# Chapter 24

# ACUTE MOUNTAIN SICKNESS AND HIGH-ALTITUDE CEREBRAL EDEMA

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## INTRODUCTION

Acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) are syndromes that probably occur along a continuum of severity from mild, benign AMS to severe, life-threatening HACE. They strike people who travel too fast beyond altitudes to which they are adjusted. AMS and HACE can destroy the effectiveness of even the fittest mountain troops on ascent to high altitude. In this chapter, we describe the clinical features of AMS and HACE, including what is known of their pathophysiology, and the best available approaches to prevention and treatment.

The scope of the chapter is limited to a critical appraisal of the scientific literature concerning AMS and HACE to provide an up-to-date perspective focused on pathophysiology. Further exhaustive information on history, incidence, treatment, and prevention are available,[1–11] and only the essence of that material is covered here. This chapter provides the information needed by military medical personnel deploying to the mountain regions of the world by (*a*) providing a thorough description of the clinical syndromes of AMS and HACE, including symptoms, signs, and diagnosis; (*b*) using the latest advances in research into the causes of AMS and HACE to thoroughly describe what is known (and hint at what is not yet known) about their pathophysiology; and (*c*) giving practical advice for the prevention and treatment of AMS and HACE based on an explanation of the underlying physiology.

The major importance of AMS to the readers of this volume is that

- AMS can sharply reduce a military unit's effectiveness in the field, especially in the first few days following insertion to high altitude, and
- if AMS worsens and HACE develops, the risk of fatality is significant and the disruption of planned activities to arrange rescue or temporizing measures can be considerable.

Fortunately, most cases of AMS and HACE can be prevented, personnel can be trained to identify the syndromes early and reliably in the field without sophisticated instruments, and if AMS and HACE are recognized early, most cases respond rapidly with complete recovery in a few hours (in the case of AMS) to days (for HACE).

Enduring descriptions in English of AMS and HACE come from observations of European travelers to the Andes Mountains in South America at or just before the turn of the 20th century. Edward Whymper[12] described the symptoms of AMS at about 3,500 m thus:

> I found myself lying on my back, incapable of making the least exertion. We...had intense headaches, and were unable to satisfy our desire for air, except by breathing with open mouths. Headache with all three of us was intense, and rendered us almost frantic or crazy. ... Of course there was no inclination to eat.[12(pp26–28)]

An early and important description of HACE comes from T. H. Ravenhill's experiences as a mining camp physician in the Andes Mountains during the early part of the 20th century.[13,14] He frequently observed AMS, called "puna" in the local dialect, and wrote a classic description of "nervous puna" as a type of AMS characterized by predominant neurological features, known today as HACE:

> The most marked case I had was a young Chileno, aged 19. He arrived at the neighboring mine in the usual way; three days later I was called to see him. He was then unable to speak, there were violent spasmodic movements of the limbs, and he resisted examination. The face was blanched, the lips almost white, the pupils slightly dilated. Temperature and respiration were normal; the pulse 140. He was unable to stand or to walk. I was told that he had been in this condition almost since his arrival, and that he had been delirious, talking all sorts of nonsense. I could find nothing organically wrong on physical examination. He was sent down the same day; three days later, ie, by the time he had just reached the coast, he had quite recovered.[13(p315)]

HACE remains rare and largely confined to altitudes over 4,000 m, although recent evidence[15] from magnetic resonance imaging (MRI) scans suggests that HACE may also occur at lower altitudes (3,000–3,500 m). In one survey of 1,925 soldiers at altitudes ranging from 3,350 to 5,000 m, only 23 men (1.2%) developed the severe neurological signs of HACE[16]; similarly, only 5 (1.8%) of 278 trekkers were diagnosed with HACE at 4,243 m.[17] (Please see Exhibit 19-1 in Chapter 19, Mountains and Military Medicine: An Overview, for definitions of climbers, trekkers, and other categories of people who visit mountains.) Increasingly, data from clinical studies support the notion that AMS is caused by cerebral edema.[15,16,18] When the degree of cerebral edema passes a critical threshold, the neurological signs are increasingly observed and diagnosis of HACE becomes clear.

## MODERN MILESTONES IN UNDERSTANDING THE SYNDROMES

Paul Bert's[19] identification in late-19th-century France of hypoxia as the main environmental challenge for balloonists (and mountaineers) was the beginning of scientific investigation into the human responses to the stress of high altitude. By the late 1950s, AMS and HACE had been described clinically, and acclimatization to high altitude was understood to be a process not to be rushed. The India–China–Pakistan border conflicts during the late 1960s focused medical attention on practical problems of military troops abruptly deployed to very high altitudes without time for acclimatization. The classic study by Singh and colleagues[16] (Figure 24-1) described the Indian Army's experience in the conflict and laid the groundwork for future research into the pathogenesis of AMS and HACE.

Who is at risk for developing AMS is a question that has only recently been explored in detail with a large study population. Investigators in Colorado completed the largest epidemiological survey to date on 3,158 travelers visiting resorts in the Rocky Mountains of Colorado.[20] Of those, 790 (about 25%) developed AMS, and most decreased their daily activity because of their symptoms. Tourists whose permanent residence was below 3,000 m had a risk for AMS that was 3.5-fold greater than those who permanently resided above 3,000 m. Women, obese persons, and those with underlying lung disease also had a slightly higher occurrence of AMS.[20] The next step in this type of research is to couple large-scale epidemiological surveys with noninvasive physiological measurements at sea level and at altitude to better describe physiological characteristics that predispose to high-altitude illness.

Singh and colleagues[16] mentioned results of several autopsies from HACE victims, but it was several more years before detailed postmortem reports and case histories of HACE were published.[20–25] Only recently have significant advances been made in the understanding of HACE. Numerous groups have attempted to use noninvasive scanning technologies (MRI and computed tomography [CT] scans) to investigate cerebral edema in mountaineers, and to follow their recoveries.[15,18,26] The recent MRI work of Hackett and colleagues[15] shows that the edema is characterized by reversible white-matter edema, which has important implications for understanding the underlying pathophysiology.

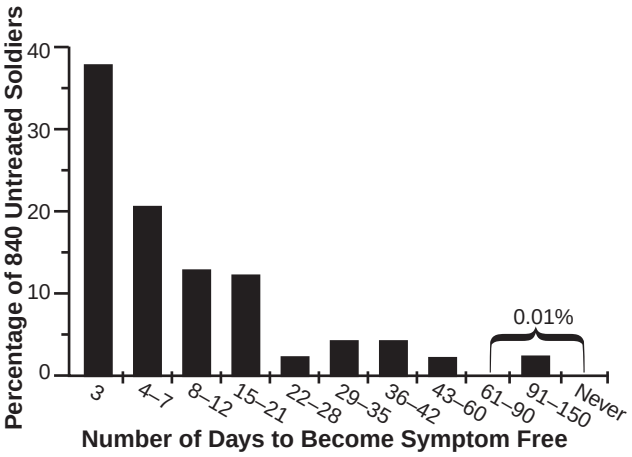


**Fig. 24-1.** The natural course of acute mountain sickness in 840 soldiers who received no treatment for their symptoms at altitudes ranging from 3,350 to 5,000 m. Note that about one third were free of symptoms after only 3 days, whereas the next third took as long as 12 days to be symptom free. Data source: Singh I, Khanna PK, Srivastava MC, Lal M, Roy SB, Subramanyam CS. Acute mountain sickness. *N Engl J Med.* 1969;280:177.

Most major problems of prevention and treatment of AMS were solved within 2 decades after Singh's seminal paper[16] had been published (ie, by 1990). Acetazolamide was identified as effective prophylaxis[17,27,28] and treatment for AMS[29] and is now considered the drug of choice for prevention of AMS.[30,31] The study of Singh and colleagues[16] also suggested that the steroid betamethasone was an effective treatment of severe AMS. Researchers have confirmed and extended these original observations with dexamethasone. Dexamethasone effectively treats severe AMS and HACE,[27,32,33] and in persons intolerant of acetazolamide, it can also be used for prophylaxis of AMS.[34] Its exact mechanism is unclear. The next advances in AMS and HACE research will likely incorporate sophisticated imaging studies, pharmacological interventions, and perhaps biochemical and molecular markers of the onset or the resolution of brain edema.

## DESCRIPTION

AMS is a syndrome that occurs in susceptible individuals when ascent to high altitude outpaces the ability to acclimatize. The symptoms, although often incapacitating, are usually self-limited. The incidence and severity of AMS depend on the rate of ascent and the altitude attained, the length of time at altitude, the degree of physical exertion, and the individual's physiological susceptibility.[35] The

chief significance of AMS for the military is that large numbers of troops rapidly deployed to high altitude may be completely incapacitated in the first few days at a new altitude. Additionally, in a few individuals, AMS may progress to life-threatening HACE or to high-altitude pulmonary edema (HAPE), which is the subject of Chapter 25, High-Altitude Pulmonary Edema.

### Symptoms and Signs

Headache is the cardinal symptom of AMS and is usually accompanied by insomnia, unusual fatigue (beyond that expected from the day's activities), dizziness, anorexia, and nausea (Table 24-1).[36] As Ravenhill[13] noted in 1913 and King and Robinson[37] confirmed in 1972, the headache is often frontal (bitemporal) and worsens during the night and with exertion. Insomnia is the next most frequent complaint (70% in Nepal trekkers at 4,243 m). The physiology of sleep at high altitude has been extensively investigated,[38–41] with general support for the view that, independent of AMS, disturbed sleep is prevalent.[42] Poor sleep can occur secondary to periodic breathing, severe headache, dizziness, and shortness of breath, among other causes. Anorexia,[43,44] nausea, and dizziness complete the list of most common symptoms.[16,17,20] Anorexia and nausea are common (~ 35%), with vomiting reported less frequently (14%) in trekkers to 4,243 m.[17]

Surprising to many sea-level residents on their first encounter with AMS is the debilitating lassitude that strikes—so severe in some cases that victims are unable to look after the most basic daily tasks.[35] Afflicted persons commonly complain of a deep inner chill, unlike mere exposure to cold temperature.[5,13] Other symptoms may include irritability and marked dyspnea on exertion.[16,17,20] The incidence and severity of AMS can be measured with a variety of tools; two (the Environmental Symptoms Questionnaire and the Lake Louise AMS symptom score) are described in detail later in this chapter.

