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Acetazolamide in the treatment of acute mountain sickness : clinical efficacy and effect on gas exchange

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ACETAZOLAMIDE IN THE TREATMENT OF ACUTE MOUNTAIN SICKNESS: CLINICAL EFFICACY AND EFFECT ON GAS EXCHANGE

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Colin Kerst Grissom

1990

ACETAZOLAMIDE IN THE TREATMENT OF ACUTE MOUNTAIN SICKNESS: CLINICAL EFFICACY AND EFFECT ON GAS EXCHANGE. Colin K. Grissom, Robert C. Roach, and Peter H. Hackett. Denali Medical Research Project, University of Alaska, Anchorage. David H. Ingbar, Pulmonary Section, Yale University School of Medicine.

Acute mountain sickness (AMS) is a neurologic syndrome that occurs upon ascent to high altitude, and is associated with impaired pulmonary gas exchange. Acetazolamide prevents AMS when given prior to ascent, but has not been proven effective for treatment. We therefore set out to determine: 1) the efficacy of acetazolamide for treatment of AMS and 2) the effect of acetazolamide on pulmonary gas exchange in AMS. Twelve climbers with AMS at 4200m on Mt. McKinley were randomized in a double blind fashion to acetazolamide (n=6) or placebo (n=6). The dose of acetazolamide was 250 mg PO at 0 and 8 hours after inclusion in the study. Assessment of AMS and physical measurements were made at 0 hours and were repeated at 24 hours.

	PLACEBO (mean ±SE)	**ACETAZOLAMIDE** (mean ±SE)
Symptom Score *	n=6	n=6
Baseline	3.8 ±0.7	3.8 ±0.2
24 hours	2.5 ±0.3	1.0 ±0.2 **
A-a Gradient (torrs)	n=6	n=3
Baseline	8.8 ±1.8	9.0 ±1.6
24 hours	12.1 ±1.7	8.2 ±1.9
(change 0-24 hrs)	(+3.3 ±0.9)	(-0.8 ±0.7) ***
PaO2 (torrs)	n=6	n=3
Baseline	45.2 ±1.3	44.2 ±3.4
24 hours	43.8 ±2.0	47.1 ±2.9
(change 0-24 hrs)	(-1.4 ±1.2)	(+2.9 ±0.5) ***

* A symptom score of 2 or greater indicated AMS.
** $p<.01$ acetazolamide versus placebo, Mann-Whitney U-test.
*** $p<.05$ for change in A-a gradient and PaO2 over 24 hours between groups, Mann-Whitney Rank-Sum test.

At 24 hours 5 of 6 acetazolamide-treated climbers were without AMS (symptom score <2), and all 6 placebo-treated climbers still had AMS (symptom score ≥2). No significant side-effects of acetazolamide were reported. Acetazolamide improved pulmonary gas exchange and PaO2 over 24 hours as compared to placebo. Change in A-a gradient for O2 correlated significantly with change in symptom score for both groups ($p<.005$). Acetazolamide was associated with a decrease in A-a gradient and a greater improvement in symptoms, and placebo was associated with an increase in A-a gradient and less improvement in symptoms. We conclude that acetazolamide is effective for the treatment of established cases of AMS, and is associated with an improvement in pulmonary gas exchange.

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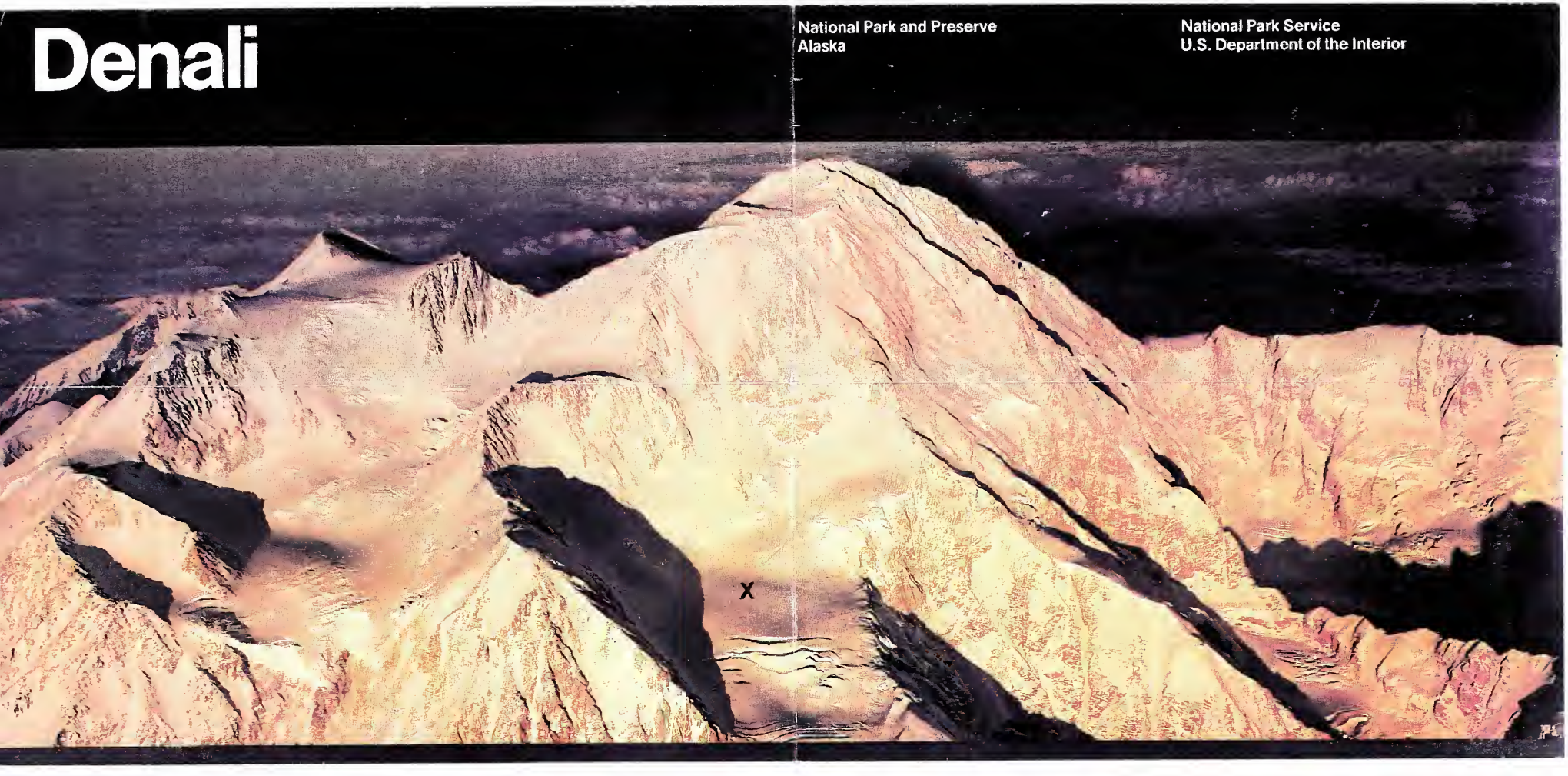
ALTITUDE CONVERSION AND BAROMETRIC PRESSURE

Meters	Feet	Barometric Pressure(torr)
Sea Level	Sea Level	760
1524	5000	627
2134	7000	581
2743	9000	538
3353	11000	497
3962	13000	462
4572	15000	426
5182	17000	395
5791	19000	366
6401	21000	339
7010	23000	314
7620	25000	291
8230*	27000*	269
8839**	29000**	249

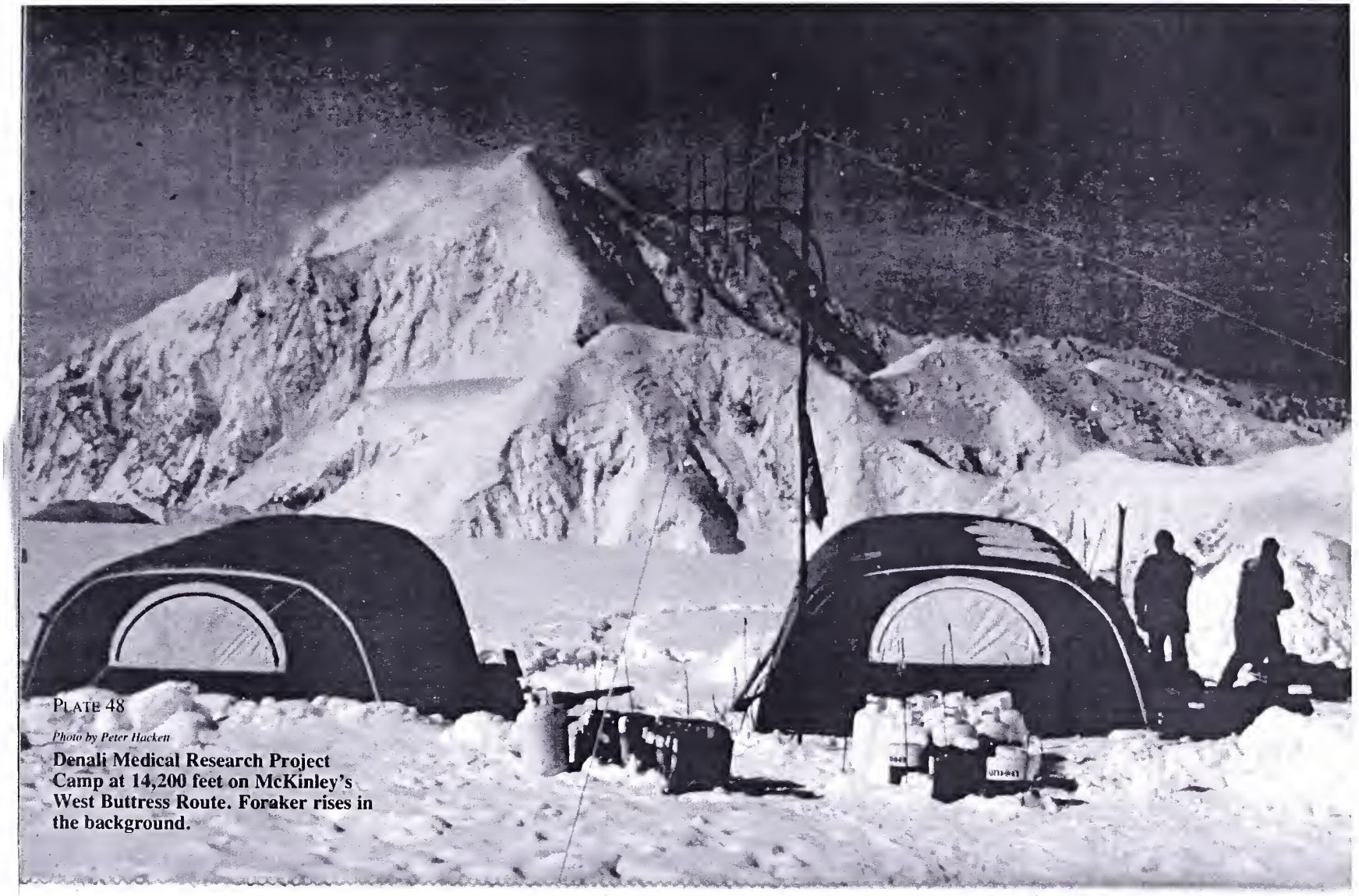
* There are 14 mountains in the world over 8000m in elevation.

