.3.6.2). The aetiology of acute mountain sickness is unknown. It has been argued that it is a mild form of cerebral oedema since it often precedes development of high-altitude cerebral oedema, and the symptoms of acute mountain sickness include symptoms of head- ache and nausea consistent with a mild increase in intracranial pressure. Brain imaging studies have not found increases in global brain volume or oedema in the first 6–10 h after exposure to hyp- oxia despite symptoms of acute mountain sickness, but it might be that these techniques lack sufficient sensitivity, particularly if the oedema is not global. However, brain volume does increase after longer exposure to hypoxia. Some recent evidence suggests that oxi- dative stress might be involved in the development of acute moun- tain sickness. Other theories include hypoxia-mediated irritation of the trigeminal system from hypoxia-mediated increase in radical oxygen species or nitrosative radicals. Mild acute mountain sickness usually resolves if the victim avoids further ascent and rests. Paracetamol (acetaminophen), nonsteroidal anti-inflammatory agents, and other analgesics might bring relief from headache. Those whose symptoms fail to resolve or worsen should descend immediately. More severe symp- toms will also resolve with descent, but some people will require treatment to facilitate descent. Supplementary oxygen might be beneficial if available. Treatment with acetazolamide (250 mg or- ally, three times daily), or dexamethasone (4 mg orally, four times daily) can be useful in severe cases. Acetazolamide is a carbonic anhydrase inhibitor, which increases renal excretion of bicar- bonate to induce a metabolic acidosis. The hyperventilation in- duced by the respiratory compensation improves oxygenation and helps relieve symptoms. Portable hyperbaric chambers are widely used on trekking routes and can be pressurized to simulate a 500–700 m descent, tempor- arily relieving symptoms in order to facilitate a true descent. These chambers are inflated with a hand or foot pump to achieve the baro- metric pressure of a lower elevation. $CO_2$ is removed by the airflow generated by the pumping action, and a $CO_2$ scrubber is included in some models. Acute mountain sickness can be avoided or prevented in most cases by carefully graded ascent. Above 3000 m, a rate of ascent of 300–600 m per day with a rest day every 1000 m will avoid symp- toms for most people. However, there is considerable individual variation. For some destinations, itineraries are rapid enough to in- duce symptoms of acute mountain sickness in a large proportion Fig. 10.3.6.2 A trekker in Kunde Clinic at 3840 m with symptoms of acute mountain sickness (headache, anorexia, lethargy, and malaise) en route to Everest Base Camp. Courtesy of T Albert.

10.3.6 Diseases of high terrestrial altitudes 1705 of travellers. For this reason, prophylaxis with acetazolamide, started on the day before ascent over 3000 m (125–250 mg twice daily or 250–500 mg daily of the slow-release preparation) is fre- quently recommended for prevention and can be quite effective. Since the side effects induced by this drug may be serious (allergic reactions), mimic acute mountain sickness in some respects (head- ache, nausea, anorexia), or be intolerable (paresthesiae), several test doses should be tried before it is used for prophylaxis during ascent. There is evidence that acetazolamide doses of 125 mg twice daily can be effective in some people. Dexamethasone can also be useful for prophylaxis, although its mechanism of action is unknown. One study found that the inhaled corticosteroid budesonide, in doses unable to generate significant blood levels to act at the brain, was as effective as oral dexamethasone. However, two subsequent studies could not confirm this efficacy. In recent trials, ginkgo biloba has been found to be ineffective and thus is not advised, particularly since it is not a regulated pharmaceutical and preparations can vary in content and contamination with other substances. Theophylline reduces periodic breathing during sleep, but not oxygenation, and probably has little utility in prophylaxis. High-altitude cerebral oedema Unlike acute mountain sickness, which is quite common among travellers to high altitude, high-altitude cerebral oedema and high-altitude pulmonary oedema are relatively uncommon. High- altitude cerebral oedema is more typical after ascent to altitudes over 4000 m, but cases have been described even at the modest ele- vation of 2100 m. As with acute mountain sickness, higher rates are found at the highest altitudes and after more rapid ascent. At