Decreased urinary output,[45–47] independent of fluid intake,[47–49] is commonly observed. In 67% of 1,925 soldiers ill with AMS, Singh and colleagues[16] noted bradycardia (average pulse rate of 66 beats per min). Localized rales are common.[50] Fever is absent unless HAPE is present.[16]

The following case history (from our [RR, PH] clinical experience in 1988) illustrates a typical clinical presentation and setting for AMS with particular reference to armed forces personnel rapidly transported to high altitudes:

***Case History 1.*** C. A., a 26-year-old Special Forces unit commander, was airlifted in 1 hour with 12 other soldiers from S. L. to 4,200 m. They immediately erected camp, consisting of mountaineering tents surrounded by hand-cut ice blocks. The labor was strenuous and time consuming. After 6 hours of heavy labor, C. A. developed a throbbing bilateral frontal headache and nausea. He had maintained fluid intake but was oliguric. His headache was so severe that he ceased work and rested. His symptoms worsened until he developed an intense, migrainelike headache, where any movement was painful. Over a few hours he became disoriented and confused, and severe nausea and occasional vomiting were also noted. At this point he transferred command of his unit to the fittest senior soldier in his unit.

Diagnostic physical findings in AMS only become apparent when the syndrome progresses to HACE. Prior to such progression, AMS is distinguished only by symptoms, absent any objective signs. The progression of AMS to HACE is marked

**TABLE 24-1**

**FREQUENCY OF SYMPTOMS OF ACUTE MOUNTAIN SICKNESS IN MOUNTAIN TREKKERS AND TOURISTS**

| Frequency of Symptom | Trekker*,1 (%) | Tourists†,2 (%) |
|---|---|---|
| Headache | 96 | 62 |
| Insomnia | 70 | 31 |
| Anorexia | 38 | 11 |
| Nausea | 35 | — |
| Dizziness | 27 | 21 |
| Dyspnea on exertion | 25 | 21 |
| Reduced urinary output | 20 | — |
| Marked lassitude | 13 | — |
| Vomiting | 14 | 3 |
| Incoordination | 11 | — |

*Data from 146 mountain trekkers ill with acute mountain sickness (AMS) at 4,243 m in the Himalayas at Pheriche, Nepal
†Data from 3,158 tourists (total tourists, not only those with AMS) studied at 1,900–3,000 m in the Rocky Mountains of the western United States.
—: Question not asked
Data sources: (1) Hackett PH, Rennie ID, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet.* 1976;2:1149–1154. (2) Honigman B, Theis MK, McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med.* 1993;118:587–592.

by development of truncal ataxia; severe lassitude; and altered mental status, including impaired mental capacity, drowsiness, and stupor.[5,21,24] Coma may develop as soon as 24 hours after the onset of ataxia or change in mental status.

The following case report describes the typical development of HACE in the field setting:

***Case History 2.*** H. E. was a 26-year-old German lumberjack with extensive mountaineering experience. He ascended to 5,200 m from 2,000 m in 4 days, and attempted the summit (6,194 m) on the fifth day. At 5,800 m he turned around owing to severe fatigue, headache, and malaise. He returned alone to 5,200 m, stumbling on the way because of loss of coordination. He had no appetite and crawled into his sleeping bag too weak, tired, and disoriented to undress. He recalled no pulmonary symptoms. In the morning, H. E. was unarousable, slightly cyanotic, and noted to have Cheyne–Stokes respirations. After 10 minutes on high-flow oxygen, H. E. began to regain consciousness although he was completely disoriented and unable to move. A rescue team lowered him down a steep slope, and on arrival at 4,400 m 4 hours later, H. E. was conscious but still disoriented, able to move his extremities but unable to stand. Respiratory rate was 60 breaths per minute and heart rate was 112 beats per minute. Papilledema and a few rales were present. The oxygen saturation of arterial blood ($Sa_{O_2}$) was 54% on room air (normal is 85% to 90%). On a non-rebreather oxygen mask with 14 L/min oxygen, the $Sa_{O_2}$ increased to 88% and his respiratory rate decreased to 40. Eight mg of dexamethasone was administered intramuscularly at 1620 hours, and continued orally, 4 mg every 6 hours. At 1720 hours, H. E. began to respond to commands. The next morning H. E. was still ataxic, although able to stand, take fluids, and eat heartily. He was evacuated by air to Anchorage, Alaska (sea level), at 1200 hours, where he recovered fully within several days.[5]

This climber was fortunate to become ill on a high mountain where a sophisticated medical research laboratory was on site. Without the medical care provided by the researchers there, HACE and HAPE would have almost certainly been fatal. The rationale for his treatment and strategies for preventing the syndromes are discussed later in the chapter.

### Incidence, Severity, and Natural Course

The incidence of AMS in visitors to the western United States, with a sleeping altitude of 2,000 to 3,000 m, is 18% to 40%,[20] and in climbers of Mount Rainier, with a sleeping altitude of 3,000 m and a summit of 4,300 m, the incidence was 67% (Figure 24-2).[27] The subgroup of patients developing HACE is much smaller and ranges from 0.01% in visitors to western states with a sleeping altitude of 2,000 m[20,51] to 1.2%

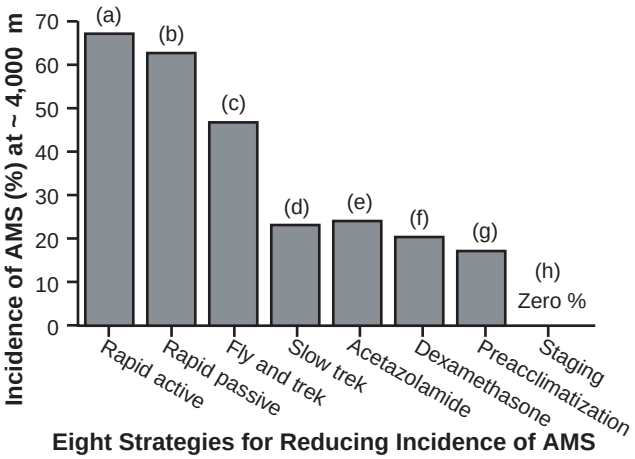


**Fig. 24-2.** The incidence of acute mountain sickness (AMS) is reduced with slower ascents. For clarity, only one or two studies are referenced in a particular category (a–h), although all done within each category support the trend illustrated here. (**a**) Climbers ascending Mount Rainier from sea level in less than 48 hours.[1] (**b**) Rapid, passive ascent from sea level by subjects in the field[2,3] or from chamber studies.[4,5] (**c**) Trekkers who flew to 2,800 m, then, over 1 to 2 days, hiked to 4,243 m.[6] (**d**) From the same study[6] as (c), but in this case the trekkers hiked for 10 to 13 days to reach 4,243 m. (**e**) Acetazolamide[1] and (**f**) dexamethasone[2,4] each reduced AMS incidence to about 20% to 25%. After acclimatizing to 4,300 m, (**g**) six men went to sea level for 8 days before being reexposed to altitude in a hypobaric chamber when their incidence of AMS was only 17%,[7] in the same range as for dexamethasone or acetazolamide. Only long and slow staging (**h**) at intermediate altitudes results in no symptoms of AMS at approximately 4,000 m. The volunteers in this study spent 1 week at 1,584 m, then 1 week at 3,500 m, before finally going up to 4,300 m.[3]
Data sources: (1) Larson EB, Roach RC, Schoene RB, Hornbein TF. Acute mountain sickness and acetazolamide: Clinical efficacy and effect on ventilation. *JAMA.* 1982;288:328–332. (2) Hackett PH, Roach RC, Wood RA, et al. Dexamethasone for prevention and treatment of acute mountain sickness. *Aviat Space Environ Med.* 1988;59:950–954. (3) Hansen JE, Harris CW, Evans WO. Influence of elevation of origin, rate of ascent and a physical conditioning program on symptoms of AMS. *Mil Med.* 1967;132:585–592. (4) Johnson TS, Rock PB, Fulco CS, Trad LA, Spark RF, Maher JT. Prevention of acute mountain sickness by dexamethasone. *N Engl J Med.* 1984;310:683–686. (5) Roach RC, Loeppky JA, Icenogle MV. Acute mountain sickness: Increased severity during simulated altitude compared with normobaric hypoxia. *J Appl Physiol.* 1996;81(5):1908–1910. (6) Hackett PH, Rennie ID, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet.* 1976;2:1149–1154. (7) Lyons TP, Muza SR, Rock PB, Cymerman A. The effect of altitude pre-acclimatization on acute mountain sickness during reexposure. *Aviat Space Environ Med.* 1995;66:957–962.

in the Indian armed forces, where the sleeping altitude is up to 5,500 m,[52,53] to 1.8% in trekkers at 4,300 m on their way to Mount Everest base camp.[17] Controlled studies have not yet determined whether men and women differ in their susceptibility to AMS. Limited epidemiological studies suggest that women have the same or slightly greater incidence of AMS but may be less susceptible to HAPE. Honigman and colleagues[20] studied 3,158 adults visiting moderate altitude (1,900–3,000 m). Of 1,255 women included in that study, 28% developed AMS, compared with 24% of the men ($P < 0.01$). In another survey conducted at a higher altitude (4,243 m), Hackett and colleagues[17] studied 278 unacclimatized trekkers in Nepal and noted no gender differences in AMS susceptibility.

Prior physical condition has little influence on incidence.[54] Older adults consistently report less AMS than younger people with similar altitude exposure. Whether this difference results from behavioral adjustments or has a basis in physiological differences is not known. It is important to note that older age, by itself, does not preclude travel to moderate high altitude. In one study of 97 elderly (average age = 69.8 y) visitors to 2,500 m, only 16% reported AMS,[55] compared with 20% to 25% persons aged about 44 years at a similar altitude.[20]

The natural course of AMS varies with the initial altitude, rate of ascent, clinical severity, and individual susceptibility. Of 840 soldiers not treated with any drugs for their AMS symptoms at 3,300 to 5,500 m, only 40% were symptom-free after 3 days[16] (see Figure 24-1). After 3 weeks, 80% were symptom-free. The remaining 20% coped with symptoms for up to 6 months; indeed, 9 soldiers were never free of AMS symptoms during the 6-month study. At lower altitudes more frequently visited by tourists, 99% of symptoms resolved within the first 36 hours at altitude, and most individuals resumed normal activities shortly thereafter.[20] Previous experience is the best predictor of an individual's response to altitude and of the natural course of AMS.

### Predisposing and Contributing Factors

An understanding of predisposing and contributing factors to the development of AMS and HACE is important to aid preventive action and early recognition. Because HACE is on a continuum with AMS,[5] risk factors for the development of AMS may be viewed as risk factors for the development of HACE in susceptible individuals. The lack of proper acclimatization (ie, too rapid ascent), or any factors that impede acclimatization, clearly increases the risk of AMS and HACE.[21] In their series of 1,925 soldiers exposed to high altitude, Singh and colleagues[16] reported that the exposure to cold environmental conditions and physical exertion seemed to aggravate the condition of individuals already having symptoms of AMS or precipitate the condition in persons who initially were well.

Ross[56] hypothesized that the person who will tolerate hypoxic brain-swelling least well is the one with small intracranial and intraspinal capacity and thus limited compliance. He based his deductions on pressure volume index measurements carried out by Shapiro and colleagues,[57] which indicate that in a person under the age of 30, the intracranial space not occupied by the brain is less than 1% and that this value increases up to 5.9% by 70 to 80 years of age. More research is necessary to fit this interesting work to the known minimal effect of age (up to 60 y) on susceptibility to AMS.