** Elevation of Mt. Everest.

(Adapted from Hackett et. al. reference 35)



The south side of Denali (Mt. McKinley). The x indicates the location of the Denali Medical Research Project High Altitude Research Station at 4200m (14,000 ft.) on a large glacial plateau. The summit elevation is 6150m (20,320 ft.).
(photo credit National Park Service, used with permission)



Denali Medical Research Project Camp at 4200m on the West Buttress Route of Denali (Mt. McKinley). Shelters are used for research and for medical care of climbers. Foraker rises in the background to a summit elevation of 5150m (17,000 ft.).
(photo credit American Alpine Club, used with permission)

"In 1935 four of us, crossing a pass of only 17,000 ft. from Sikkim into Tibet, suffered extremely, and although carrying no loads were quite incapable of keeping pace with our transport which, since it included some yaks, was not exactly devouring the ground. Such discrepancies are difficult to explain and a great deal has yet to be learnt about acclimatisation."

H.W. Tillman, from The Ascent of Nanda Devi.

I. INTRODUCTION

Human populations have lived for centuries at elevations between 4000m and 5000m on the Tibetan plateau in Asia and on the high plateaus of Peru and Bolivia (47). The need for cultures to exchange goods led to the development of trade routes that traversed high mountain passes, and it was in this context that acute mountain sickness was first described in ancient China (70). Although the European population was well aware of the breathlessness experienced in the Alps, it was not until the early sixteenth century, during the Spanish invasion of the Incan empire in South America, that the extent of altitude illness became known to the western world (53). Still, deaths among Spanish troops crossing high passes in the Andes were attributed to "the sickness of the Andes", or "soroche", and not to a specific effect of the air at high altitude. The Jesuit father Jose de Acosta, travelling in the Andes after the Conquistadors, was the first to attribute illness experienced crossing the high passes in the Andes "to the air and the wind blowing there". In an account of his experiences, The Natural and Moral History of the Indies, published in 1590 some forty years after his travels, Acosta gives a vivid description of altitude illness (3,47):

> "when I began to mount the stairs, as they call the highest part of this mountain, I was suddenly attacked and surprised by an illness so deadly and strange, that

> I was almost on the point of falling from my horse to the ground ... I was seized by such a spasm of panting and vomiting that I thought I should give up the ghost... That lasted only three or four hours until we had descended pretty low and had reached a temperature more suited to nature"

With the increasing numbers of individuals ascending to higher altitudes today, altitude illness has become more common and the study of altitude illness more relevant. Advances in passive transportation and an increased interest in activities such as sightseeing, skiing, hiking, and mountaineering combined with increased leisure time have brought more individuals to higher altitudes at faster rates of ascent. In 1984, over 34 million persons visited recreation areas above 2400m in Colorado and Utah. Hundreds of thousands annually visit Nepal, Tibet , and South America, many travelling to altitudes over 4000m (62). All individuals ascending to altitude undergo the physiologic process of acclimatization and some individuals experience one of the forms of altitude illness. This encompasses a spectrum ranging from the more common acute mountain sickness (AMS) to the more life threatening high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE).

AMS is a symptom complex that is commonly seen in individuals a few hours to a few days after ascending to altitudes above 2500m (30,31). In the milder forms it is characterized by headache,

insomnia, malaise, and anorexia. In the more severe forms it is characterized by nausea, vomiting, ataxia, psychological changes, lassitude, and breathlessness (30,34). AMS is generally self limited, although it can be incapacitating, and can progress to life threatening HAPE or HACE. With the increasing numbers of high altitude sojourners, knowledge of the pathophysiology, recognition, and treatment of acute altitude illness becomes more relevant, to increase both the enjoyment and safety of those travelling to high altitude areas. The purpose of this thesis is to review information relevant to altitude illness with particular attention to the syndrome of AMS, and then to present a study investigating the efficacy of acetazolamide in the treatment of AMS and its effect on gas exchange in AMS. This has important implications for the treatment of this most common form of altitude illness.

II. HIGH ALTITUDE ACCLIMATIZATION

The initial insult in individuals ascending to altitude is a fall in the partial pressure of inspired oxygen (PiO2), resulting from a logarithmic fall in the barometric pressure with increasing altitude. The work of a French physiologist, Paul Bert, in the 1870's proved that the effects of high altitude on the human body result from reduced partial pressure of oxygen, and not from isolated hypobaria. Until Bert's work, conducted on both men and animals in an altitude chamber, there had been a sharp divergence of opinion as to whether mountain sickness was due to diminished barometric pressure per se, or to diminished oxygen pressure. Bert's interest in high altitude physiology arose from both mountain journeys and the difficulties encountered by the balloonists of his day. Bert was in fact a sponsor of the ill fated ascent of the balloon "The Zenith" to an altitude of 8000m over three hours in 1875, which resulted in the death of two of the three balloonists (3).

Just as with the balloonists in "The Zenith", sudden ascent from sea level to the summit of Mt. Everest (8848m) may lead to unconsciousness and death soon thereafter (73), yet mountaineers have accomplished gradual ascents over many weeks to the summit of Mt. Everest without the use of supplemental oxygen and without

adverse effects. The process by which humans adjust to the hypoxia of high altitude is termed acclimatization, and the primary physiologic mechanism in acclimatization is increased minute ventilation.

Control of breathing, and ventilatory acclimatization, are governed at two sites: the peripheral chemoreceptors in the carotid body, and the central chemoreceptors in the medulla. The central chemoreceptors are surrounded by brain extracellular fluid and respond to changes in its H+ concentration. An increase in H+ concentration stimulates ventilation while a decrease inhibits it. When the blood PCO2 rises, CO2 diffuses into the cerebrospinal fluid (CSF) from the cerebral blood vessels, liberating H+ ions that stimulate the chemoreceptors. Although the composition of the extracellular fluid around the receptors is primarily governed by the CSF, local blood flow and local metabolism also can influence the H+ concentration. The peripheral chemoreceptors, located in the carotid body at the bifurcation of the common carotid arteries, respond primarily to decreases in the partial pressure of arterial oxygen (PaO2) and, to a lesser extent, to decreases in pH and increases in the partial pressure of arterial carbon dioxide (PaCO2). The peripheral chemoreceptors are responsible for all the increase of ventilation that occurs in man in response to arterial hypoxemia. The response of these receptors can be very fast, as

their discharge rate alters during the respiratory cycle in response to cyclic changes in blood gases (87).

Increased minute ventilation during ascent to high altitude starts as low as 1500 m, and within the first few hours of altitude exposure. The increase of ventilation during acute exposure to high altitude is mediated through the carotid body which senses a decrease in PaO2. This response is termed the hypoxic ventilatory response (HVR) which varies among individuals and is partly determined genetically (86). A high HVR may aid in acclimatization (68), but a blunted ventilatory response is not necessarily deleterious (71), although some studies have suggested that a low HVR may play a role in susceptibility to AMS (63).

Acutely, increased ventilation at high altitude leads to hypocapnia and a respiratory alkalemia that serve to decrease central respiratory drive, limiting further increases in ventilation. Over the ensuing hours to days at high altitude, however, a progressive increase in minute ventilation occurs, reaching a maximum after four to seven days at the same altitude (10). This increase in ventilation initially is achieved more by an increase in tidal volume than in frequency, but over time respiratory rate also increases. The role that the HVR plays in the progressive increase in ventilation observed over days of exposure to high altitude is unclear. Some investigators report

an increased HVR during acclimatization and others report no such change. An increase in mouth occlusion pressure ($P_{0.1}$), however, is consistently observed during acclimatization reflecting increased central respiratory drive (73).

The classic explanation for the progressive increase in minute ventilation over several days is that a bicarbonate diuresis occurs within 24 to 48 hours after arrival at high altitude. This returns both blood and CSF pH towards normal, thus removing the inhibitory effect of alkalemia on central respiratory drive. However, observations of persistent alkalosis in the blood and CSF even after ten days at high altitude, and as minute ventilation begins to stabilize at a higher level, indicate that the process is more complex than the classic explanation suggests (18). Some investigators have examined other factors besides the CSF pH that might influence the environment of the central chemoreceptors. Lactate generated from the brain during hypoxia and hypocapnic alkalosis appears to create an acid environment in the brain's interstitial fluid despite an alkaline CSF. This might contribute to an increases central respiratory drive. Recent data, however, suggest that the time course of this central nervous system (CNS) acidosis does not correspond to the ventilatory response during acclimatization (73).

Other studies have shown that although hypoxic chemosensitivity does not change on exposure to high altitude, the hypercapnic ventilatory response (HCVR or $\Delta V_E/\Delta PCO2$) increases (59). This stimulates a greater level of minute ventilation for a given level of PCO2 than at sea level, as the entire HCVR curve shifts to the left. The enhanced central responsiveness to CO2 may be explained, at least in part, by a greater change in [H+] for a given level of CO2 crossing the blood brain barrier due to the lower bicarbonate concentration in the brain intracellular fluid and CSF (73). Hypocapnic hypoxia appears essential to ventilatory adaptation, because when individuals are exposed to isocapnic hypoxia for 75 hours, no change in the HCVR is seen (9). While apparently a CNS phenomenon, the mechanism for this enhanced ventilatory response to CO2 is unknown.

The persistent alkalemia observed during acclimatization to high altitude suggests that the oxyhemoglobin dissociation curve shifts to the left. Work by Ancel Keys in the 1930's demonstrated a left shift in the oxyhemoglobin dissociation curve up to 4400m, but then a right shift was observed from 4400m up to 6100m (52). Keys proposed that the right shift at higher altitudes was advantageous because it enhanced oxygen unloading at the systemic tissues. This right shift of the oxyhemoglobin dissociation curve occurs because of increased 2,3 DPG generated during hypoxia.

However in more recent experiments, during a simulated ascent to the summit of Mt. Everest (8848m), the oxyhemoglobin dissociation curve was observed to shift to the left because of extreme hyperventilation and respiratory alkalosis (85). This would facilitate oxygen loading of red blood cells (RBCs) in the lung and raise arterial oxygen saturation. Improved unloading of oxygen from RBCs at the tissues may not be beneficial unless sufficient saturation of hemoglobin with oxygen has occurred during passage through the lungs. Thus a left shift of the oxyhemoglobin dissociation curve may be more advantageous at extreme altitudes. A more long term physiologic adaptation to altitude is an increase in erythropoietin leading to increased marrow production of red blood cells and an enhanced oxygen carrying capacity (79).