4000 to 5500 m, rates of 1% have been described amongst trek- kers. High-altitude cerebral oedema is usually preceded by acute mountain sickness and is frequently associated with high-altitude pulmonary oedema since the greater hypoxemia occurring with high-altitude pulmonary oedema is the equivalent to suddenly being at an even higher altitude (see following paragraphs). Symptoms of acute mountain sickness have usually been present for 1 to 2 days before the onset of high-altitude cerebral oedema. Risk factors for the development of high-altitude cerebral oedema are probably similar to those recognized for other forms of altitude illness. high-altitude cerebral oedema might be more common in the presence of intracranial space-occupying lesions such as cysts or tumours. Worsening symptoms of acute mountain sickness and ataxia are typical early signs of development of high-altitude cerebral oedema. Behavioural changes (being irrational, withdrawn, or exuberant), confusion, and a change in conscious level leading to coma might ensue. Papilloedema might be present. Both focal neurological signs and cranial nerve lesions can occur. Brain imaging studies show typical signs of cerebral oedema, particularly in the splenium of the corpus callosum, with changes in white matter signal, compression of sulci, and blunting of gyri. Lumbar puncture, if undertaken, re- veals elevated pressures but is otherwise normal. High-altitude cere- bral oedema is indistinguishable clinically from many other causes of compromised cerebral function. There is a very high mortality among those who develop coma. It is likely that high-altitude cerebral oedema is a vasogenic oe- dema resulting from injury to the blood–brain barrier, following disturbances in cerebral autoregulation. Cytotoxic oedema from release of mediators in the central nervous system in response to hypoxia might also contribute. In view of the seriousness of high-altitude cerebral oedema, treat- ment is urgently required, and the most important measure is imme- diate descent. Oxygen therapy or simulated descent using a portable hyperbaric chamber can improve oxygenation and symptoms and thus facilitate descent. Intravenous dexamethasone (8 mg followed by 4 mg, orally four times per day) might improve symptoms and is widely recommended. high-altitude cerebral oedema tends to re- cover more slowly than other forms of altitude illness and ataxia is often the last sign to disappear. High-altitude cerebral oedema is probably prevented by slow, graded ascent (as with acute mountain sickness described previ- ously) and prophylaxis with dexamethasone might be beneficial for those with a risk of the condition. High-altitude pulmonary oedema High-altitude pulmonary oedema typically occurs within 4  days of ascent to altitudes over 2500 m and might be accompanied by symptoms of acute mountain sickness or high-altitude cerebral oe- dema. It presents more frequently with increasing altitude: 1–2% of people may be affected at 4500 m, but rates as high as 10% have been reported after rapid ascent at this altitude. Previous episodes of high-altitude pulmonary oedema for an individual repeating the same ascent rate and altitude gain confer a 60–70% likelihood of re-currence. It can also occur in those who have become acclimatized at one altitude and then make a further ascent. A form of high-altitude pulmonary oedema, known as re-entry high-altitude pulmonary oe- dema, can occur in adults and often more in children living at high altitude after returning home from a lowland vacation. It is a serious form of altitude illness and is associated with fatality when not man- aged urgently and appropriately. High-altitude pulmonary oedema is slightly more common in men than women. The risk of it developing is increased by cold, rapid ascent, exertion, coexistent viral infection, and possibly by drugs or ingestions that cause respiratory depression, such as al- cohol. Individual susceptibility is well recognized and those who have previously suffered from it appear to be more susceptible in the future. There are various genetic associations described including pulmonary surfactant protein A, HLA DR6, HLA DQ4, epithe- lial sodium channel protein, and endothelial nitric oxide synthase. People with raised pulmonary blood flow or an exaggerated hypoxic pulmonary vascular response might also be more susceptible (i.e. those with atrial septal defect, unilateral absence of a pulmonary ar- tery or a chronic respiratory condition). People with high-altitude pulmonary oedema typically present with dyspnoea out of proportion to others in the group and cough. The breathlessness is made worse with exertion and can present with blood-tinged frothy sputum and frank haemoptysis. Other symp- toms include chest pain, orthopnoea, nausea, insomnia, headache, dizziness, and confusion. Low-grade fever is a common finding to- gether with tachycardia, tachypnoea, crackles on auscultation of the chest, and cyanosis in late disease. Signs of right ventricular enlargement can be present with an accentuated pulmonary second heart sound and right ventricular heave. Oxygen saturations are decreased from the prevailing levels of those acclimatizing well, the electrocardiogram shows right axis de- viation, tachycardia, and peaked P-waves, and the chest radiograph