Lack of acclimatization can certainly predispose climbers, hikers, and others to AMS. Mentioned earlier (see Case History 2) was the effect on $Sa_{O_2}$ during exercise, as affected by the degree of acclimatization: the better the acclimatization, the higher the $Sa_{O_2}$ during exercise. For example, among 104 climbers studied at 4,200 m before attempting to climb to the summit of Mount McKinley (6,200 m),[58] those whose $Sa_{O_2}$ fell the furthest during exercise were the most likely to develop AMS during their climb.

In another attempt to predict subsequent AMS, Savourey and colleagues[59] completed a number of tests at sea level in both normoxia and hypoxia. On a subsequent high-altitude trek, the AMS score did not relate to body size, pulmonary function, hypoxic or hypercapnic ventilatory responses, or the cold pressor test. The end-tidal partial pressure of oxygen ($P_{ETO_2}$) during submaximal exercise at sea level was highly correlated ($r = 0.92$, $P < 0.001$) with the subsequent AMS score. Reeves and colleagues[60] had earlier reported that $Sa_{O_2}$ at altitude was best predicted by the sea-level resting end-tidal partial pressure of carbon dioxide ($P_{ETCO_2}$), such that the lower the sea-level $P_{ETCO_2}$, the higher was the $Sa_{O_2}$ on ascent to altitude. Further investigations into breathing pattern, hypoxia, oxygen and carbon dioxide chemosensitivity, and AMS are necessary to clarify these relationships.

### Scoring Systems

Awareness of the scoring systems is of practical importance to the military medical officer to allow identification and rapid quantification of the severity of AMS and HACE. In the context of mountaineering, the rule of thumb is that a severe headache with nausea, vomiting, dizziness, or undue fatigue

is probably AMS. The lack of objective criteria to identify AMS has put an emphasis on techniques to score AMS symptoms. Questionnaires have been developed based on survey or clinical approaches and yield similar results. The Environmental Symptoms Questionnaire (ESQ) contains 67 questions and was developed to survey large groups of US armed forces personnel exposed to a variety of harsh environments.[61–63] Twenty-one of the 67 questions are necessary to derive the two subscores used for AMS research: the AMS-Respiratory and the AMS-Cerebral scores (Exhibit 24-1). These 21 questions com-

**EXHIBIT 24-1**

**THE ENVIRONMENTAL SYMPTOMS QUESTIONNAIRE ITEMS AND THE DERIVATIVE AMS-CEREBRAL AND AMS-RESPIRATORY SCORES**

The 21 Environmental Symptoms Questionnaire (ESQ) items necessary to derive the Acute Mountain Sickness-Cerebral (AMS-C) and -Respiratory (AMS-R) scores are listed below, followed by the equations for using the questionnaire. Subjects are instructed to complete the questionnaire regarding how they feel *at that moment* and to score each item from 0 to 5. ESQ score weight: zero = none at all; 1 = slight; 2 = somewhat; 3 = moderate; 4 = quite a bit; 5 = extreme or severe.

| ESQ Items | Word Association Score | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| I feel lightheaded | | | | | |
| I have a headache | | | | | |
| I feel dizzy | | | | | |
| I feel faint | | | | | |
| My vision is dim | | | | | |
| My coordination is off | | | | | |
| I am short of breath | | | | | |
| It is hard to breathe | | | | | |
| It hurts to breathe | | | | | |
| I have stomach cramps | | | | | |
| I feel weak | | | | | |
| My back aches | | | | | |
| My stomach aches | | | | | |
| I feel sick to my stomach | | | | | |
| My nose feels stuffed up | | | | | |
| I've been having nose bleeds | | | | | |
| I've lost my appetite | | | | | |
| I feel sick | | | | | |
| I feel hungover | | | | | |
| I couldn't sleep | | | | | |
| I feel depressed | | | | | |

AMS-C score equation: (lightheaded • 0.489 + headache • 0.312 + dizzy • 0.446 + faint • 0.346 + vision • 0.501 + coordination off • 0.519 + feel weak • 0.387 + sick to stomach • 0.347 + lost appetite • 0.413 + feel sick • 0.692 + feel hungover • 0.584) / 25.95

AMS-R score equation: (headache • 0.312 + short of breath • 0.745 + hard to breathe • 0.763 + hurts to breathe • 0.734 + stomach cramps • 0.516 + back aches • 0.686 + stomach aches • 0.744 + sick to stomach • 0.691 + nose stuffy • 0.534 + nose bleeds • 0.578 + could not sleep • 0.355 + depressed • 0.48) / 35.69

Adapted with permission from Sampson JB, Cymerman A, Burse RL, Maher JT, Rock PB. Procedures for the measurement of acute mountain sickness. *Aviat Space Environ Med.* 1983;54(12):1065.

prise a questionnaire of reasonable length and proven reliability, and a lengthy literature is available for comparison. The major shortcoming of the ESQ is that the entire system is based on the statistical agreement between artificial clusters of symptoms used for the AMS-Cerebral and AMS-Respiratory scores and the single response of "I feel sick."

Clinicians, favoring a more direct approach, have developed a number of scoring systems that recently have evolved into an international standard, known as the Lake Louise AMS scoring system (Exhibit 24-2).[64] This system has two parts, a symptom score section

**EXHIBIT 24-2**

**LAKE LOUISE ACUTE MOUNTAIN SICKNESS SCORING SYSTEM**

The Lake Louise Acute Mountain Sickness (AMS) score provides a system for both self-assessment and clinical assessment of the symptoms and signs of AMS. The self-assessment score can also be administered by a healthcare provider or researcher. A person is considered to have AMS *only* if he or she has a headache score of at least mild severity and one additional symptom. The person's total points (maximum 15) are summed to become his or her AMS score.

1. Self-Assessment

a. Headache
- 0 No headache
- 1 Mild headache
- 2 Moderate headache
- 3 Severe headache (incapacitating)

b. Gastrointestinal symptoms
- 0 No gastrointestinal symptoms
- 1 Poor appetite or nausea
- 2 Moderate nausea or vomiting
- 3 Severe nausea or vomiting (incapacitating)

c. Fatigue, weakness, or both
- 0 Not tired or weak
- 1 Mild fatigue or weakness
- 2 Moderate fatigue or weakness
- 3 Severe fatigue or weakness (incapacitating)

d. Dizziness or Lightheadedness
- 0 Not dizzy or lightheaded
- 1 Mild dizziness or lightheadedness
- 2 Moderate dizziness or lightheadedness
- 3 Severe dizziness or lightheadedness (incapacitating)

e. Difficulty Sleeping
- 0 Slept as well as usual
- 1 Did not sleep as well as usual
- 2 Woke many times, poor night's sleep
- 3 Could not sleep at all

2. Clinical Assessment

a. Change in mental status
- 0 No change in mental status
- 1 Lethargy or lassitude
- 2 Disoriented or confused
- 3 Stupor or unconsciousness

b. Ataxia (heel to toe walking)
- 0 No ataxia
- 1 Maneuvers to maintain balance
- 2 Falls down
- 3 Can't stand

c. Peripheral edema
- 1 No peripheral edema
- 2 Peripheral edema at one location
- 3 Peripheral edema at two or more locations

3. Functional Score

Overall, if you had any symptoms, how did they affect your activity?
- 0 No reduction in activity
- 1 Mild reduction in activity
- 2 Moderate reduction in activity
- 3 Severe reduction in activity

Adapted with permission from Roach RC, Bärtsch P, Hackett PH, Oelz O, and the Lake Louise AMS Scoring Consensus committee. The Lake Louise Acute Mountain Sickness scoring system. In: Sutton JR, Houston CS, Coates G, eds. *Hypoxia and Molecular Medicine*. Burlington, Vt: Queen City Press; 1993: 273–274.

and a clinical examination section. The symptom score may be completed by clinical interview or it can be self-administered, like the ESQ can. An important feature of this scoring system is that it emphasizes the importance of headache in the definition of AMS. To have AMS in this scoring system, the respondent must have a headache of at least mild severity. The second part of the questionnaire is useful for identifying the progression of AMS to HACE because it asks about mental status, ataxia, and peripheral edema, and it includes a functional score that assesses the impact of any symptoms on normal daily activity. An added advantage of the Lake Louise AMS symptom score is that the score can be derived in a few seconds by hand (even at 4,000 m!), whereas the ESQ requires considerably more time for manual calculation.

In summary, both systems adequately quantify subjective AMS symptom responses and are appropriate for use in field or laboratory studies of AMS. The scores could also be used by field medics for triage or in making initial management decisions (eg, should the casualty be evacuated?)

### Differential Diagnosis

Symptoms suggestive of AMS in a setting of recent ascent to a new altitude are probably due to altitude sickness and should be treated as such until proven otherwise.[35] It is common to misdiagnose AMS as a viral flulike illness; and alcohol hangover, exhaustion, and dehydration are also invoked. All misdiagnoses must be eliminated by physical exam, history, or treatment. As noted previously, fever is usually absent in AMS, and alcohol or other drug use can be excluded by the history. Rest and rehydration can eliminate fatigue and dehydration in the differential diagnosis of AMS. Mental confusion and ataxia, the hallmarks of HACE, are also present with hypothermia.

## PATHOPHYSIOLOGY

Despite dozens of investigations, the basic mechanisms of AMS (and HACE) remain elusive. The extremely low incidence of HACE limits research into its pathophysiology largely to conclusions drawn from the similarity in the pathophysiology of AMS and HACE. Available evidence suggests that the pathophysiology of AMS is brain swelling. This is aggravated by poor ventilatory response, fluid retention or overhydration, and cerebral vasodilation and leakage of the blood–brain barrier.

The pathophysiology of AMS and HACE includes many common features, some well-understood and others that remain obscure despite intense scientific scrutiny. Singh and colleagues[16] proposed in 1969 that the high-altitude syndromes are secondary to the body's responses to hypobaric hypoxia, not due simply to hypoxemia. They based this conclusion on two observations: (1) there is a delay between the onset of hypoxia and the onset of symptoms after ascent (from hours to days) and (2) not all symptoms are immediately reversed with oxygen. Scientists have long assumed that AMS and HACE are due solely to the hypoxia of high altitude, based largely on two reports: the pioneering experiments of Paul Bert[19] and the Glass House experiment of Barcroft.[65] Until recently, no studies have challenged the assumption that hypoxia *alone* was responsible for the symptoms of AMS. A comparison of symptom responses to simulated altitude, hypoxia alone, and hypobaric normoxia revealed more AMS with simulated altitude, compared with either normobaric hypoxia or normoxic hypobaria[66] (Figure 24-3).