For the circulatory system, ascent to high altitude increases catecholamine levels leading to peripheral vasoconstriction and a mild increase in both systolic and diastolic blood pressures. Heart rate, cardiac output, and venous tone are modestly elevated. Resting heart rate returns to near sea level values with acclimatization, except at extreme altitude. Maximum heart rate is limited by maximal oxygen uptake - which declines with increasing altitude. This occurs because cardiac output is not a limiting factor for performance at high altitude. Instead the decreased oxygen delivery to the tissues limits the work performed.

During a simulated ascent to a barometric pressure equal to that at the summit of Mt. Everest, cardiac function was equivalent to values obtained for the same level of work performed as at sea level (65).

The pulmonary circulation responds to the global hypoxia at high altitude with pulmonary vasoconstriction. This results in elevated pulmonary artery pressure that increases further with the high cardiac output of exercise. Pulmonary hypertension at high altitude is not completely reversible with oxygen administration, which suggests that the increased pulmonary vascular resistance at altitude may not be due solely to hypoxic pulmonary vasoconstriction (22,48). Some individuals with a history of HAPE are particularly susceptible to pulmonary hypertension at altitude (48). Still, even with mean pulmonary artery pressures up to 60 torr, cardiac output remains appropriate and right atrial pressures do not rise above sea level values, suggesting that right ventricular function remains intact (22). This is an interesting contrast to the patient with respiratory failure at sea level.

The mechanisms of acclimatization discussed so far may begin as low as 1500m, and continue to occur with ascent to progressively higher altitudes. The degree of arterial hypoxemia and resulting physiological responses, however, vary according to the eventual altitude reached. At 1500m the barometric pressure of 630 torr

results in a partial pressure of inspired oxygen (PiO2) of 122 torr, a PaO2 of 80 torr, and a PaCO2 of 33 torr. On the summit of one of the 14 peaks in the world over 8000m the barometric pressure is less than 280 torr, the PiO2 less than 50 torr, the PaO2 approximately 35 torr, and the PaCO2 approximately 13 torr (35). Clearly, the same degree of acclimatization is not required to travel to Denver, Colorado, at just over 1500m, as is required to climb an 8000m peak in the Himalaya. Therefore, Hackett defined three different ranges of altitude that elicit a progression of physiological responses and may result in differing severities of altitude illness: high altitude (1500m to 3500m), very high altitude (3500m to 5500m), and extreme altitude (over 5500m) (35).

At high altitude, 1500m to 3500m, the onset of physiologic effects of diminished PiO2 include decreased exercise performance and increased ventilation at rest. Arterial oxygen saturation at rest remains above 90%. Still, AMS is common with one or two day ascents from sea level to over 2500m. At very high altitude, 3500m to 5500m, arterial oxygen saturation at rest falls to less than 90% as the PaO2 falls to or below 60 torr. Extreme hypoxemia may occur during exercise, sleep, and altitude illness. This is the most common range for serious altitude illness. At extreme altitude, over 5500m, marked hypoxemia and hypocapnia occur as the PiO2 falls even further and ventilation continues to increase. This range is

above the highest permanent human habitation because, at these altitudes, acclimatization does not prevent progressive deterioration of physiologic function (35).

III. HIGH ALTITUDE ILLNESS: HAPE AND HACE

Almost all individuals physiologically acclimatize to high altitude given sufficient time, but only some individuals experience one of the spectrum of high altitude syndromes. These include but are not limited to: acute hypoxia, disordered sleep, sleep periodic breathing, AMS, HAPE, and HACE. Other high altitude illnesses that will not be discussed here include thromboembolic problems, cerebrovascular syndromes, and high altitude retinopathy (35).

It can be difficult at times to clearly separate high altitude illnesses, as considerable overlap may exist in their presentation and progression. An individual may present with symptoms consistent with AMS and then go on to develop HAPE or HACE. Likewise, disordered sleep or sleep periodic breathing frequently occur without clinically defined AMS, or a sleep disturbance may be part of the symptom complex of AMS. An understanding of some of the more important high altitude syndromes is therefore important, as it provides a background from which to evaluate the presentation and follow the progression of AMS.

High Altitude Pulmonary Edema:

HAPE is a form of noncardiogenic pulmonary edema that occurs predominately in young healthy individuals without underlying pulmonary or cardiac disease after acute ascent to high altitude (70). The incidence varies with the ultimate altitude attained and with the rate of ascent. The incidence has been reported as high as 15% in Indian troops airlifted from sea level to altitudes between 3500m and 5500m (76), 1-2% in climbers during ascents of Mt. McKinley, Alaska at elevations up to 6150m (69), .01% in male visitors to Vail, Colorado at an elevation of 2500m (77). The clinical presentation consists of fatigue, dyspnea at rest, marked decrease in exercise tolerance, and a dry cough that becomes productive of white frothy sputum over 24 to 48 hours (70).

The definitive treatment for HAPE is descent, with symptoms most often resolving within 24 to 48 hours (70). Even a modest decent of 500m to 1000m may lead to improvement (69). If descent is not undertaken death may follow within days of the onset. In some situations, however, descent may not be a viable option, as with climbers or trekkers caught in adverse weather conditions in difficult terrain. In these situations supplemental oxygen is helpful, if available. Another alternative, that does not require the bulk and weight of bottled oxygen, is a continuous positive airway pressure (CPAP) mask. The CPAP mask is effective in

improving ventilation - perfusion mismatch and oxygenation in HAPE (74), similar to the use of positive airway pressure in other forms of diffuse pulmonary edema with hypoxemia. Still, the CPAP mask should be used only as a temporizing measure until evacuation or descent is undertaken.

Beginning with the first description of HAPE by Charles Houston in 1960 (45), and subsequent work by Hultgren clearly showing that HAPE is a form of noncardiogenic pulmonary edema occurring after ascent to high altitude (48), the etiology of HAPE has been debated. High pulmonary artery pressures at altitude observed in individuals with a history of HAPE led to speculation that HAPE results from overperfusion of a constricted pulmonary vascular bed with a resulting transudative leak (48). An "experiment of nature" supported this theory when Hackett reported four cases of HAPE at moderate altitude in four individuals with congenital absence of the right pulmonary artery (27). Schoene, however, performed fiberoptic bronchoscopy and bronchoalveolar lavage on individuals with HAPE and controls at 4200m on Mt. McKinley, and found high concentrations of protein and cells in the lavage fluid from the HAPE subjects, indicating increased capillary permeability and an inflammatory component (72). Although the exact mechanism leading to transvascular protein and fluid flux in HAPE is still unknown, it appears that both pulmonary hypertension

and a compromise in the pulmonary vascular endothelium play roles in the pathogenesis. It is also notable that a few authors postulate that an element of neurogenic pulmonary edema may contribute to this process (40), perhaps by augmenting pulmonary vascular resistance and increasing central blood flow.

High Altitude Cerebral Edema:

HACE is characterized by progression of global cerebral signs and symptoms in the setting of AMS, and may occur with HAPE. Common features include truncal ataxia, severe headache, vomiting, impaired motor and sensory functions, hypo- or hyperreflexia, papilledema, and altered level of consciousness. Less common features include hallucinations, scotoma, visual field defects, pupillary changes, blurred vision, speech difficulty, cranial nerve palsies, rigidity or flaccidity, tremor, hemiparesis, convulsions, obtundation, stupor, and coma (35,40). The most common clinical presentation, however, is change in consciousness associated with ataxia, without focal neurological signs (35,76). The progression from mild AMS to unconsciousness may be as fast as 12 hours, but usually requires 1-3 days (35). The preferred treatment for HACE is descent, although symptoms may not resolve quickly as with HAPE. Supplemental oxygen, if available, is probably useful but should not substitute for descent. Anecdotal reports suggest that

dexamethasone also may be useful in treatment, with therapy earlier in the illness producing better results (40).

Gross cerebral edema in HACE has been documented on CT scans (54), as well as on necropsy (11,12). Pathological features of HACE seen at autopsy include edema of the white matter, widespread petechial hemorrhages, and sludging of erythrocytes in capillaries (40). Elevated CSF pressures of up to 210 mm H2O also are seen (76). At present, two pathophysiological theories are proposed to explain the brain edema seen in HACE. One view suggests that high altitude brain swelling is caused by a cerebral vasodilatory response to hypoxia with subsequent increased cerebral blood flow. Moderate cerebral hypertension and strenuous exercise then overwhelm the integrity of the blood - brain barrier, leading to transcapillary and transarteriolar leakage, and a vasogenic, multifocal cerebral edema ensues. This contrasts sharply with the view that HACE is caused by massive hypoxic cell damage leading to cytotoxic edema. In this theory, failure of the sodium pump, Na+ - K+ ATPase, at the cell membrane would lead to accumulation of Na+ and water within cells, resulting in cell death (16). If this process occurred in the cerebral endothelial cells, a superimposed vasogenic edema also would occur (40). Steroids may be beneficial in the treatment of vasogenic cerebral edema, but not other kinds of cerebral edema (40). Reports of the successful treatment of

HACE with dexamethasone suggest that vasogenic edema, whether primary or secondary to cytotoxic edema, plays a role in the pathophysiology of HACE.

IV. AMS: DIAGNOSIS, PATHOPHYSIOLOGY, AND NATURAL HISTORY

AMS is a symptom complex commonly seen in individuals from six to 96 hours after ascending to altitudes above 2500m (30,31,76). Most individuals with AMS present with a milder form, characterized by headache, anorexia, nausea, vomiting, oliguria, and malaise. The more severe form of AMS presages HAPE or HACE and can be characterized by an altered level of consciousness, ataxia, rales, cyanosis, and dyspnea at rest (31,35). Although the symptoms and severity of AMS vary, AMS is characterized by greater severity with more rapid ascent to higher altitudes. For persons who are partially acclimatized, abrupt ascent to a higher altitude, overexertion, and use of respiratory depressants are common contributing factors (35).

The most effective prophylaxis for AMS is slow ascent. Most people, however, exceed the ascent rates recommended for prophylaxis and thus increase their susceptibility to AMS. The incidence is as high as 67% in climbers making a rapid ascent (33 hours) to 4392m on Mt. Ranier (57), 31% in trekkers walking from Kathmandu (1300m) to Pheriche (4243m) (30), and 12% in skiers going from Denver (1600m) to resorts in the Colorado Rockies at 2400m to 2800m (46).