shows pulmonary oedema (Fig 10.3.6.3), often more prominently on the right. In patients who have been studied with cardiac catheterization during high-altitude pulmonary oedema, pulmonary arterial pres- sure is often quite elevated, but pulmonary wedge pressures are normal, ruling out heart failure. Most people who are susceptible to high-altitude pulmonary oedema show an abnormal rise in their pulmonary arterial pressure at sea level during exposure to hyp- oxia or on normoxic exercise. Hypoxic pulmonary vasoconstriction varies almost fivefold among healthy persons, and at sea level or low altitudes poses no problems. The clinical syndrome is not unique, and similar findings occur in other respiratory diseases, including acute bacterial or viral pneu- monia and pulmonary embolism. High-altitude cough (see fol- lowing paragraph) might also cause diagnostic confusion. As described earlier, high-altitude pulmonary oedema appears to result from an exaggerated hypoxic pulmonary vasoconstrictor response. Because there is regional unevenness in the response, this leads to downstream pressure increase in over-perfused areas that lead to capillary leak, either from pressure induced changes in permeability or at the extreme capillary stress failure and frank bleeding into the alveolar space. Once high-altitude pulmonary oedema is recognized, the victim must descend. Even descent of several hundred metres can be enough to raise the barometric pressure sufficiently to increase inspired oxygen tensions and re- duce pulmonary artery pressure. Without appropriate manage- ment, it can be fatal, and further ascent should not be undertaken. In a mountain environment, immediate descent might be im- possible because of weather or other circumstances. The patient might be so breathless that they cannot move and, as mentioned earlier, at a very high risk to develop high-altitude cerebral oe- dema. Adjunctive therapies might improve symptoms and allow descent. The patient should be encouraged to sit up to prevent orthopnoea. Oxygen should be given if available. As a strong inhibitor of hypoxic pulmonary vasoconstriction, nifedipine (20 mg slow release preparation, four times daily) reduces pul- monary artery pressure and relieves symptoms. Side effects of ni- fedipine include headache, dizziness, and postural hypotension, but the drug is generally well tolerated. Other pulmonary vaso- dilators such as hydralazine, phentolamine, inhaled nitric oxide, and sildenafil have been used and might be beneficial, but nifedi- pine is most widely used. Portable hyperbaric chambers are often available on commercial trekking routes (see Fig. 10.3.6.4). They can simulate descent, improve oxygenation, and relieve symptoms. Devices that help provide positive expiratory airway pressure might also improve oxygenation. The risk of high-altitude pulmonary oedema is reduced by slow, graded ascent. Above 3000 m, a rate of ascent of 300–600 m per day with a rest day every 1000 m is recommended. Nifedipine (20-mg slow release preparation, three times daily) and other calcium channel blockers, dexamethasone (8 mg twice daily), inhaled salmeterol, a β2-andrenoceptor agonist, and phosphodiesterase-5 inhibitors are effective for prophylaxis in those known to be susceptible. Acetazolamide, which inhibits hypoxic pulmonary vasoconstriction by a mechanism unrelated to its action as a carbonic anhydrase in- hibitor, might also be effective in its prevention, although it has not been formally tested for this indication. Dexamethasone, while ef- fective in prevention for high-altitude pulmonary oedema-susceptible persons, does not appear to be efficacious in treatment. This might stem from the fact that its action largely is dependent on changes in gene transcription that require many hours to become effective. High-altitude retinal haemorrhage Retinal haemorrhages occur frequently at altitudes of 5000 m or higher, even in those without acute mountain sickness or high- altitude cerebral oedema. Although usually asymptomatic, they can cause visual problems if the macula is involved (Fig. 10.3.6.5). The causes of high-altitude retinal haemorrhage can include in- creased cerebral blood flow, Valsalva manoeuvres (during exer- tion or coughing), polycythaemia, and hypoxia-mediated capillary endothelial permeability. In most instances of high-altitude retinal haemorrhage without altitude illness, descent might not be neces- sary. The haemorrhages usually resolve within days to weeks. If vi- sion is compromised or there is concomitant altitude illness, descent is mandatory. Peripheral oedema Swelling of the hands, face, and ankles commonly occurs at high altitude and might not be related to acute mountain sick ness, high-altitude cerebral oedema, or high-altitude pulmonary Fig. 10.3.6.3 Chest X-ray and CT scan of a patient with high altitude pulmonary oedema. Courtesy of E. Swenson.