The pathophysiology of AMS that has been described

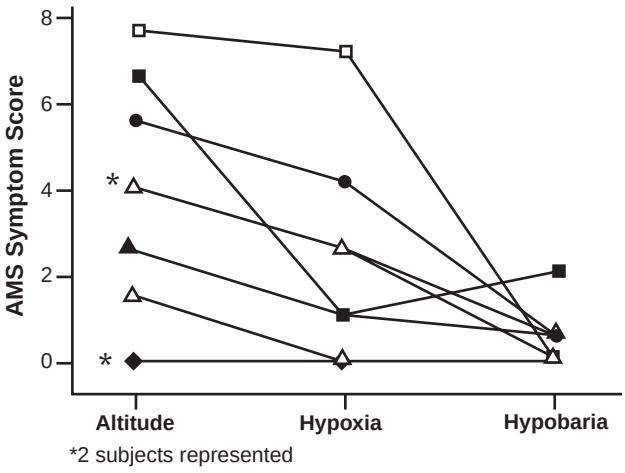


**Fig. 24-3.** Acute mountain sickness (AMS) symptom scores (averages for hours 6 and 9) from nine subjects exposed to simulated altitude, normobaric hypoxia, and normoxic hypobaria. Overall, symptoms were worse during the altitude exposure, although some illness was present with normobaric hypoxia. See Exhibit 24-2 for AMS scoring. Reproduced with permission from Roach RC, Loeppky JA, Icenogle MV. Acute mountain sickness: Increased severity during simulated altitude compared with normobaric hypoxia. *J Appl Physiol.* 1996;81(5):1909.

includes relative hypoventilation,[46,67] a widened alveolar–arterial oxygen tension difference ($P_{AO_2} - Pa_{O_2}$),[29,68] and decreased vital capacity and peak expiratory flow[16,27,69]; subclinical pulmonary edema may be common.[70] Fluid retention,[46,47,71–73] proteinuria,[74,75] weight gain,[46] increased cerebrospinal fluid (CSF) pressure,[16,76,77] and cerebral edema are also noted.[16,18,26] We quickly recognize pulmonary, fluid-balance, and cerebral components in the pathophysiology of AMS. What determines how AMS will progress is not presently known. The findings documented in HACE related to pathophysiology include elevated CSF pressures,[16] evidence of cerebral edema on CT scan[18] and MRI,[15] and gross cerebral edema on postmortem examination.[23–25] Well-documented cases of HACE often include pulmonary edema.

Writing in 1924, Barcroft[65] elegantly argued that the brain's response to hypoxia was central to understanding the pathophysiology of mountain sickness. He wrote:

> Taking it, therefore, as settled that mountain sickness is due to oxygen want, the question arises, "oxygen want of what?" And the answer is, "of the brain." Such evidence as is at our disposal goes to show that the brain wants but little oxygen; that little, however, it wants very badly indeed.[65(p91)]

By 1970, enough had been learned of the basic pathophysiology of AMS and HACE to allow Hansen and Evans[78] to develop an elegant hypothesis of the pathogenesis of these illnesses. Their theory is that compression of the brain, either by increased cerebral venous volume, reduced absorption of CSF, or increased brain-tissue hydration, initiates the development of the symptoms and signs of AMS and HACE. This approach is increasingly supported by studies of brain edema in the syndromes (Figure 24-4). That the pulmonary and fluid-balance abnormalities of AMS and HACE are secondary to central nervous system (CNS) responses to sustained hypoxia may help explain the varied results from the large number of studies done on these topics since about 1950. Consequently, the following discussion of the pathophysiology of AMS and HACE primarily deals with the response of the brain to sustained hypoxia. But first we shall briefly review the known factors associated with AMS and HACE.

### Ventilation and Gas Exchange

Relative hypoventilation is an inappropriately low ventilation for the level of hypoxemia encountered at high altitude. Reports of low ventilatory response and increased symptoms of AMS led to intensive investigation of a link between the chemical control of ventilation and the pathogenesis of AMS.[46,79,80] By and large, the results of these investigations indicate that for most people, the ventilatory response to hypoxia has little predictive value. If the extremes of ventilatory responsiveness are contrasted, those with low ventilatory drives are more likely to suffer AMS than those with high. Ventilatory responses of eight men with known AMS susceptibility and from four men without a history of AMS—and free of AMS on this occasion—are shown in Figure 24-5. The "sick" subjects had a low hypoxic ventilatory response at sea level and breathed less and had disproportionately lower $Sa_{O_2}$ values at altitude, although the difference in oxygenation between the "sick" and "well" groups was small.[80] The protective role of the hypoxic ventilatory response may be due to increased oxygen transport and decreased arterial carbon dioxide levels, with less cerebral hypoxia and vasodilation.

Pulmonary dysfunction in AMS includes decreased vital capacity and peak expiratory flow,[27,69,70] increased $P_{AO_2} - Pa_{O_2}$,[29,68] decreased transthoracic impedance,[81,82] and a high incidence of rales.[50,70] These findings are compatible with interstitial edema (ie, increased extravascular lung water). Careful measurements of ventilation–perfusion ratios ($\dot{V}/\dot{Q}$) in the lung at various altitudes (4,300–8,848 m) confirmed gross inequalities consistent with increased lung water in subjects without clinical evidence of pulmonary edema or even AMS.[83] Accumulation of interstitial fluid is most likely minor or low-grade pulmonary edema, with a mechanism perhaps similar to that of HAPE (see Chapter 25, High-Altitude Pulmonary Edema). Interstitial fluid will impair gas exchange and worsen hypoxemia.

### Fluid Homeostasis and Permeability Abnormalities

As persons become ill with AMS, the handling of renal water switches from net loss or no change to net gain of water. Singh and colleagues[16] noted less of a diuresis (fluid intake minus urinary output: –1,100 to +437 mL) in 118 soldiers with known susceptibility to AMS, compared with that seen in 46 "absolutely immune" (+930 to +4,700 mL) soldiers. They also noted that clinical improvement was preceded by diuresis. Subsequent investigations[46,47,84–89] have failed to elucidate the exact mechanism of the fluid retention. It is likely to be multifactorial and capable of dynamically adjusting to oxygenation, neural input and hormonal action.

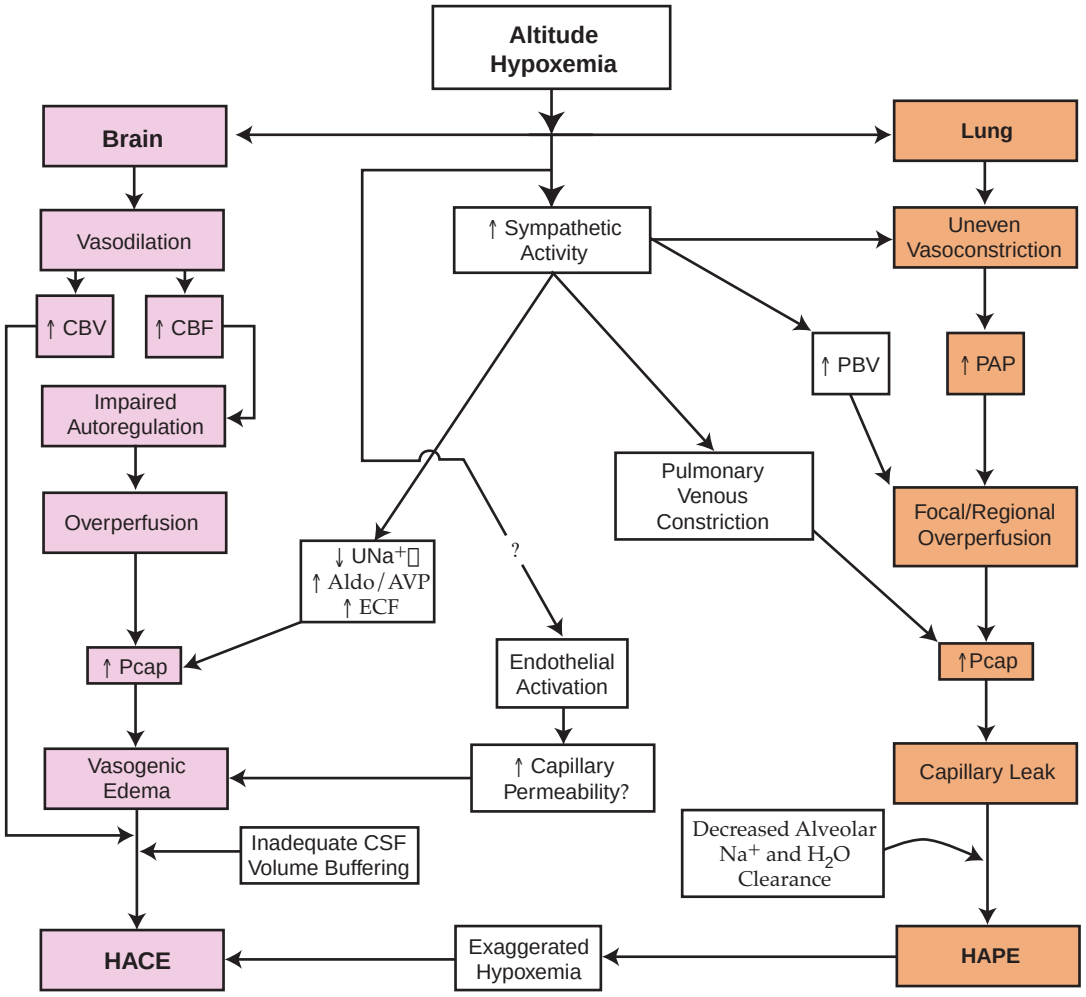


**Fig. 24-4**. Proposed pathophysiology of acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE). At high altitudes, hypoxemia can lead to overperfusion, elevated capillary pressure, and leakage from the cerebral and pulmonary microcirculation.[1–3] Increased sympathetic activity has a central role in this process, and increased permeability of capillaries, as a result of endothelial activation (inflammation), may also have a role. Reproduced with permission from Hackett PH, Roach RC. High-altitude illness. *N Engl J Med.* 2001;345:109.
Aldo: aldosterone; AVP: arginine vasopressin; CBF: cerebral blood flow; CBV: cerebral blood volume; CSF: cerebral spinal fluid; ECF: extracellular fluid; PAP: pulmonary artery pressure; PBV: pulmonary blood volume; Pcap: capillary pressure; $UNa^+$: urinary sodium
(1) Hackett PH, Roach RC. High-altitude medicine. In: Auerbach PA, ed. *Wilderness Medicine*. St Louis, Mo: Mosby; 2001: 2–43. (2) Hackett PH. High altitude cerebral edema and acute mountain sickness: A pathophysiology update. In: Roach RC, Wagner PD, Hackett PH, eds. *Hypoxia: Into the Next Millennium*. New York, NY: Plenum/Kluwer Academic Publishing; 1999: 23–46. (3) Bartsch P, Roach RC. Acute mountain sickness and high-altitude cerebral edema. In: Hornbein TF, Schoene RB, eds. *High Altitude: An Exploration of Human Adaptation*. New York, NY: Marcel Dekker; 2001: 731–776.