Diagnosis of AMS:

The diagnosis of AMS is based on the symptoms and physical findings in the setting of acute ascent to high altitude. To diagnose AMS, it is not necessary that an individual exhibit all the common symptoms seen in the milder form, as symptoms and severity of AMS vary widely among persons. Symptoms of AMS, however, usually are consistent in a given individual from one altitude exposure to the next (76). In clinical research a symptom score is used to diagnose AMS (25,14), rather than a specific constellation of symptoms. A symptom score diagnostic of AMS would require only that a certain number of symptoms be present, or that a given severity of one symptom is observed.

The most common symptoms of AMS are headache, malaise, anorexia, and nausea (31). The headache is throbbing, bilateral, frontal, and is worse at night or in the morning after awakening. The latter may be due to arterial oxygen desaturation observed during sleep at high altitude (80). Sleep may be fragmented by frequent awakenings caused by periodic breathing during sleep at high altitude, but this is common in all individuals above 2800m and does not constitute an absolute diagnostic symptom (80,37). Lassitude can be disabling, causing loss of interest in activities of daily living, and sometimes requiring the care of others. Pulmonary symptoms vary considerably. Dyspnea on exertion at high

altitude is common, and occurs in virtually all persons at extreme altitude. At more moderate altitudes it may be difficult to determine when dyspnea on exertion is of an abnormal degree. Dyspnea on exertion forcing frequent stops or dyspnea at rest, however, are distinctly abnormal and suggest the development of HAPE (707).

Just as with symptoms, specific physical findings diagnostic of mild AMS are not present in every case. Some authors describe tachycardia, while others note a mild bradycardia in AMS (76). A 25% - 35% incidence of rales localized to one side of the chest is present in AMS (31,76). Fluid retention causes peripheral edema and weight gain, and contrasts with the normal diuresis at altitude (31,76). As AMS progresses, physical findings become more prominent with ataxia being the single most useful sign of progression from mild to severe (35). Lassitude and mental status changes may also become more severe.

Pathophysiology of AMS:

Although hypobaric hypoxia is the initial insult leading to AMS, the onset of AMS is delayed after initial exposure to high altitude, and the administration of oxygen does not completely relieve symptoms (35). This contrasts with the consequences of acute hypoxia, which occur immediately after an abrupt hypoxic

insult and are due directly to the effects of hypoxia. The symptoms of acute hypoxia are primarily due to cerebral hypoxia and are readily relieved by oxygen inhalation (35,76).

The delay in onset of AMS after ascent to high altitude suggests that it is the body's response to hypoxia, rather than the direct effects of hypoxia itself, that determines the character of the illness. These pathophysiologic responses to hypoxia in AMS include: relative hypoventilation (29,63); fluid retention and antidiuresis (29,31); shift of fluid from the extracellular to the intracellular space (41); increased CSF pressure (76); impaired pulmonary gas exchange (78); and decreased forced vital capacity (1).

Relative hypoventilation is seen in AMS and may be due to a low HVR, or ventilatory depression associated with AMS . It is unclear whether a low HVR measured at sea level correlates with susceptibility to AMS. Some investigators have found an association between low HVR values and susceptibility to AMS (63). Other studies show no correlation between the HVR measured at sea level and the severity of AMS on ascent to altitude (78). In individuals with established cases of AMS, however, lower alveolar ventilation and a higher PaCO2 are observed as compared to healthy individuals at the same altitude (29,78). Furthermore individuals susceptible to AMS show a greater blunting of ventilation in

response to respiratory alkalosis at high altitude (63). A very low HVR measured before ascent to altitude may indicate susceptibility to AMS, but for the majority of individuals with intermediate HVR values, ventilatory drive probably has no predictive value (35). The relative hypoventilation seen in AMS, then, may be primarily due to ventilatory depression associated with the CNS effects in AMS.

Antidiuresis, peripheral edema, and weight gain occur early in the development of AMS (29,31,76), whereas those individuals who remain healthy on ascent to high altitude diurese one to five liters (76). Relative hypoventilation (the absence of hypocapnia) is associated with water retention and weight gain in AMS (29), although the mechanism for this relationship is unclear. Possible mechanisms contributing to fluid retention in AMS include: increased antidiuretic hormone (ADH); abnormalities in the renin - aldosterone axis; and intracellular fluid shifts. A study by Hackett and colleagues demonstrated increased blood ADH levels in individuals with AMS (28). It could not be discerned, however, whether increased ADH is a primary abnormality that is a major factor in the pathophysiology of AMS, or followed as a result of AMS. Increased ADH secretion could be an appropriate secondary response to intravascular volume depletion from fluid shifts out of the vascular bed, or simply a direct result of stress. Nausea,

a common symptom in AMS, also stimulates ADH release (44). Other studies have failed to show changes in blood ADH levels, or urinary ADH excretion, at high altitude (44).

Some investigators have examined the renin-aldosterone axis during ascent to high altitude. At rest, hypoxia results in decreased plasma renin activity (PRA) (4,44). Although exercise at sea level results in increased PRA, studies measuring PRA during exercise at high altitude have shown conflicting results. One study demonstrated significantly lower levels of PRA during exercise at high altitude that were not related to beta - adrenergic activity (4), while other studies have demonstrated increased PRA during exercise at high altitude (44). Plasma aldosterone levels, however, are depressed both at rest and during exercise at high altitude (4,44). It is tempting to speculate that those individuals susceptible to AMS do not suppress aldosterone secretion to the same degree as individuals who remain healthy at high altitude. Measured aldosterone levels in individuals with AMS, however, have been surprisingly low (44), and thus cannot explain fluid retention. Interestingly, in a double blind placebo - controlled study, spironolactone was shown to be partially effective in preventing AMS (56). Angiotensin converting enzyme (ACE) also is reduced during hypoxia, and those individuals susceptible to AMS show less of a reduction in ACE levels as

compared to healthy individuals (60). Some studies of the renin - angiotensin system, however, have shown no consistent changes (35). The role of atrial natriuretic factor in the development of AMS has not been well studied.

With ascent to altitude, a shift of fluid from the extracellular and interstitial compartments to the intracellular space is well established, and can be as much as three liters in volume (41). A possible mechanism for the intracellular fluid shift might be failure of the sodium pump, Na+ - K+ ATPase, resulting in intracellular sodium retention and consequent water accumulation (16). These fluid shifts may increase brain tissue water and contribute to the CNS symptoms in AMS and progression to HACE (42).

Increased intracranial pressure has been observed in more advanced cases of AMS (76), suggesting a similar pathophysiology as discussed for HACE. Cellular swelling due to hypoxic injury, or vasogenic edema from increased permeability of the blood brain barrier, may cause the increased intracranial pressure in both AMS and HACE (40). The fact that dexamethasone improves AMS (14,50) and possibly also vasogenic cerebral edema, but not other types of cerebral edema, suggests that vasogenic edema may be a mechanism in AMS (35).

The etiology of headache in AMS is unclear, and may be due to increased intracranial pressure, increased cerebral blood flow, or

cerebral vasoconstriction - similar to a migraine episode. Hypoxia and hypercapnia dilate, while hypocapnia constricts the cerebral blood vessels (49). Some authors speculate that the hypocapnic hypoxia of altitude favors cerebral vasodilation, and may be responsible for the headache in AMS (49). The relative hypoventilation in AMS leads to higher PaCO2 and lower PaO2 values (29) that would tend to cause cerebral vasodilation. Studies measuring cerebral blood flow at high altitude have shown conflicting results; some studies reveal increased cerebral blood flow (2) and others show no change (39). Studies using CO2 rebreathing to relieve high altitude headache also have had conflicting results. A recent study by Harvey and colleagues indicates that breathing a 3% CO2 mixture in ambient air at high altitude relieved the headache in AMS (43), and the authors speculate that this is due both to increased oxygen delivery to the brain and to cerebral vasodilation. Hackett points out that relief of headache in this study could have been due to increases in PaO2 observed in the subjects, rather than to any effect of cerebral blood flow (23). In the only study where subjects with AMS breathed an added CO2 mixture and had alveolar oxygen tension maintained at the same level as controls, the headache in AMS was not relieved (58). Based on experience treating individuals with AMS at 4200m on Mt. McKinley, Hackett and colleagues claim that

oxygen, but not increased cerebral blood flow, improves high altitude headache (23).

The clinical presentation in AMS is consistent with cerebral dysfunction, but pulmonary dysfunction also occurs. A decreased forced vital capacity and peak expiratory flow rate (1,76,57), and a 25% to 35% incidence of rales are observed in AMS (31,76). Impaired pulmonary gas exchange as evidenced by an increased alveolar to arterial oxygen pressure difference (A-a oxygen gradient or (A-a)DO2) is also seen in AMS, indicating a greater degree of hypoxemia for a given level of ventilation. Sutton and colleagues showed that an increasing (A-a)DO2 on exposure to 5360 m correlated with more severe symptoms of AMS (78), while Hackett found that individuals at 4200m with moderate AMS had an (A-a)DO2 of approximately 16 torr as compared to an (A-a)DO2 of approximately 7 torr in healthy individuals (38). These findings are consistent with increased extravascular lung water in AMS, leading to interstitial and perivascular pulmonary edema.

Reeves found that (A-a)DO2 increased in seven subjects from 6 torr at sea level to 12 torr after acute exposure to 425 torr in a hypobaric chamber (66). In a more recent study subjects were gradually acclimatized to extreme altitude (4500m to 8800m) in a hypobaric chamber. Marked ventilation perfusion ($\dot{V}_A/\dot{Q}$) mismatching was observed with both exercise and acute increases in altitude,

and correlated with the level of pulmonary artery pressure. The pattern of development of $\dot{V}_A/\dot{Q}$ mismatch in this study, characterized by areas of shunt or very low $\dot{V}_A/\dot{Q}$ ratio, and the correlation with pulmonary artery pressure, suggested to the authors that pulmonary interstitial edema occurs in individuals without clinical evidence of HAPE at extreme altitude (85).

The low grade pulmonary edema that may occur in AMS appears to be distinct from HAPE. Schoene performed bronchoalveolar lavage on four individuals with AMS at 4200m on Mt. McKinley (72). Despite gas exchange abnormalities in AMS, the bronchoalveolar lavage fluid from subjects with AMS showed no evidence of abnormal protein or cell concentrations. This contrasts with HAPE where large concentrations of proteins and cells are seen in the bronchoalveolar lavage fluid.

The coexistence of pulmonary dysfunction and cerebral dysfunction in AMS raises the question of cause and effect. Impaired pulmonary gas exchange leads to a greater degree of hypoxemia for a given level of ventilation, and thus a greater degree of cerebral hypoxia. Some authors have speculated, however, that there may be a neurogenic component to the pulmonary edema at high altitude (13). Thus pulmonary dysfunction and cerebral dysfunction may each compound the other, but which comes first is still an unanswered question (24).