10.3.6 Diseases of high terrestrial altitudes 1707 oedema. Anasarca is seldom seen. Descent or diuretics will treat the oedema. High-altitude cough Dry hacking cough is a common, bothersome problem at high altitude, and has caused rib fractures in some severe cases. High- altitude cough is probably multifactorial in origin: water loss from the airways due to hyperventilation of cold-dry air, post nasal drip, acute mountain sickness, high-altitude pulmonary oedema, and bronchoconstriction have all been invoked as possible causes of alti- tude related cough. Breathing through a silk scarf, throat lozenges, and steam inhalation might be helpful. If there is nasal congestion, a decongestant nasal spray is useful. Effects of high altitude on pre-existing medical conditions Hypertensive patients should continue their medications at high altitude, and the vast majority of hypertensive skiers and trekkers do very well despite a transient rise in the blood pressure. Some pa- tients with labile hypertension might have a sudden, dangerous rise in their blood pressure at high altitude and, for them, blood pres- sure monitoring might be necessary. The exaggerated blood pres- sure response to high altitude is apparently mediated by increased α-adrenergic activity. Hence an α-blocker might be useful or, as shown recently in a well-conducted randomized study, angiotensin receptor blockade with valsartan up to 3500 m is effective. People with stable coronary artery disease tolerate intermediate and high altitudes relatively well, even while exercising. This might be partly attributable to the marked reduction in maximal exer- cise at high altitude, which reduces myocardial oxygen demand and maximal heart rate. Animal experiments at high altitude have also demonstrated down-regulation of the β-receptors of the heart. However, travel to high altitude can precipitate new-onset an- gina, although it is unclear whether this is related to exertion or to hypobaric hypoxia as such. People with cardiac risk factors or with previous myocardial ischaemia, coronary artery bypass surgery, or angioplasty are considered to be at high risk if they have a strongly positive exercise treadmill test. Although cold air and exercise are triggers for asthma, many asth- matics remain well at high altitude. This might be due to decreased density of the air, a lack of allergens, or the increase in steroid hor- mones produced under hypoxic stress. However, it is important for asthmatics going up to high altitude to carry their medicines (including an oral corticosteroid) with them and have a well-defined action plan to deal with any exacerbation. Many people with well-controlled epilepsy can venture safely to high altitudes, but there remain some causes for concern. Hyperventilation leading to hypocapnia and hypoxia are themselves triggers for seizure activity. People with sickle cell disease or trait are at high risk of sickle crises above 2000 m, and should avoid staying at altitude. Diabetics might find that increased energy expenditure at high altitude alters carbohydrate and insulin requirements. Consequently, rapidly acting insulin, close monitoring, availability of oral and intravenous glucose, and knowledgeable companions are im- portant. Loss of diabetic control due to intercurrent infections, like diarrhoea, is also possible. It is especially important that insulin pre- parations never freeze, and one option for prevention is by keeping them close to the body. Pre-existing pulmonary hypertension from any cause can be a problem at high altitude and comes close to being an absolute contraindication to travel above very modest altitudes (<2500 m). Mitral stenosis, kyphoscoliosis, and congenital cardiac defects with pulmonary hypertension can predispose to high-altitude pulmonary Fig. 10.3.6.4 An example of a portable hyperbaric chamber being set up in the Alps. Courtesy of E Swenson.