Renal responses to hypoxia are variable and depend in part on the hypothalamic arginine vasopressin (AVP) response. Increases in urinary AVP excretion with increasing hypoxia have been demonstrated,[90–93] but caution in interpreting these results is called for because nausea, independent of AMS, stimulates AVP,[94] as does exercise.[95] Aldosterone increases or does not change in persons ill with AMS, compared with those free of illness.[90] Plasma renin activity increases with AMS.[86] Atrial natriuretic peptide is also increased in AMS,[90] and although the rise is likely compensatory, increases in this cardiac-secreted amino acid compound may significantly worsen AMS by increasing microvascular permeability.[96,97]

An important link has been described among hypoxia, ventilation, and fluid balance. In a study of 15

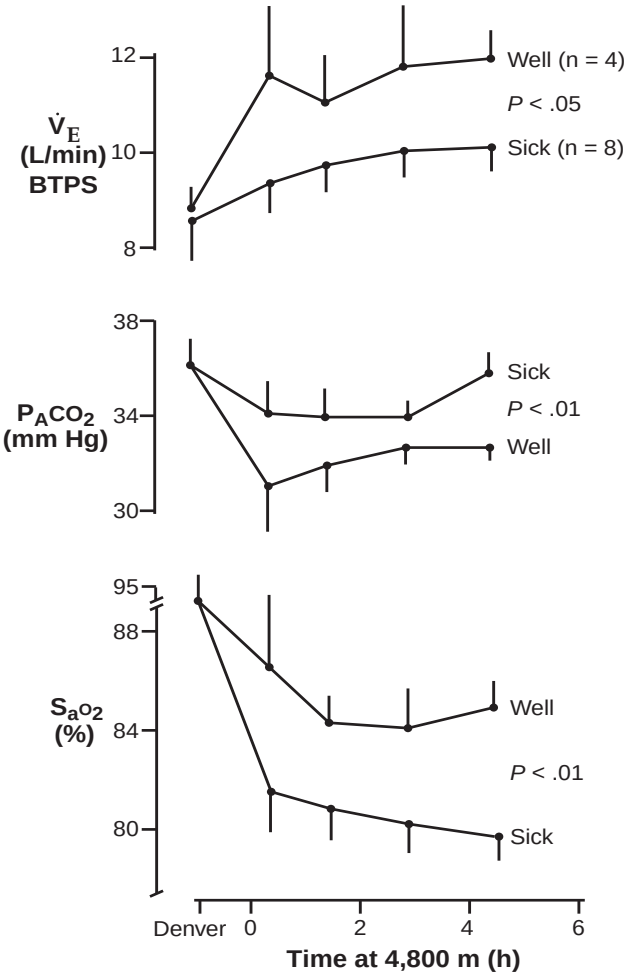


**Fig. 24-5.** Ventilation and oxygenation were lower and $P_{ACO_2}$ greater in subjects who had a prior history of acute mountain sickness (AMS) (sick) , compared with subjects who were immune to AMS on previous visits (well), suggesting that the sick subjects have a low hypoxic sensitivity. Reproduced with permission from Moore LG, Harrison GL, McCullough RE, et al. Low acute hypoxic ventilatory response and hypoxic depression in acute altitude sickness. *J Appl Physiol.* 1986;60:1407–1412.
$\dot{V}_{E\ BTPS}$: expiratory ventilation at *b*ody *t*emperature, (ambient) *p*ressure, *s*aturated (with $H_2O$ vapor); $P_{ACO_2}$: end-tidal $CO_2$ tension; $Sa_{O_2}$: $O_2$ saturation of arterial blood

volunteers breathing hypoxic gas mixtures for 6 hours, Swenson and colleagues[98] found a positive relationship between increased ventilatory sensitivity to hypoxia and hypoxic diuresis (Figure 24-6). In other words, individuals who breathed more when hypoxic also had a greater urinary output. This phenomenon had previously been well described in animals,[99] but Swenson's[98] was the first careful study in humans. It could be that the hypoxic ventilatory response varies widely in its relationship to AMS because the ventilatory response exerts its influence on AMS through fluid balance, which is ultimately influenced by other, perhaps overriding, factors.

The hypothesis that CNS responses to hypoxia cause AMS and HACE may explain the observed fluid abnormalities via increased activation of the sympathetic nervous system. Krasney[100] postulated that cerebral edema causes brain compression and that this will lead to an increase in peripheral sympathetic nervous system activity. Increased sympathetic stimulation causes vasoconstriction of the renal circulation and subsequent renal hypoperfusion, increased aldosterone and antidiuretic hormone levels, and reduces glomerular filtration rate and urinary output.

Increased sympathetic activity is consistent with the increased norepinephrine levels in AMS victims, which has been noted in some studies.[90,101] During 8 hours of normobaric hypoxia, Kamimori and colleagues[101] noted that epinephrine was increased in all subjects with AMS, but arterial norepinephrine values did not discriminate between those with and those without AMS, suggesting that adrenal medullary responses may play an important role in the pathophysiology of AMS. In men exposed to a simulated altitude of 4,500 m, muscle sympathetic nerve

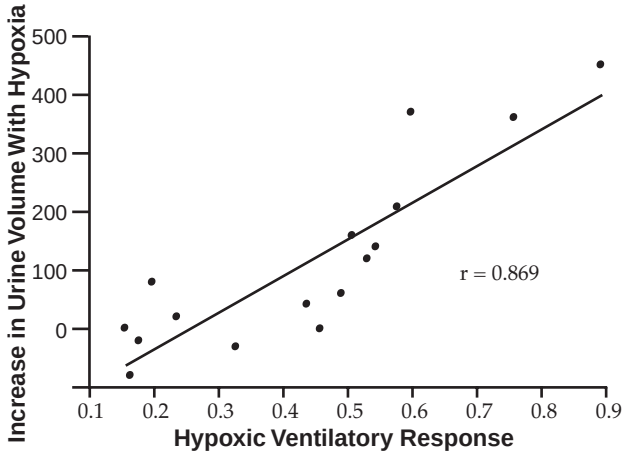


**Fig. 24-6.** The hypoxic ventilatory response (HVR) of 16 subjects was measured before they breathed hypoxic ($F_{IO_2}$ = 0.12) gas for 6 hours. Here, the HVR is plotted against the subsequent increase in urinary volume that occurs with hypoxia. Those with a strong HVR had the greatest hypoxic diuresis. Reproduced with permission from Swenson ER, Duncan TB, Goldberg SV, Ramirez G, Ahmad S, Schoene RB. Diuretic effect of acute hypoxia in humans: Relationship to hypoxic ventilatory responsiveness and renal hormones. *J Appl Physiol.* 1995;78:380.

activity increased 2-fold after 1 hour at simulated altitude and remained elevated after 24 hours.[102] Too few subjects experienced AMS in this study to draw conclusions about a relationship between elevated sympathetic tone and AMS; the important point is that direct measurements of sympathetic activity indicate a high degree of activation by hypoxia that is maintained during at least the first 24 hours of altitude exposure. Whether differences in the intensity of this response may be related to who gets sick and who remains free of AMS remains to be determined. Additionally, α-adrenergic blockade has been shown to be effective for the treatment of HAPE,[103] acting presumably by decreasing sympathetically mediated pulmonary hypertension (see Chapter 25, High-Altitude Pulmonary Edema).

Additional support for a role of sympathetic activation in the pathogenesis of AMS comes from the work by Fulco and colleagues,[104] showing that subjects with β-adrenergic blockade had less AMS than subjects taking placebo. More complete adrenergic blockade may result in even greater decrease in AMS responses if the hypothesis is correct that sympathetic activation plays a central role in the pathogenesis of AMS. Taken together, the evidence points to the possibility that the sympathetic nervous system has a role in the early development of AMS and HACE.

A generalized permeability defect has been hypothesized as an early defect common to the edemas of altitude.[105] With the discovery of many vasoactive mediators of endothelial permeability, several studies briefly explored this important area. Urinary leukotriene $E_4$ levels were measured in 8 healthy men at sea level and after 36 hours at 4,300 m.[106] Leukotriene $E_4$ levels were nearly doubled at altitude, and the concentration was related to the severity of AMS symptoms. In another study in 10 subjects exposed to 4,350 m for 8 days, leukotriene $B_4$ levels mirrored the increase in AMS symptom score from sea level to high altitude, and decreased as symptoms resolved over time at altitude.[107] Further studies are needed to establish cause and effect for these modulators of endothelial permeability in the pathogenesis of AMS and HACE.

## The Brain

Factors that determine the brain's responses to sustained hypoxia include changes in cerebral blood flow (CBF) and metabolism, CSF pressure, and cerebrovascular hemodynamics. Each response is now considered and examined for how they comprise the brain's responses to sustained hypoxia.

### *Cerebral Blood Flow and Metabolism*

For a better understanding of the concepts that will be discussed in this and the following section, it is useful to recall a few physiological principles regarding CBF. The three variables on which CBF depends are systemic blood pressure, vascular resistance, and intracranial pressure; their relationship can adequately be described by Equation 1:

$$\text{CBF} = \frac{\text{CPP}}{\text{CVR}} = \frac{\text{BP} - \text{IP}}{\text{CVR}} \quad (1)$$

where *CBF* represents cerebral blood flow; *CPP*, cerebral perfusion pressure; *BP*, systemic blood pressure; *IP*, intracranial pressure; and *CVR*, cerebrovascular resistance.

Various factors influence regulation of the cerebral vasculature, acting especially on the arterioles. Chemoregulation, autoregulation, and possibly neuromodulation[108–111] are distinguished by sympathetic nerves that innervate the cerebral vessels as principal mechanisms that affect CBF. Cerebral vessels vasodilate with a decrease in extracellular pH, increase in $P_{CO_2}$, and marked decrease of $P_{O_2}$ (< 50 mm Hg). Cerebral vasoconstriction is seen as a reaction to decreases in $P_{CO_2}$ and increases in extracellular pH. Autoregulation is the term given to the ability of the cerebral vasculature to maintain a constant CBF despite fluctuations of cerebral perfusion pressure (CPP) within certain limits. This means that a drop in CPP will produce a vasodilatory response, and an increase in CPP, a vasoconstriction. The capability for autoregulation fails if CPP is less than 60 mm Hg or is greater than 160 mm Hg. It is not known if these cerebrovascular autoregulatory mechanisms remain intact during periods of prolonged hypoxia or if they are reset to a higher level of CBF in an attempt to adapt to the persistent hypoxic stimulus.[100] Data gathered by Curran-Everett, Meredith, and Krasney[112] in an experimental sheep model for HACE showed powerful cerebrovascular vasodilation during hypoxia and hypercapnia. After ventilatory acclimatization, the same stimuli induced paradoxical cerebral vasoconstriction. Krasney[100] hypothesized that this response may be due to increased activation, by the arterial chemoreceptors, of sympathetic vasoconstrictor nerves innervating the cerebral vasculature and concluded that this physiological mechanism may protect the blood–brain barrier from cerebral autoregulatory breakthrough.