Natural History of AMS:

The natural course of AMS exhibits considerable individual variation. Singh (76) studied men, 18 to 53 years old, who were transported by ground or air from sea level to elevations of 3300m to 5500m as part of Indian military exercises. Symptoms began between six and 96 hours after arrival at high altitude. No correlation between the severity of illness and increasing altitude was found, but illness was aggravated by colder weather and physical activity. Symptoms were worse after air travel and correlated with time of ascent during road travel. Also, individuals with a prior history of AMS were more likely to experience symptoms after ascent to altitude. In 840 untreated individuals experiencing AMS, the duration of incapacitating illness varied from two to five days. During their prolonged stay at altitude, 38% were symptom free within three days, another 21% were symptom free within four to seven days, and another 25% were symptom free within eight to 21 days. The remaining approximately 15% required up to five months to become symptom free, with 1% (nine individuals) failing to acclimatize within six months.

Hackett studied 278 trekkers passing through 4243m in the Himalayas of Nepal (30), and also found unpredictable individual variation in the natural course of AMS. The overall incidence of AMS was 53%. AMS occurred more frequently in the young, in those

who flew to 2800m before trekking to 4243m, and in those who spent fewer nights acclimatizing en route. The severity of AMS was inversely related to age and the highest altitude attained, and was highly correlated with speed of ascent. Out of 146 individuals experiencing AMS, 63% were able to continue their ascent, dosing themselves with mild analgesics and sleeping pills for headache and insomnia. The remaining 37% had to stop ascending for two to three days to obtain relief of symptoms, or more often, had to descend and reascend later. Some (8.2%) required intensive medical therapy and evacuation because of the development of pulmonary and/or cerebral edema.

At the more intermediate altitudes of the ski resorts in the Rocky Mountains (2000 - 2500m) the natural history of AMS appears to be milder, although this has not been well studied. Montgomery reported that among 454 individuals travelling to Park City, Utah (2090m), or Steamboat Springs, Colorado (2100m), for week long medical meetings, 90% of AMS symptoms resolved within 72 hours of onset (61).

V. AMS: PREVENTION AND TREATMENT

Prevention of AMS:

Clearly the best prevention for AMS is a gradual ascent. If symptoms occur, descent is recommended early in the course of the illness to prevent progression. This is especially important in more isolated mountainous terrain where progression of AMS to a more severe form, or to HAPE or HACE, could require medical attention in a situation where rescue can be both difficult and dangerous. A common method used by mountaineers at high altitude to prevent AMS and aid acclimatization is to climb at higher altitudes and sleep at lower altitudes, moving the sleeping altitude up every few days. For individuals trekking at less extreme altitudes, sleeping two nights at the same altitude for every 600m gained above 3000m will achieve the same result. Proceeding to a higher sleeping altitude in the presence of symptoms is contraindicated (35).

Acetazolamide, a potent carbonic anhydrase (CA) inhibitor, is beneficial in the prophylaxis of AMS, decreasing both its incidence and severity (30,57,8). Inhibition of renal CA results in a bicarbonate diuresis and the generation of a metabolic acidosis. This increases inspiratory minute ventilation due to an increased hypercapnic ventilatory response (84,51). In individuals ascending

to high altitude, acetazolamide increases resting minute ventilation (57), decreases PaCO2, and increases PaO2 (8,51). Perhaps quite importantly, acetazolamide also decreases periodic breathing and increases arterial oxygen saturation during sleep at high altitude (37,80). Because of its diuretic action, acetazolamide may counteract the fluid retention that occurs in AMS (35). Acetazolamide also diminishes CSF production and volume, and possibly CSF pressure (75).

The effects of acetazolamide on CA are complex because of different isoenzymes of the enzyme. This causes a complex response to different doses of the drug; low doses of acetazolamide inhibit only renal CA, while higher doses inhibit both renal and RBC CA (7). The RBC contains both more CA isoenzyme II (the main renal and RBC enzyme) and contains an isoenzyme not found in the kidney that is ten fold less sensitive to inhibition by acetazolamide (81). Acetazolamide doses of less than 5 mg/kg produce no respiratory effect, but a marked renal effect (7).

Inhibition of renal CA results in a metabolic acidosis due to the renal loss of bicarbonate. Inhibition of RBC CA results initially in carbon dioxide retention and a respiratory acidosis. This occurs because CO2 does not completely equilibrate during its transit through the pulmonary capillary bed. Also, in the tissues inhibition of RBC CA reduces the fraction of metabolically produced

CO_2 that can be converted to HCO_3^- and carried in the RBC or plasma to the lungs. In order to effectively eliminate CO_2 in the lungs, a gradient is created with a high CO_2 in the tissues and venous circulation to a lower CO_2 in the lungs. The ensuing respiratory acidosis, particularly in the tissues of the CNS, increases minute ventilation. In normal individuals, both the metabolic acidosis caused by renal CA inhibition and the respiratory acidosis caused by RBC CA inhibition increase ventilation, improve PaO_2, and decrease $PaCO_2$. In individuals with lung disease or defects in ventilatory control, however, if minute ventilation does not increase in response to the respiratory acidosis caused by inhibition of RBC CA, an increase in $PaCO_2$ and a further drop in pH will result (81). Relative hypoventilation occurs in AMS (29) and a blunted ventilatory drive occurs in HAPE (70). Therefore, inhibition of RBC CA in individuals with AMS or HAPE may not be advantageous.

Benzolamide, a preferential renal CA inhibitor, prevents AMS and eliminates sleep periodic breathing at high altitude, but was found to be no better than acetazolamide for AMS prophylaxis (51,82). Still, Swenson suggests that low doses of acetazolamide (5 mg/kg), inhibiting only renal CA, may be most appropriate for prevention of both AMS and sleep periodic breathing at high altitude (81). Benzolamide might be ideal for this purpose, but

is not commercially available.

In an early study Cain used acetazolamide given as a one time dose of 750 mg and found that it was effective in preventing AMS during acute exposure to 4270m (8). Larson and colleagues used acetazolamide 250 mg every eight hours beginning one day before ascent in a study of climbers making a rapid ascent of Mt. Rainier (4394m) and demonstrated effective prophylaxis of AMS (57). Hackett suggests the use of low doses (125 to 250 mg) of acetazolamide twice daily beginning 24 hours before ascent to aid acclimatization and prevent AMS (35). Most authors recommend continuing acetazolamide for the first day or two at altitude, and then discontinuing the drug once acclimatization is established and the danger of AMS is passed. The 500 mg sustained release capsule taken once daily may be ideal for AMS prophylaxis. Once at altitude a dose as low as 125 mg every evening will result in less side effects and may still prevent sleep periodic breathing (34).

Dexamethasone, a potent synthetic glucocorticoid with negligible mineralocorticoid activity, also is effective in the prophylaxis of AMS in both passive and rapid active ascent to high altitude (14,50,67). Ellsworth demonstrated effective prophylaxis of AMS during rapid active ascent of Mt. Ranier (4394m) using 4 mg of dexamethasone every eight hours beginning 24 hours before ascent (14). Rock studied individuals exposed to a simulated altitude of

4570m in a hypobaric chamber for 45 hours and determined that 4 mg of dexamethasone every 12 hours, but not 1 mg every 12 hours, was effective in preventing AMS (67). Dexamethasone did not alter fluid balance or plasma volume, but did suppress cortisol secretion. Dexamethasone 2 mg every six hours beginning one hour prior to air transport from sea level to 4200m was not effective in preventing AMS in military personnel who were physically active after arrival at altitude (25). Therefore, it appears that 4 mg every 12 hours is the minimum dose of dexamethasone effective in the prevention of AMS. Although dexamethasone may be as effective as acetazolamide in preventing AMS (14), most authors warn that because of the potential toxic effects of dexamethasone its use should be reserved for treatment of severe AMS, or for prophylaxis in individuals allergic to acetazolamide (35,14).

Treatment of AMS:

The most effective treatment for AMS is descent to an altitude below that where the first symptoms of AMS were experienced. Still, it is clear that in many individuals symptoms will resolve after halting ascent and waiting for acclimatization to improve, which may take several days or longer (30,76). Proceeding to a higher altitude in the presence of symptoms is contraindicated as it may lead to HAPE or HACE, and immediate descent should be

undertaken if there is any evidence of an abnormal neurological examination (ataxia or changes in consciousness) or with evidence of pulmonary edema (35). In some situations, however, descent may not be an option because of adverse weather conditions encountered by both climbers and trekkers in the high mountain ranges of the world. Therefore, effective pharmacological treatment for AMS has been sought.

Oxygen, if available, is effective in relieving the symptoms of AMS. In addition to increasing PaO2, oxygen also lowers pulmonary artery pressure (48) and reduces cerebral blood flow (36,23). Oxygen is particularly effective in improving disordered sleep in AMS, and may be given at low flow rates (1-2L/min) during the night. Oxygen many times, but not always, relieves the headache associated with AMS (35). Still, most experienced mountain doctors and lay mountaineers have consistently observed that descent is more effective than oxygen in the treatment of AMS (24). Also, when oxygen therapy is discontinued, symptoms of AMS return. When combined with the bulk and expense of carrying supplemental oxygen, this provides further motivation for finding effective pharmacological treatment.

Symptomatic therapy for AMS includes analgesics such as aspirin and acetaminophen (35). Aspirin is useful in reducing headache and promoting sleep, but is not effective for treating

other symptoms of AMS (76). Prochlorperazine (compazine) can be given for the nausea and vomiting and has the advantage of augmenting the HVR (64). Other antiemetics may depress the HVR. Persons with AMS should avoid alcohol and sedative hypnotics near bedtime because of the danger of respiratory depression during sleep (35). Short-acting, short half-life, benzodiazepines are probably safe to use (34), but if insomnia is primarily due to periodic breathing the respiratory stimulant acetazolamide is superior (37,80). Almitrine, used to increase SaO2% during sleep at sea level in patients with COPD, also improves SaO2% during sleep at high altitude, but increases periodic breathing - apparently by increasing the HVR (37).

The respiratory alkalosis at high altitude serves to decrease central respiratory drive and, at least theoretically, an agent that normalizes the blood pH at high altitude might be useful in treating AMS. However, Singh gave ammonium chloride orally, in a dose of 2 gm three times a day for three days, to 30 patients with AMS and found that it resulted in no improvement in symptoms. In fact, 23 patients felt worse after ammonium chloride therapy (76). This is surprising because one of the presumed mechanisms for the increase in central ventilatory drive seen with acetazolamide is the generation of a metabolic acidosis.