SECTION 10 Environmental medicine, occupational medicine, and poisoning 1708 oedema and are therefore hazardous at high altitude. Those with chronic obstructive pulmonary disease frequently report increased dyspnoea and reduced exercise tolerance when they ascend to high altitude. Other illnesses at altitude Focal neurological problems are occasionally encountered at high altitude. Transient ischaemic attacks and strokes, cerebral venous thrombosis, subarachnoid haemorrhage, high-altitude syncope, delirium, transient global amnesia, cranial nerve palsies, cortical blindness, and amaurosis fugax have all been reported. However, it is unclear whether these deficits are related to hypoxia of high altitude and most need to be distinguished from acute mountain sickness and high-altitude cerebral oedema. Venous thrombosis has been reported at high altitude, although its association with high-altitude exposure is uncertain. Cases of cerebral venous thrombosis at high altitude have been reported in previously asymptomatic people with heterozygous protein C and S deficiency and antiphospholipid syndrome. Risk of thrombosis might have been increased by dehydration and polycythaemia. Immobility during inclement weather, coupled with dehydration and polycythaemia, might also predispose to deep vein thrombosis leading to pulmonary embolism. Unanswered questions about the effects of high altitude on blood coagulation include the use of oral contraceptives and whether prophylactic aspirin prevents throm- bosis. Subjects taking warfarin might experience changes in the drug’s metabolism and monitoring may be needed, thus restricting high altitude destinations to those places where international normalized ratio measurements are possible, such as large ski re- sorts with medical centres. Chronic mountain sickness (Monge’s disease) and high-altitude pulmonary hypertension Excessive erythrocytosis, severe hypoxaemia, and, in some cases, moderate to severe pulmonary hypertension leading to cor pulmonale are the features of chronic mountain sickness. This dis- ease, also known as Monge’s disease, is a disease of long-term resi- dents of altitudes above 2500 m. Besides South America, where this condition was originally described, chronic mountain sickness has also been documented in Colorado and in the Han Chinese population in Tibet. Migration to low altitude cures the problem. Venesection, acetazolamide and, possibly, angiotensin converting enzyme inhibitors have been shown to be helpful. It is important to distinguish chronic mountain sickness from chronic obstructive pulmonary disease. High-altitude pulmonary hypertension is now the accepted term for diseases that include adult subacute mountain sickness and infantile subacute mountain sickness. Unlike chronic mountain sickness, which is characterized by erythrocytosis, the primary fea- ture of this condition is pulmonary hypertension leading to heart failure. The adult form has been described exclusively in Indian sol- diers living at extreme altitudes for prolonged periods. The infantile form has been seen mainly in Han Chinese immigrants in Tibet. These conditions bear a striking pathophysiological resemblance to brisket disease in cattle. Descent from high altitude completely cures the problem. High-altitude pulmonary hypertension of chronic onset is also well described. FURTHER READING Bärtsch P, et al. (2004). Acute mountain sickness: controversies and advances. High Alt Med Biol, 5, 110–24. Bärtsch P, et al. (2005). Physiological aspects of high-altitude pul- monary edema. J Appl Physiol, 98, 1101–10. Bärtsch P, Swenson ER (2013). Acute high-altitude illnesses. NEJM, 368, 2294–302. Basnyat B, Murdoch DR (2003). High-altitude illness. Lancet, 361, 1967–74. Baumgartner RW, Siegel AM, Hackett PH (2007). Going high with preexisting neurological conditions. High Alt Med Biol, 8, 108–16. Dehnert C, et al. (2005). Identification of individuals susceptible to high-altitude pulmonary oedema at low altitude. Eur Respir J, 25, 545–51. (a) (b) Fig. 10.3.6.5 Contrasting retinal appearances on Mount Everest. (a) Normal retina of a well-acclimatized and well-oxygenated climber shortly after reaching the summit (8848 m). (b) Retinal haemorrhages in a poorly acclimatized climber at the North Col (7100 m). Copyright Daniel Morris, Newcastle.

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