In a person ascending to high altitude, two physiological alterations occur:

1. the reduced partial pressure of inspired oxygen ($P_{IO_2}$) leads to progressive hypoxia, and
2. the ventilatory acclimatization induces hyperventilation with subsequent hypocapnia.

The former (reduced $P_{IO_2}$) leads to a decrease in CVR; the latter usually induces cerebrovascular constriction, but its effects are offset by the hypoxic stimulus. The net effect is an increase in CBF; this fact has been documented in animal models[113–115] and in human subjects[116–118] exposed to high altitude. The magnitude of the increase of CBF reaches up to 40%.[116–118] The increased CBF correlates nicely with increased middle cerebral artery flow-velocities measured with transcranial doppler.[76,119,120] Interestingly, in a study performed by Jensen and colleagues[121] in 12 subjects, the increase in CBF (up to +24% at an altitude of 3,475 m, measured by the radioactive xenon technique) did not correlate with symptoms of AMS. In a study by Baumgartner and colleagues[120] (Figure 24-7), CBF was measured by transcranial doppler and found to be higher in subjects with AMS than in healthy climbers, with a direct correlation between CBF and symptom severity. A follow-up study[122] did not support these early results, however, and a similar study by Otis and colleagues[119] also did not find such a correlation.

The key question in this context is, To what, if any, extent, is increased CBF responsible for symptoms of AMS? Judging from available evidence it appears doubtful that increased CBF is a primary factor. The rise in CBF is virtually instantaneous, as opposed to the symptoms of AMS and HACE, which arise only after several hours to days. Another important issue in this context is whether the cerebrovascular bed is homogeneous in its reactivity and susceptibility to hypoxia-induced changes. Hackett and colleagues[15] found in 1998 that edema appears to form preferentially in the corpus callosum (especially in its splenium) of subjects with HACE, as seen on examination with MRI scans. In part, this particular distribution could be explained by the fact that the posterior cerebral arteries receive less adrenergic innervation[108–111] than the other CNS arteries, rendering them more susceptible for breakthrough of autoregulation. Experimental work in conscious, hypoxic rats showed a greater increase in CBF in the brainstem and posterior circulation than in the cerebral cortex.[123] Studies by Cutler and Barlow[124] in guinea pigs subjected to severe hypercapnia (25% $CO_2$) showed that transcapillary fluid leakage in the CNS was nonuniform, with distinct predilection to leakage in the thalamus, hypothalamus, mesencephalon, and medulla. The CBF re-

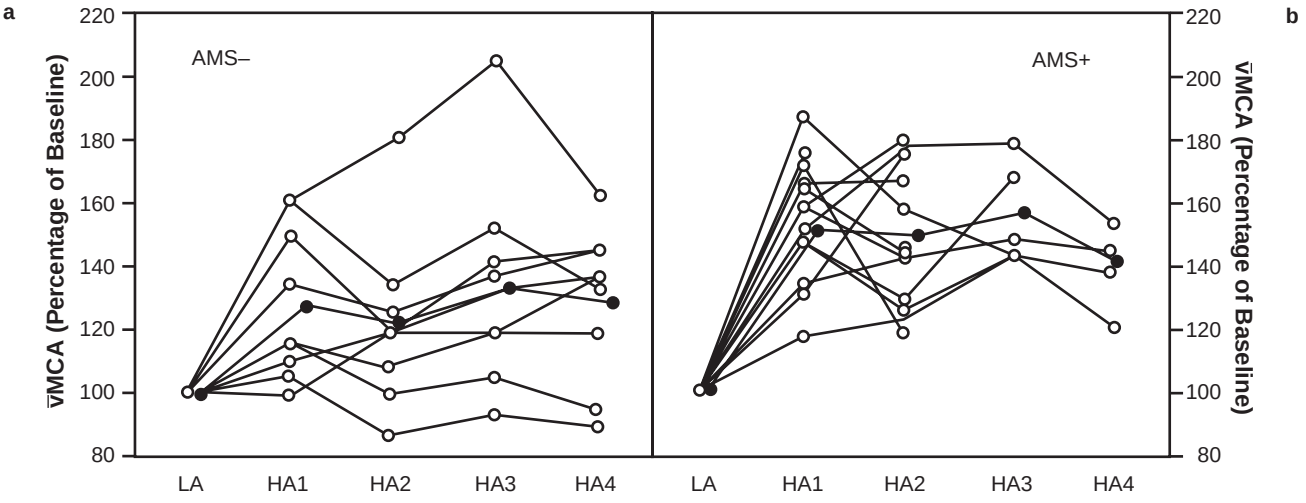


**Fig. 24-7.** In 24 healthy men (open circles) exposed to 4,559 m altitude for 4 days (HA1–HA4), mean blood flow velocity of the middle cerebral arteries ($\bar{v}$MCA) was significantly higher in (**b**) the 14 men with AMS (AMS+) after day 1, compared with (**a**) the 9 men who remained free of AMS (AMS–). $\bar{v}$MCA remained higher on day 2, but by day 3, symptoms of AMS and $\bar{v}$MCA were similar in the two groups. Closed circles represent mean values ± 95% confidence intervals. Difference of mean values between AMS+ and AMS– subjects were statistically significant ($P < .025$) on HA1 and HA2. Reproduced with permission from Baumgartner RW, Bärtsch P, Maggiorini M, Waber U, Oelz O. Enhanced cerebral blood flow in acute mountain sickness. *Aviat Space Environ Med.* 1994;65:726–729.
LA: low altitude (490 m); HA: high altitude (4,559 m)

mained constant or even decreased in these areas, as opposed to in the cerebral hemispheres, which experienced the most significant increase in CBF without any edema formation. Certainly, many questions remain open in this regard.

Early hypotheses of the pathogenesis of HACE postulated that hypoxia may cause a dysfunction in cellular $Na^+/K^+$ adenosine triphosphatase (ATPase), producing an influx of sodium into cells and thus causing cytotoxic CNS edema.[125] Metabolic studies focusing on cerebral oxygen and glucose uptake revealed that these parameters are maintained even during prolonged hypoxic exposure of 5 days.[112] In fact, the CNS optimizes oxygen uptake during hypoxemia, resulting in increased oxygen extraction. Interestingly, there appears to be a relationship between oxygen extraction capacity and the propensity to develop the AMS–HACE continuum in sheep, as described by Curran-Everett and colleagues.[126] They found that animals susceptible to AMS and HACE showed a lower oxygen extraction and higher CBF during normoxic conditions, and hypothesized that this predisposed the animals to high cerebral capillary pressures during hypoxia, leading to a transcapillary fluid shift. A similar investigation needs to be done in humans.

### *Changes in Cerebrospinal Fluid Pressure and Cerebral and Intracranial Hemodynamics*

In the following section, hemodynamic and CSF pressure changes observed during the development of AMS and HACE are discussed. To that end, it is useful to recall a few pertinent physiological concepts and classifications.

The blood–brain barrier is the physiological mechanism that prevents free transition of substances from the bloodstream into the extracellular CNS compartment. The anatomical structure responsible for the barrier function is at the tight junctions between adjacent endothelial cells, and in the CNS parenchyma astrocytic foot-processes that are closely associated with the endothelial cells and their basement membrane. The blood–brain barrier is not uniform, and in select areas of the CNS it is virtually absent. In other areas (eg, eminentia mediana hypothalami, glandula pinealis), it is diminished by the presence of fenestrated capillaries.

### Classification of Central Nervous System Edema

In his classic description in 1967, Klatzo[127] divided the pathological entity of brain edema into two distinct categories:

1. *Vasogenic* edema: protein-rich fluid spreads into the extracellular space through a compromised blood–brain barrier. The preferential site for this type of edema is the white matter.
2. *Cytotoxic* edema: intracellular fluid accumulation in neurons and neuroglia occurs after a severe insult (eg, toxins, ischemia). This type of edema is preferentially located in the gray matter.

A third type of brain edema was later added to the classification to include the edema associated with derangements of CSF[125] (Figure 24-8):

3. *Interstitial* edema: block of CSF absorption results in increased cerebral fluid located in the cellular interstitium. This type of cerebral edema is preferentially located in the periventricular white matter.

Clear distinctions among these subtypes are often not possible, because a mixed picture may be seen with the progression of the causative pathology. For example, severe anoxia may compromise cellular metabolism and lead to cytotoxic edema, but the concomitant vascular damage will produce progressive vasogenic edema as well. In his original description, Klatzo[127] commented on the particular predilection of white matter in the setting of vasogenic edema and hypothesized that the regular arrangement of extracellular channels offers less resistance to the invasion of edema fluid than does the dense meshwork of the cerebral gray matter. The following overview synopsizes the events that occur:

- During the initial stages of AMS and HACE, responses related to decreased $P_{IO_2}$ and the hypobaric environment predispose to, or act as risk factors for the development of, the ensuing pathophysiological cascade.
- Next, hypobaric hypoxia generates a compensatory increase in CBF and ventilation. The concomitant hypocapnia (caused by the increased ventilation) causes a respiratory alkalosis, which in turn acts as a slowing mechanism on the central respiratory center, preventing excessive increases in ventilation.[5] The kidneys excrete bicarbonate to compensate for the respiratory alkalosis. The cerebrum also compensates for the respiratory alkalosis by reducing the bicarbonate content of the CSF. A progressive, mild, increase in CSF pressure is seen with in-