Adding CO2 to inhaled air also has been used for the treatment of AMS. In a recent study, Harvey and colleagues found that breathing a 3% CO2 mixture in ambient air at altitudes between 3400m and 5400m relieved the symptoms of AMS, increased PaO2, and decreased blood pH (43). The clinical benefit lasted for 30 to 60 minutes after inhalation of CO2, but symptoms returned on breathing of ambient air.

Dexamethasone is effective in the treatment of AMS after both passive and active ascent to high altitude (15,25,55). Ferrazzini used an 8 mg dose initially and then 4 mg every six hours in 17 individuals with AMS at 4459m in the Alps. Dexamethasone relieved symptoms, improved arterial oxygen saturation, and slightly, but significantly, improved forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) as compared to placebo (15). Hackett treated 11 individuals with AMS after air transport from sea level to 4400 m on Mt. McKinley with a 4 mg dose of dexamethasone, given IM or PO, and noted relief of symptoms in 24 hours. Dexamethasone was discontinued after 24 hours and five of 11 developed symptoms again (25,33). Levine and colleagues conducted a double blind, placebo - controlled, crossover trial using dexamethasone in the treatment of AMS after ascent to 3700m in a hypobaric chamber by six subjects (55). Dexamethasone relieved the symptoms of AMS, but in spite of this, one subject had

mild cerebral edema on brain CT after both placebo and dexamethasone. Dexamethasone had no effect on oxygenation, sleep apnea, urinary catecholamine levels, the appearance of chest radiographs or perfusion scans, serum electrolyte levels, intravascular volume, hematologic profiles, or the results of psychometric tests. All authors agree that because of the potential side effects of dexamethasone, and the question of whether it improves pathophysiologic changes occurring in AMS at high altitude, its use should be reserved for situations in which descent is impossible or in conjunction with descent to facilitate a patient's cooperation with evacuation efforts.

Fluid retention in AMS provides a rationale for treatment with diuretics. Singh and colleagues found that furosemide, 80 mg every twelve hours for two days, effectively prevented AMS in Indian military personnel airlifted from sea level to 3500m, and decreased dyspnea in the treated group. They also used furosemide for the treatment of AMS with successful results (76). In the only other study, furosemide, 40 mg twice a day, was given to five subjects airlifted to 5400m on Mt. Logan, in Canada. All five subjects developed severe AMS and the authors, Gray and colleagues, speculated on the possible deleterious role of dehydration (21). The contrast in results between these two studies is striking, and might be explained by the different environments. Both studies

used military personnel airlifted from low altitude to high altitude, but the environment was very different in the two studies. First, the altitude was higher in the North American study than in the Himalayan study; 5400m as compared to 3500m. More important, though, Singh conducted his studies at Indian military bases below the glacier level in the Himalaya, while Gray's study took place at a research camp high on a glacial plateau on Mt. Logan. The stresses of daily life are much greater living on a glacier; snow must be melted for water, tents are used for sleeping, and temperatures are colder. These factors increase required physical activity and the potential for dehydration. Gray's study more closely resembled situations encountered by climbers at high altitude, and has discouraged subsequent use of furosemide in North America. Still, furosemide might be helpful in treating severe AMS or HAPE in more controlled situations and warrants further study.

VI. ACETAZOLAMIDE IN THE TREATMENT OF AMS

VI.A. BACKGROUND

Acetazolamide has been used for the treatment of AMS, but only one controlled clinical study supports this practice. Bradwell and colleagues studied 12 individuals with AMS during a ten day ascent to 5400m in a double blind, placebo controlled, design that is published only in abstract form (5). Subjects were randomly assigned to receive acetazolamide 1500 mg in a single dose or placebo, and were stratified according to previous altitude performance. The authors did not define in the abstract how they diagnosed AMS. Five subjects were randomized to the acetazolamide group and three showed improvement in symptoms in one to six hours, the other two showed improvement in symptoms in 24 hours. Of the seven subjects randomized to the placebo group, two showed improvement in symptoms and five were worse overnight. After 24 hours the placebo group crossed over to acetazolamide, with four subjects receiving a single dose of 1500 mg and three subjects a single dose of 250 mg. Six out of seven subjects in the crossover study improved in one to eight hours and one remained unchanged (the authors did not distinguish between higher and lower dose acetazolamide in the crossover study). Arterialized ear lobe capillary PO2 levels were increased in the acetazolamide - treated

subjects, including crossovers, as compared to controls. Interestingly, three individuals who were not included in the study because they did not have AMS took 1500 mg of acetazolamide in a single dose at 5400m and developed severe headache and nausea.

Bradwell and colleagues concluded that acetazolamide is effective in the treatment of AMS. However, there are several problems with this study. First, acetazolamide doses of 1500 mg are higher than any reported previously for the prophylaxis of AMS. Because higher doses inhibit red cell CA as well as renal CA, lower doses may be more efficacious than higher doses. Second, at the doses used in this study, a true double blind design probably was not maintained. As Sutton points out, the frequency of paresthesia and increased urination make it difficult to conduct a true double blind study with acetazolamide (80). Lastly, ear lobe capillary PO2 levels are not accurate with local reductions in blood flow (20), as may occur at high altitude because of peripheral vasoconstriction secondary to cold, stress, and hypoxemia.

Hackett has also proposed that acetazolamide might be useful in the treatment of AMS. In an uncontrolled study of five subjects with AMS, acetazolamide reduced the A-a gradient for O2 (Hackett, personal communication). This study suggested that acetazolamide may be beneficial in the treatment of AMS in part because it improves pulmonary gas exchange. A decreased (A-a)DO2 combined

with the increase in ventilation seen with acetazolamide might lead to marked improvements in blood oxygenation and symptoms.

VI.B. HYPOTHESIS AND SPECIFIC AIMS

The purpose of this thesis was to validate the current clinical use of acetazolamide in the treatment of AMS, and to further investigate the effect of acetazolamide on gas exchange, in a placebo controlled clinical trial. The hypothesis was that acetazolamide is useful in the treatment of AMS because it relieves symptoms and improves pulmonary gas exchange. In order to confirm or refute the hypothesis the specific aims of this study were to: 1) determine the efficacy of acetazolamide in the treatment of AMS as judged by symptom scores; 2) determine the effect of acetazolamide on the A-a gradient for O2 in individuals with AMS; 3) observe the correlation between change in symptoms of AMS and change in the A-a gradient in AMS.

If acetazolamide improves the symptoms of AMS and improves pulmonary gas exchange, it would support a current clinical use of acetazolamide, and would suggest one possible mechanism for acetazolamide's benefit in the treatment of AMS. Improvement in gas exchange might directly relieve those AMS symptoms due to pulmonary dysfunction. Improvement in gas exchange would also improve cerebral oxygen delivery, and might relieve those AMS

symptoms attributed to CNS hypoxia. If acetazolamide improves gas exchange it might also be useful in the prophylaxis of HAPE. The low grade pulmonary edema that presumably causes the impaired gas exchange in AMS could be the precursor of HAPE, and thus treatment of AMS might prophylax against HAPE.

If acetazolamide improves the symptoms of AMS but does not improve gas exchange, it would indicate that there may be other beneficial mechanisms of acetazolamide that require further investigation. For example, acetazolamide may be useful in AMS because of its ability to lower CSF production and volume, perhaps decreasing intracranial pressure (75).

Finally, if this study shows that acetazolamide does not improve the symptoms of AMS, but does improve pulmonary gas exchange, it would suggest that functional changes in the central nervous system may have occurred in AMS that cannot be reversed by improving pulmonary function. It also would indicate that current clinical use of acetazolamide for therapy of AMS might be inappropriate.

VI.C. METHODS

Site of Project:

This study took place during a four week period in June 1989 at the Denali Medical Research Project high altitude research station on Mt. McKinley (Denali), Alaska, where studies on high altitude illness have taken place since 1982. All high altitude studies were completed in a heated (15°C) laboratory shelter (Weatherport, Gunnison, CO) on a glacier at 4200m, on the West Buttress Route of Denali. This medical research facility is located at the "14,000 ft. camp" on the West Buttress Route which was attempted by over 700 climbers during the May to June climbing season in 1989. Because of its location on a large glacial shelf at an altitude that is ideal for acclimatization before attempting the 6150m summit of Mt. McKinley, the 14,000 ft. camp is continuously occupied during May and June. This provides an ideal population for the study of altitude illness, especially given the excellent cooperation from climbers in participating in medical research on Denali. Climbers reach the 14,000 ft. camp after ascending from the air landing strip at 2100m (7,000 ft.) on the Kahiltna glacier. This takes about one week depending on the size and strength of the party.

Subjects:

Subjects with AMS, and with onset of symptoms at 4200m within 24 hours, were recruited from among approximately 350 climbers that passed through the 14,000 ft. camp during June 1989. Approval for this study was obtained from the University of Alaska Anchorage Institutional Review Board, and informed consent was obtained from volunteers. Information regarding the study and the inclusion criteria (Table 1) were conveyed to the climbing community through discussions with climbers and guides. The medical research camp is located about 30 meters from the climbers' camp, and many climbers come to the medical research camp to ask questions, to obtain medical care, or simply to have their percent saturation of hemoglobin with oxygen (SaO2%) measured with a digital pulse oximeter. In that case information about the study was discussed with the climbers.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria:	Exclusion Criteria:
1. AMS as judged by symptom scores.*	1. Acetazolamide use within the past week.
2. Less than 60 years of age.	2. Sulfa allergy.**
	3. HAPE.
	4. HACE.
	5. Heart disease.
	6. Renal disease.
	7. Liver disease.
	8. Pregnancy.

*refer to Table 2

** Subjects with a history of sulfa-drug allergy were excluded from the acetazolamide group and were non-randomly assigned to the placebo group.

The study group consisted of 12 volunteers, 11 men and one woman, from the climbers' camp at 4200m on Denali. With an incidence of AMS on Denali of 30% (32), about 100 of the climbers passing through the 14,000 ft. camp during the time period of this study would have had AMS at some point during their climb. Several factors account for the small size of the study group compared to a relatively large number of potential subjects. First, only subjects who experienced symptoms of AMS at 4400m were included in the study. Some climbers experience symptoms of AMS before reaching the 4400m, and may delay their climb at lower altitudes until symptoms resolve. Other climbers may not experience symptoms until reaching 5150m (the 17,000 ft. camp). Even if those with AMS at 5150m descended to 4400m, they were not used in the study because symptoms would most likely improve with descent. Secondly, the benefit of acetazolamide in the prophylaxis of AMS is well known among climbers on Denali. Some take acetazolamide prophylactically, or therapeutically, even though the benefit of acetazolamide in the treatment of AMS is unproven. Lastly, not all individuals with AMS agreed to enter the study.

Assessment of AMS:

The AMS Symptom Questionnaire was used to diagnose AMS and evaluate severity (Table 2). The AMS Symptom Questionnaire has

been used in several studies requiring diagnosis and evaluation of AMS (31,25,26). Scores on the AMS Symptom Questionnaire also correlate well with scores on the Environmental Symptom Questionnaire (25) used by other authors (50,55).