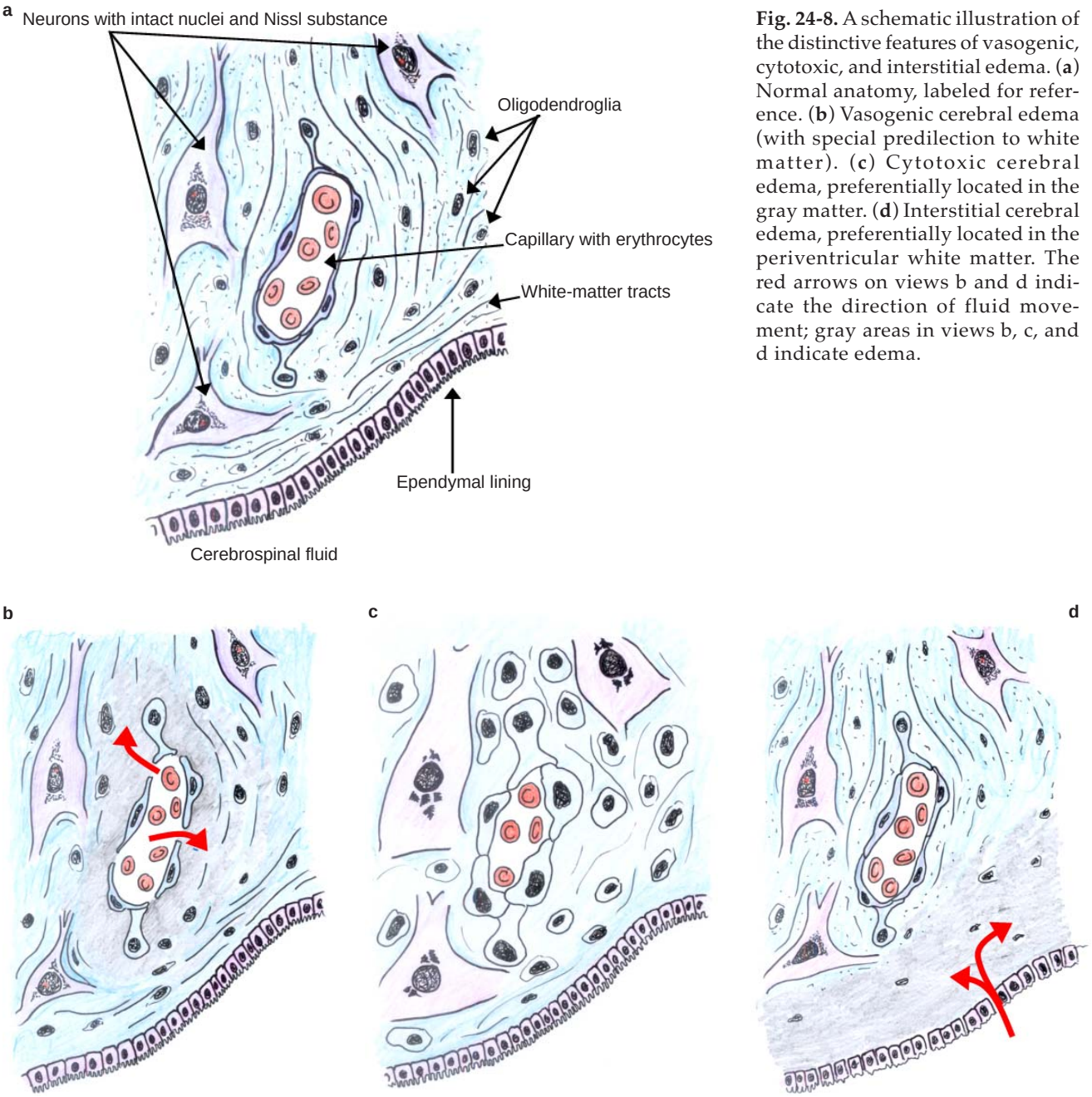


**Fig. 24-8.** A schematic illustration of the distinctive features of vasogenic, cytotoxic, and interstitial edema. (**a**) Normal anatomy, labeled for reference. (**b**) Vasogenic cerebral edema (with special predilection to white matter). (**c**) Cytotoxic cerebral edema, preferentially located in the gray matter. (**d**) Interstitial cerebral edema, preferentially located in the periventricular white matter. The red arrows on views b and d indicate the direction of fluid movement; gray areas in views b, c, and d indicate edema.

creasing hypoxia.[76] In the sheep model[128] for HACE, the choroid plexus blood flow clearly declines during progressive hypocapnic hypoxia, leading to a decrease in CSF production. In HACE and severe AMS, compensation for edema formation may begin with increases in CSF absorption, and CSF may finally shift caudally.

- Finally, progressive edema formation and accompanying anatomical changes occur. At this stage, CSF pressure increases markedly (as does intracranial pressure) and anatomical shifts start to occur, leading to severe neurological symptoms. These changes may range from focal neurological deficits to coma and potentially to death if vital centers of the medulla oblongata are compressed during caudal herniation of brain parenchyma.

The pathogenesis of AMS and HACE has been and is still being studied intensely, and although

many advances have been made in the understanding of the pathophysiology, many questions still remain open and require further study. With a focus on the blood–brain barrier and the role of the endothelium and its mediators, as well as the role of the neuroglial component, and with the use of the available animal models, further advances should be forthcoming.

## PROPHYLAXIS

The fundamentals of prevention are similar for AMS and HACE. They are based on slow ascent, time for acclimatization, a low sleeping altitude, and avoidance of any factors that increase hypoxemia, such as sedative hypnotics and alcohol.

### Acclimatization and Staging

Gradual ascent with appropriate time to adjust to new altitudes above 2,500 m is the safest prophylaxis for AMS. How slow is best determined by previous experience. A general guideline is to avoid rapid ascent from sea level to a sleeping altitude above 3,000 m, and to spend 2 to 3 days at this altitude for initial acclimatization. As Heber and Bristol wrote in 1921, the "altitude of happiness" varies for each individual, noting that they felt good at 3,300 m but "a good deal less so" at 4,100 m.[129(p1148)] The concept of "sleeping altitude" is important to understanding the practical aspects of the acclimatization process. As is mentioned in Chapter 25, High-Altitude Pulmonary Edema, respiration can vary widely among individuals at high altitude, with the two extreme conditions being respiration during exercise and during sleep. By sleeping at too high an altitude too soon after arrival, severe periodic breathing during sleep can occur, causing marked arterial oxygen desaturation and poor sleep and thus hindering acclimatization. After acclimatization to approximately 3,000 m, stopping for an extra night is recommend every time the sleeping altitude increases 500 to 1,000 m. Above 3,000 m, climbing or hiking to higher altitudes during the day aids acclimatization. Abrupt increases of more than 500 to 1,000 m in sleeping altitudes should be avoided without prior daytime exposures to the higher sleeping altitudes. Spending several nights at 3,000 m and climbing to 4,000 m in the intervening days will allow the sleeping altitude to be increased to 4,000 m with few problems; in contrast, the increase to 4,000 m after several days and nights spent at only at 3,000 m would likely result in difficult acclimatization and perhaps AMS. Staged acclimatization is time consuming but very effective (see Figure 24-1). By having subjects spend 1 week at 1,584 m followed by 1 week at 3,500 m before driving them to 4,300 m, Hansen, Harris, and Evans[54] were able to completely prevent AMS in their volunteers.

Overexertion should be avoided while ascending.[130] Early in their altitude exposure, six of seven volunteers experienced significantly worse AMS when they exercised compared with when they were resting. During exercise, $Sa_{O_2}$ levels dropped 8%, but at rest after exercise, ventilation and fluid balance were not significantly different than the same variables measured during rest without exercise.[130]

After acclimatization, in contrast, $Sa_{O_2}$ is better defended during exercise than on sudden exposure to high altitude.[58,131] Diets high in carbohydrate content (> 70% of caloric intake as carbohydrate) may influence acclimatization by increasing $Sa_{O_2}$ levels.[132] High-carbohydrate diets decreased AMS symptoms 30%,[133] presumably by increasing the respiratory quotient ($\dot{V}_{CO_2}/\dot{V}_{O_2}$) and thereby stimulating ventilation and increasing oxygenation.[134,135] These findings were not confirmed in subjects who breathed hypoxic gas at sea-level pressure for 12 hours.[135]

Climbers maintain that recent acclimatization is protective. Scientific support for this argument comes from Lyons and colleagues[136] who took six young, healthy men to the US Army Pikes Peak Laboratory Facility (a part of the US Army Research Institute of Environmental Medicine, Natick, Mass), located at 4,300 m, for 16 days, and measured AMS symptoms and $Sa_{O_2}$. On day 1, four of the six (67%) had AMS, and their average $Sa_{O_2}$ was 77%. After 14 days at 4,300 m, as expected, their AMS scores had decreased to near zero and their $Sa_{O_2}$ levels had increased about 10%. The new finding from this study came a week later when the same subjects, who had been at sea level for the intervening week, were reexposed to altitude in a hypobaric chamber. Their symptoms were much less pronounced than they had been during their initial exposure (only one subject of six was ill with AMS) and their $Sa_{O_2}$ levels were 83%—higher than on day 1 on Pikes Peak (77%) but somewhat lower than on day 14 (87%). This suggests that factors that protect against AMS are activated during acclimatization, and they con-

tinue to function after 1 week (or more?) at sea level.

**Drugs**

When rapid ascent is unavoidable, or known susceptibility to AMS and HACE exists, several drugs are helpful for prevention of the conditions (Exhibit 24-3; also see Figure 24-1). Acetazolamide is the drug of choice for prophylaxis of AMS.[6,30] As a carbonic anhydrase inhibitor, acetazolamide reduces reabsorption of bicarbonate and sodium in the kidney, thus causing a bicarbonate diuresis and a metabolic acidosis. These effects start within 1 hour after oral ingestion and rapidly enhance ventilatory and renal acclimatization to high altitude. Arterial oxygenation is improved. Acetazolamide's diuretic action counteracts the fluid retention characteristic of AMS, and perhaps more importantly, decreases CSF production and volume and possibly CSF pressure.[93]

Indications for acetazolamide prophylaxis include rapid ascent (≤ 1 d) to altitudes higher than 3,000 m, a rapid gain in sleeping altitude, a history of recurrent AMS, and troublesome periodic breathing. Doses of 125 to 250 mg twice daily, starting 24 hours prior to ascent, are as effective as higher doses started earlier.[5,6,30] A 500-mg sustained-action capsule of acetazolamide given once every 24 hours is probably equally effective.[5,137] Once acclimatization is established, acetazolamide can be safely discontinued or reserved solely for prevention of persistent periodic breathing during sleep.[6,138] Spironolactone and other diuretics have shown equivocal results for AMS prevention.[139–141]

Another drug, dexamethasone, has also proven effective for AMS prophylaxis. In eight healthy, young men rapidly exposed to 4,570 m in a hypobaric chamber, 4 mg every 6 hours decreased AMS symptoms 75%, compared with placebo treatment.[34] A field study on Pikes Peak (4,300 m) reported a 21% reduction in AMS symptoms.[142] Various dexamethasone dose regimens have been tested, from 4 mg every 6 hours to 0.25 mg every 12 hours. Based on the findings of Rock and colleagues,[143] the lowest effective dose for AMS prophylaxis is 4 mg given every 12 hours, which reduced symptoms by 52%. In one study, combined acetazolamide and dexamethasone proved superior to the use of either agent alone.[144] Unlike acetazolamide, however, dexamethasone does not aid acclimatization. Once dexamethasone is discontinued, rebound of AMS is likely.[32,143] Dexamethasone, therefore, should

**EXHIBIT 24-3**

**FIELD TREATMENT OF ACUTE MOUNTAIN SICKNESS AND HIGH-ALTITUDE CEREBRAL EDEMA**

Mild Acute Mountain Sickness
- Stop ascent; rest and acclimatize at the same altitude
- Administer acetazolamide, 125 to 250 mg twice daily, to speed acclimatization
- Treat symptoms as necessary with analgesics and antiemetics
- *Or,* descend 500 m or more

Moderate Acute Mountain Sickness
- Administer low-flow oxygen, if available
- Administer acetazolamide, 125 to 250 mg twice daily, with or without dexamethasone, 4 mg every 6 hours, by mouth, intramuscularly, or intravenously
- Administer hyperbaric therapy
- *Or,* immediately descend 500 m or more

High-Altitude Cerebral Edema
- Descend immediately until symptoms resolve
- Administer oxygen, 2 to 4 L/min
- Administer dexamethasone, 4 mg every 6 hours, by mouth, intramuscularly, or intravenously
- Hyperbaric therapy (simulated descent)
- Consider administering furosemide 80 mg orally every 12 hours for a total of 2 doses

Sources: (1) Hackett PH, Roach RC. High-altitude medicine. In: Auerbach PA, ed. *Wilderness Medicine.* St Louis, Mo: Mosby; 2001: 2–43. (2) Hackett PH, Roach RC. High-altitude illness. *N Engl J Med.* 2001;345:107–114.

be reserved for *treatment* of AMS and HACE, rather than *prevention*, except when necessary in persons intolerant of acetazolamide.

Two studies have found that a herbal remedy made from the plant *Ginkgo biloba* (*a*) prevented AMS during a gradual ascent to 5,000 m[145] and (*b*) reduced both the symptoms and the incidence of AMS by 50% during an abrupt ascent to 4,100 m.[146] Extracts from the plant *G biloba* are potent antioxidants, and it may be this property that is responsible for the herbal remedy's effectiveness in AMS.[147]

With respect to high-altitude headache, prophylactic aspirin (325 mg every 4 hours for a total of three doses) reduced the incidence from 50% to 7%.[148]

## TREATMENT

Treatment of mild AMS can include additional time to acclimatize at the present altitude, symptomatic therapy for headache and nausea, or both. Symptoms often resolve in 1 to 2 days (see Figure 24-2). Moderate-to-severe AMS and HACE should be treated with immediate descent when possible. In a patient with mild AMS, any deterioration of neurological status or signs of pulmonary edema demand immediate descent. In the following descriptions of simulated descent, oxygen therapy and pharmacological approaches to the treatment of AMS and HACE are expected, in moderate-to-severe illness, to serve only as temporizing measures until real descent can be accomplished. Treatment options are summarized in Exhibit 24-3.

### Descent, Both Real and Simulated

"When in doubt, DESCEND," is the mantra of altitude medicine. Mountaineering physicians have noted that descent of as little as 500 m yields striking clinical improvement in AMS and HACE victims. Descent is not always practical, however, and with the advent of pressure chambers in the late 1970s and early 1980s, simulated descent is now an option widely available to expeditions and trekking groups. The first portable chamber for treating altitude illness was assembled and tested at the Himalayan Rescue Association clinic in Pheriche, Nepal, in 1975 (Figure 24-9). Results from 15 patients with AMS, HACE, and HAPE confirmed previous clinical observations that descent was a safe, effective means of reversing altitude illness. Subsequent controlled studies verified and extended these findings.[149–151]

In summary, hyperbaria is as effective as oxygen breathing for the treatment of AMS and HACE. Real descent is the safest form of treatment for all the high-altitude illnesses because neither equipment failure (eg, pumps, chambers) nor supply limitation (eg, of oxygen) can interfere with recovery once descent is accomplished.

### Oxygen and Pharmacological Treatment

Oxygen does not immediately relieve all the symptoms of AMS and HACE, although it provides


**Fig. 24-9.** Increasing pressure by descent or by putting a patient in a hyperbaric chamber effectively treats acute mountain sickness (AMS) and high-altitude cerebral edema (HACE). Hyperbaric pressurization, descent, and oxygen therapy are of equivalent effectiveness for treating AMS and HACE. (**a**) This pressure chamber was first used in Pheriche, Nepal, in 1975 for recompression of patients ill with AMS or HACE. (**b**) A fabric hyperbaric chamber has the advantage over portable oxygen cylinders of being lightweight, being easy to transport, and offering simulated descent for as long as the operator can pressurize the chamber by manual pump.

significant symptomatic relief in mild-to-moderate cases. Oxygen can be a life-saving temporizing measure in cases of severe AMS and HACE.

In mild AMS, acetazolamide (125–250 mg, administered orally twice daily) will speed acclimatization and alleviate illness. Headache can be treated with analgesics[6] such as aspirin (650 mg), acetaminophen (650–1,000 mg),[148,152] or ibuprofen (≥ 200 mg).[153] Nausea and vomiting respond well to prochlorperazine (5–10 mg, administered intramuscularly). Alcohol and sedative hypnotics should be avoided because of their depressive effect on respiration, especially during sleep. In moderate AMS, acetazolamide (250 mg, given three times daily) was effective in relieving symptoms and improving pulmonary gas exchange and $Sao_2$%.[29] Dexamethasone is effective for treatment of moderate AMS. Using a dose of either 4 mg every 6 hours[32] or an 8-mg initial dose followed by 4 mg every 6 hours,[33] symptoms were notably minimized, with no significant side effects. However, dexamethasone does not aid acclimatization, and symptom rebound has repeatedly been observed.[32,33,142] Therefore, dexamethasone could be used to relieve symptoms and acetazolamide to speed acclimatization.

Successful treatment of HACE requires early recognition. At the first sign of ataxia or change in consciousness, descent should be started, dexamethasone (initially 4–8 mg intravenously, intramuscularly, or by mouth, followed by 4 mg every 6 h) administered, and oxygen (2–4 L/min by mask or nasal cannula) applied, if available. Oxygen can be titrated to maintain $Sao_2$ at or higher than 90% if oximetry is available. Comatose patients require additional airway management and bladder drainage. Attempting to decrease intracranial pressure by intubation and hyperventilation is a reasonable approach, although these patients are already alkalotic and over-hyperventilation could result in cerebral ischemia. Loop diuretics such as furosemide (40–80 mg) or bumetanide (1–2 mg) may help reduce brain hydration, but an adequate intravascular volume to maintain perfusion pressure is critical. Hypertonic solutions of saline, mannitol, and urea have been suggested[7] but are used rarely in the field. Controlled studies are lacking, but empirically, the response to steroids and oxygen seems to be excellent if given early in the course of the illness and disappointing if not started until the patient is unconscious. Coma may persist for days, even after evacuation to low altitude, in which case other causes of coma must be considered and ruled out by appropriate evaluation. Sequelae lasting weeks are common; longer-term follow-up has been limited.

## MILITARY OPERATIONS AT ALTITUDE

The rapid deployment of troops to high altitude (ie, > 2,500 m) may pose significant logistical, technical, environmental, tactical, and medical problems.[16,154,155] The routes for supply in difficult mountainous terrain may be restricted to air-drop and may be hampered by unfavorable weather conditions—necessitating autonomy in regard to food, clothing, and equipment. The environment may require special attention to dangers of rockfall; high ultraviolet light exposures; difficult technical ascents requiring special gear; avalanches; and severe, prolonged periods of cold weather in the winter season. The human factors that have to be taken into consideration are more likely to be crucial in this setting. The lack of experience in a new environment and insufficient physical and psychological preparedness are factors that can be overcome by careful planning and training for the specific operation. The environmental conditions (eg, low temperatures, difficult ascents) can produce a state of physical and psychological exhaustion that may affect decision making and result in faulty assessments of terrain and the feasibility of tasks at hand. The medical issues that arise during a military operation at high altitude are multiple and complex; the following discussion will focus on the potential dangers of AMS and HACE.

The symptomatology of the two syndromes is unfortunately not specific in its initial presentation and thus requires constant attention from the medical officer for early detection. Headache, lassitude, and mild ataxia are early warning signs that should be carefully watched and acted on as necessary. The observations by Singh and colleagues[16] are the most comprehensive series of published observations made in troops exposed to a high-altitude environment. Singh studied 1,925 soldiers, aged 18 to 53 years, air-lifted to the Indian Himalaya at altitudes of 3,350 to 5,500 m. A variety of neurological manifestations were observed, including headaches (the most prevalent and most persistent symptom), decreased ability to concentrate, blurred vision, and, in 24 soldiers, more-severe signs and symptoms including papilledema, stupor, coma, seizures, and focal neurological deficits. In Singh's series, three patients died from neurological complications and two had marked cerebral edema on postmortem examination.

The neurological changes seen in AMS after rapid exposure to high altitude may thus have significant impact on the physical and mental functioning of susceptible individuals. These changes in conjunction with the hardships of the environment can make troop leadership difficult. Constant attention to the physical and mental state of the troops is necessary to detect early changes that can be appropriately treated. Lack of attention to these early issues will entail secondary dangers to the military operation, such as misjudgments of tactical situations and mistakes made during the operation of vehicles, weapons, or complex instruments. The capability for rapid deployment is a hallmark of today's modern armies and confers obvious strategic advantages. However, rapid deployment itself exposes the troops to a higher risk of altitude-related illnesses in the mountainous environment. To avoid disability and death of the troops, the following actions must be taken by the commanding officer, in collaboration with the medical officer:

1. Allow time for acclimatization through graded ascent to high altitude.
2. Educate troops about signs and symptoms of AMS and HACE to ensure early reporting (make use of the "buddy-system," in which individuals observe each other for occurrence of symptoms).
3. Evaluate the need for pharmacological prophylaxis, in view of the nature of the mission and the available time.
4. Minimize severe exertion and exposure to cold as possible precipitating factors.
5. Plan ahead for rapid evacuation (to lower altitude) for severe cases.
6. Plan for treatment of AMS to keep soldiers functional and to avoid evacuations.

## SUMMARY

Altitude-related illnesses such as AMS are usually a nuisance (eg, headaches, anorexia, nausea) rather than a threat to life and are most commonly self-limited. However, they may have a significant impact on an individual's ability to function. Military commanders and medical officers can prevent or reduce altitude-related illnesses by following the six actions enumerated just above.

To avoid fatal outcomes, severe complications such as HACE in susceptible individuals may require rapid recognition and efficient treatment, such as evacuation to lower altitude, simulated descent in a hyperbaric bag, and pharmacological therapy. If descent is not an option, then acetazolamide and dexamethasone effectively reverse AMS, and HACE is reversed with dexamethasone. Aspirin successfully treats high-altitude headache.

Pharmacological prevention can include acetazolamide, dexamethasone, and a herbal remedy made from the plant *Ginko biloba*. Recent studies support the effectiveness of *G biloba* extract in small study groups; larger trials are underway. Prevention can largely be achieved by slow, staged ascent. All travelers to high altitude should be mindful that awareness of the early symptoms of AMS and HACE can be the most effective strategy for preventing fatal outcomes.

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