The AMS Symptom Questionnaire, along with an interview and examination technique, was used by an investigator to evaluate seven different AMS symptoms. Milder symptoms received a score of 1, and more severe symptoms received a score of 2 or 3. For some symptoms the interviewer graded severity, assigning a score of 1, 2, or 3. For other symptoms, only mild or only severe, scoring was predetermined. For example, insomnia, as defined by difficulty falling asleep or frequent awakening, received a score of 1. Dizziness received a score of 1. Lassitude, in contrast, received a score of 3 if the severity was such that a subject required assistance with tasks of daily living. Less severe lassitude was not scored in the AMS Symptom Questionnaire, as it was subjectively difficult to evaluate. An AMS symptom score of 2 or greater was used to diagnose AMS.

Table 2. AMS Symptom Questionnaire

SYMPTOM	REMARKS	SCORE
Headache	transient, relieved with analgesic	1
	severe or not relieved with analgesic	2
Insomnia	difficulty falling asleep, frequent waking	1
Dizziness		1
Ataxia	difficulty maintaining balance	1
	steps off line	2
	falls to ground or cannot finish test	3
Severe Lassitude	requires assistance for tasks of daily living	3
Anorexia or Nausea	true anorexia, not distaste for diet	1
Vomiting		2
Dyspnea on Exertion	dyspnea forces frequent halts, slow to recover	2
Dyspnea at Rest	marked dyspnea at rest	3

A global functional assessment was also made at the time of the interview and examination by the evaluating investigator (Table 3). On a scale of 0 to 4 this estimated the overall degree of impairment of the subject's activities with respect to continuing or halting ascent.

Table 3. Global Functional Assessment

Global Functional Assessment	no symptoms	0
	symptoms, but able to continue	1
	symptoms, stopping ascent	2
	intensive medical treatment and/or evacuation to lower altitude required	3

Double Blind Study Design:

Entrance criteria required that subjects had symptom scores of 2 or greater on the AMS Symptom Questionnaire. Baseline evaluation included a physical examination and measurements of pulse, blood pressure, and respiratory rate. The percent saturation of hemoglobin with oxygen (SaO2%) was measured with the subject in the sitting position using a portable finger pulse oximeter (Criticare 503+). Spirometry measurements included forced vital capacity (FVC) and peak expiratory flow (PEF). FVC was measured with a hand held turbine spirometer (Boehringer Laboratories, Wynnewood, PA) and PEF was measured with a mini-Wright's peak flow meter (Clement Clark, Ltd., England). End tidal CO2 ($P_{ET}CO2$) was measured with the subject in the sitting position using an infra-red CO2 analyzer (Beckman LB-2). A baseline arterial blood gas sample was drawn into a heparinized syringe from the radial artery after infiltration with lidocaine.

After the above baseline measurements, subjects were randomly assigned to receive either acetazolamide or placebo in a double blind fashion. Subjects reporting a history of sulfa-drug allergy were non-randomly assigned to the placebo group (one subject). The dose of acetazolamide was 250 mg or placebo at time zero, and acetazolamide 250 mg or placebo at eight hours. Packets assigning randomization to acetazolamide or placebo were prepared in blocks

of four by an independent observer from the staff of the medical research camp. The same independent observer administered doses of acetazolamide or placebo by crushing 250 mg acetazolamide tablets and mixing with an orange drink or by giving an equal amount of orange drink alone. The principal investigator was not present during preparation or administration of the study drug. After the above baseline measurements subjects returned to their camp. Subjects were not permitted to use any self prescribed drugs during the study.

Subjects presented to the medical research camp eight hours after entry to receive the second dose of acetazolamide or placebo. Measurements of pulse, respiratory rate, and SaO2% were repeated. Subjects again returned to their camp.

Subjects presented to the medical research camp at 24 hours after inclusion for a repeat assessment of AMS symptoms using the AMS Symptom Questionnaire. A physical examination was done that included measurement of pulse, respiratory rate, blood pressure, and SaO2%. Measurements of FVC, PEF, and $P_{ET}CO2$ were repeated. A second arterial blood gas sample was drawn from the radial artery. This concluded the double blind portion of the study.

Single Blind Crossovers:

At the end of 24 hours, after the second assessment of AMS symptoms, physical exam, and physiological measurements, subjects who still had a symptom score of 2 or greater were offered the option of crossing over in the study by the independent observer. Three subjects agreed, and all crossed over from placebo to acetazolamide. The only subject from the acetazolamide group eligible to crossover to placebo, subject 6, declined to continue in the study. Following their decision to continue in the study, the independent observer revealed to all three subjects who crossed over from placebo to acetazolamide that they had been on placebo during the first 24 hours. This was done at the subjects' request. Investigators involved in the study remained blinded as to whether the subject was on acetazolamide or placebo.

Subjects choosing to crossover were given acetazolamide 250 mg at 24 hours and again at 32 hours after initial entry. At 48 hours another assessment of AMS using the AMS Symptom Questionnaire was done, and a physical examination was performed that included measurement of pulse, blood pressure, respiratory rate, and SaO2%. PEF, FVC, and $P_{ET}CO2$ were measured using the same methods as at time zero and 24 hours and a third arterial blood gas sample was drawn from the radial artery.

Measurement of (A-a)DO2:

Arterial blood gas samples drawn at time zero and at 24 and 48 hours were used for measurement of the arterial partial pressure of oxygen (PaO2) and partial pressure of carbon dioxide (PaCO2) using a blood gas analyzer (Instrumentation Laboratories Micro 13). All samples were placed on ice and analyzed within 30 minutes.

The partial pressure of alveolar oxygen (PAO2) was calculated from a simplified version of the alveolar air equation, (PAO2 = PIO2 - PACO2/R), assuming a respiratory exchange ratio (R) of 0.85 (1890). The partial pressure of alveolar carbon dioxide (PACO2) was determined from end tidal CO2 using an infra-red CO2 analyzer (Beckman LB-2). The apparent respiratory exchange ratio was measured for two subjects using standard techniques (88). The respiratory exchange ratio was .80 for subject 9 and .88 for subject 10.

Data Analysis:

Change in (A-a)DO2 over 24 hours in the acetazolamide and placebo groups were compared using the Mann-Whitney Rank-Sum test (two-tailed). Symptom score data from the placebo and acetazolamide groups were compared using the Mann-Whitney U-test (two-tailed). Correlation between change in AMS symptom score over 24 hours and change in (A-a)DO2 over 24 hours in both the

acetazolamide and placebo groups was evaluated using the Spearman Rank Correlation Coefficient. Change in SaO2%, PEF, FVC, $P_{ET}CO2$, PaCO2, and PaO2 over 24 hours in the acetazolamide and placebo groups were compared using the Mann-Whitney Rank-Sum test. For all methods used in data analysis, a p value of less than .05 was accepted as indicating statistical significance.

Nonparametric methods were used to determine statistical significance rather than the more commonly used parametric methods, such as Student's t test. Parametric methods are based on the assumption that the observations are drawn from normally distributed populations. When the sample size is small or when the population studied deviates from normality, interpreting the mean and standard deviation in terms of a normal distribution may give a misleading picture. In contrast, nonparametric methods use information about the relative sizes of the observations and does not assume that the sample population is representative of a normally distributed population. When the observations are drawn from populations that are not normally distributed, nonparametric methods are not only more reliable but also more powerful (19). Nonparametric methods are therefore more appropriate in this study for two reasons. First, the sample size is small. Second, the observations are made at high altitude where the normal distribution of physiologic parameters is not well documented.

VI.D. RESULTS

Subject Population:

The 12 subjects included 11 men and one woman ranging in age from 25 to 46. All subjects lived at sea level and were non-smokers, except for subject 1 who smoked cigarettes. The average number of days spent climbing from 2100m to 4400m was 8.9, and the average number of nights at the 14,000 ft. camp before inclusion in the study was 1.8. Nine out of the 12 subjects reported a past history of altitude illness. Of those nine, three had a past history of AMS and high altitude headache, four had a past history of AMS without high altitude headache, and two gave a past history of high altitude headache alone. None of the subjects reported a past history of HAPE or HACE. All subjects had climbed above 3000m prior to their attempt on Denali, eight had climbed above 4000m, and two had climbed to 6800m in South America. Seven subjects were members of guided parties. The subject populations randomized to receive placebo or acetazolamide are compared in Tables 4 and 5.

All subjects in the study had Global Functional Assessment Scores of 1 or 2, and these data are not listed in the results. Instead, success in reaching the summit after concluding the study was used as a general indicator of the overall degree of impairment of the subject's activities with respect to continuing or halting ascent. This information is listed in Tables 4 and 5 under

comments as reached summit, attempted summit, or descended.

Table 4. High Altitude History: Placebo Group

Sub	Sex	Age	Altitude*** Climbing Hx	Hx of High** Altitude Illness	nights at 14K* Prior to Study
#3	M	37	4000 m	AMS and Headache	1
#4	M	46	3000 m	none	2
#5	F	31	6800 m	AMS	3
#8	M	42	3000 m	none	2
#10	M	32	4000 m	AMS	1
#12	M	40	4000 m	AMS	1
mean age=		$\overline{38.0}$	±5.8 SD	mean # nights=	$\overline{1.7}$

Table 5. High Altitude History: Acetazolamide Group

Sub	Sex	Age	Altitude*** Climbing Hx	Hx of High** Altitude Illness	nights at 14K* Prior to Study
#1	M	32	6800 m	AMS and Headache	1
#2	M	28	4000 m	Headache	3
#6	M	25	3000 m	AMS and Headache	3
#7	M	29	4000 m	AMS	0
#9	M	32	3000 m	Headache	1
#11	M	31	3000 m	none	3
mean age=		$\overline{29.5}$	±2.7 SD	mean # nights=	$\overline{2.0}$

*** Altitude climbing history denotes approximate highest altitude reached on previous climbs. Choices were above 3000 m, above 4000 m, or if above 5000 m then actual altitude.

** Choices for history of altitude illness were AMS, high altitude headache, HACE, or HAPE.

* Number of nights at 14,000 ft. camp before inclusion in study.

Table 6. AMS Symptom Scores: Placebo Group

Subj	AMS Symptom Score** 0 hrs	24 hrs	Change in*** AMS Score	Comments
#3	5	4	(-1)	descended[+]
#4	6	2	(-4)	reached summit
#5	5	2	(-3)	attempted summit
#8	2	3	(+1)	reached summit[+]
#10	2	2	(0)	reached summit[+]
#12	3	2	(-1)	reached summit
mean*	$\overline{3.8 \pm .7}$	$\overline{2.5 \pm .3}$	$\overline{(-1.3 \pm .8)}$	

Table 7. AMS Symptom Scores: Acetazolamide Group

Subj	AMS Symptom Score** 0 hrs	24 hrs	Change in*** AMS Score	Comments
#1	4	1	(-3)	reached summit
#2	4	1	(-3)	not known
#6	4	2	(-2)	descended
#7	3	1	(-2)	developed HAPE
#9	4	1	(-3)	reached summit
#11	4	0	(-4)	descended
mean*	$\overline{3.8 \pm .2}$	$\overline{1.0 \pm .2}$	$\overline{(-2.8 \pm .3)}$	

* For both groups n=6, mean $\pm$ SE is given.
** $p<.01$ for comparison of symptom score after 24 hours between groups, Mann-Whitney U-test.
*** $p>.05$ for comparison of change in symptom score over 24 hours between groups, Mann-Whitney U-test.
[+] Crossover to acetazolamide after double blind study.

Figure 1. Change in AMS Symptom Score: Acetazolamide Group

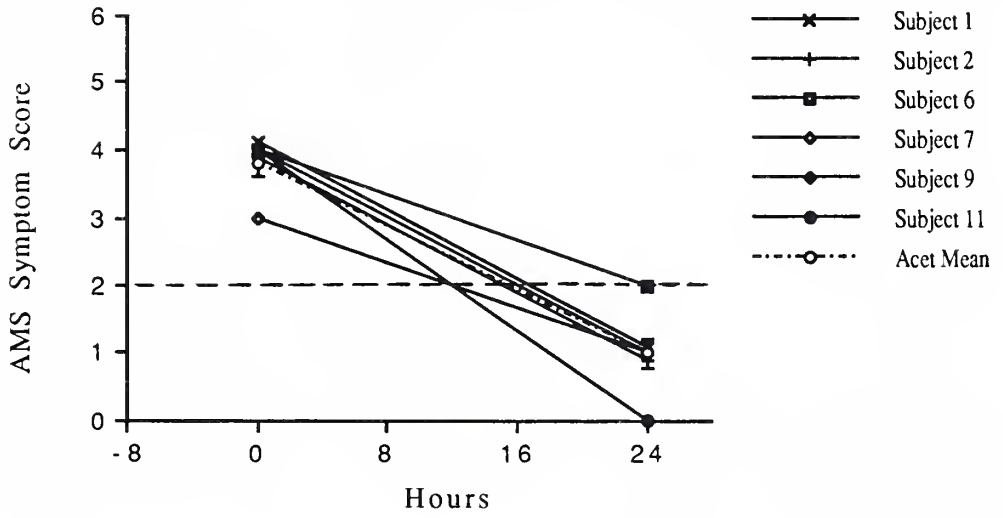
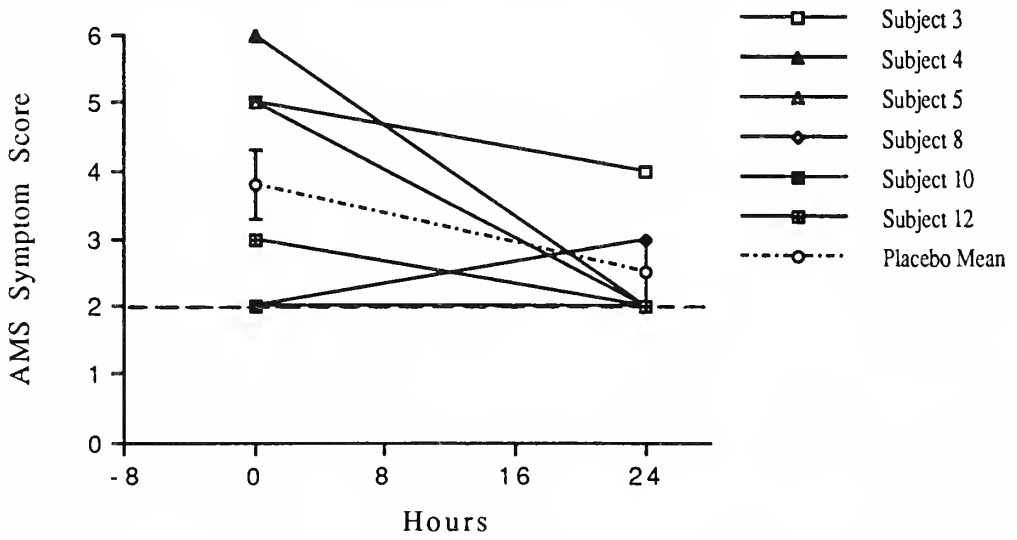


Figure 2. Change in AMS Symptom Score: Placebo Group



Figures 1 and 2. Change in AMS symptom score over 24 hours in the acetazolamide and placebo groups. The dark horizontal dashed line corresponds to a symptom score of 2, the minimum symptom score defining AMS. Assessment of AMS was made at 0 and 24 hours. Change in symptom score over 24 hours for each subject is indicated by the solid lines. Mean change in symptom score for each group is indicated by the light dashed lines. Error bars indicate $\pm$ standard error for the mean at 0 and 24 hours.

Table 8. Presence or Absence of AMS after 24 Hours

	AMS*	Healthy*
Acetazolamide	1	5
Placebo	6	0

p<.05**

* "AMS" indicates the number of subjects who had clinically defined AMS after 24 hours as defined by symptom scores of 2 or greater. "Healthy" indicates the number of subjects who had symptom scores of less than 2 after 24 hours.

** Mann-Whitney U-test.

AMS Symptom Score Data:

Inclusion criteria dictated that all subjects entering the study had AMS symptom scores of 2 or greater. Twelve subjects were entered into the double blind portion of the study with equal numbers in the acetazolamide and placebo groups. Subject 12 was non-randomly assigned to the placebo group after reporting a history of sulfa-drug allergy.

Symptom score data are shown in Tables 6 and 7. At 24 hours five out of six subjects in the acetazolamide group were healthy with AMS symptom scores of less than 2, and all six subjects in the placebo group still had AMS with symptom scores of 2 or greater ($p<.05$, Table 8). The one subject in the acetazolamide group still exhibiting clinically defined AMS after 24 hours (subject 6) had an AMS symptom score of 2, improved from an initial score of 4.

AMS symptom score after 24 hours was also significantly different between groups ($p<.01$, Tables 6 & 7). However, the change in AMS symptom score over 24 hours was not significantly different between groups ($p>.05$, Tables 6 & 7). The improvement in symptom score over 24 hours occurring in both groups is graphically displayed in Figures 1 and 2.

Change in (A-a)DO2 and PaO2:

Data on (A-a)DO2 was not obtained on all subjects during the double blind portion of the study because some radial puncture samples had values more consistent with venous blood and the subjects declined a second attempt at a radial artery blood draw. Data on change in (A-a)DO2 over 24 hours were obtained in three subjects in the acetazolamide group and six subjects in the placebo group. In the acetazolamide group two out of three subjects had a decrease in (A-a)DO2 over 24 hours, and in the placebo group five out of six subjects had an increase in (A-a)DO2 over 24 hours. Change in (A-a)DO2 over 24 hours was significantly different between the placebo and acetazolamide groups at the $p<.05$ level (Table 9,Figures 3 & 4). This appears to be more a result of an increase in the A-a gradient in the placebo group, rather than a decrease in the A-a gradient in the acetazolamide group.

Data on change in PaO2 over 24 hours was obtained on three subjects in the acetazolamide group and six subjects in the placebo group. All three subjects in the acetazolamide group increased their PaO2 over 24 hours, and four out of 6 in the placebo group decreased their PaO2 over 24 hours. Change in PaO2 over 24 hours was significantly different between the placebo and acetazolamide groups at the $p<.05$ level (Table 10,Figures 5 & 6).

Changes in PaCO2, $P_{ET}CO2$, SaO2%, FVC, and PEF over 24 hours were not significantly different between the acetazolamide and placebo groups (Table 11). A larger sample size, however, might have revealed significant differences in the change of some of these parameters between the acetazolamide and placebo groups. For example, the mean change in PaCO2 for the acetazolamide group appears significantly different from the mean change in PaCO2 for the placebo group. However, nonparametric methods, which do not rely on mean values, were used to determine statistical significance.

Table 9. Change in (A-a)DO2 Over 24 hrs in Double Blind Study

Acetazolamide				Placebo			
Subject	(A-a)DO2 in torrs			Subject	(A-a)DO2 in Torrs		
	0hrs	24hrs	Change		0hrs	24hrs	Change
#6	8.2	8.5	(+0.3)	#3	7.3	10.4	(+3.1)
#9	12.1	11.4	(-0.7)	#4	12.2	12.1	(-0.1)
#11	6.8	4.7	(-2.1)	#5	5.2	7.0	(+1.8)
				#8	14.3	18.9	(+4.6)
				#10	10.8	14.8	(+4.0)
				#12	2.9	9.4	(+6.5)
		mean =	$\overline{(-0.8)}$			mean =	$\overline{(+3.3)}$
		SE =	$\pm$0.7	p<.05*		SE =	$\pm$0.9

* Change in (A-a)DO2 is significantly different between the placebo and acetazolamide groups using the Mann-Whitney Rank-Sum Test.

Table 10. Change in PaO2 Over 24 Hours in Double Blind Study

Acetazolamide				Placebo			
Subject	PaO2 in torrs			Subject	PaO2 in torrs		
	0hrs	24hrs	Change		0hrs	24hrs	Change
#6	40.5	44.0	(+3.5)	#3	47.0	42.0	(-5.0)
#9	41.0	44.3	(+3.3)	#4	43.0	44.0	(+1.0)
#11	51.0	53.0	(+2.0)	#5	50.0	53.0	(+3.0)
				#8	42.0	40.0	(-2.0)
				#10	43.0	40.0	(-3.0)
				#12	46.0	44.0	(-2.0)
		mean =	$\overline{(+2.9)}$			mean =	$\overline{(-1.4)}$
		SE =	$\pm$0.5	p<.05*		SE =	$\pm$1.2

* Change in PaO2 is significantly different between the placebo and acetazolamide groups using the Mann-Whitney Rank-Sum Test.

Table 11. Change in CO2, SaO2 and Spirometry: Double Blind Study

(all values are mean ± SE)

	Acetazolamide *			Placebo		
	0hrs	24hrs	Change	0hrs	24hrs	Change
PaO2 (torrs) n=**	44.2 ±3.4	47.1 ±2.9	(+2.9) ±0.5	45.2 ±1.3	43.8 ±2.0	(-1.4) ±1.2
PaCO2 (torrs) n=**	28.2 ±1.6	25.6 ±0.9	(-2.5) ±1.8	28.3 ±0.9	28.4 ±0.6	(+0.1) ±0.6
$P_{ET}CO2^{+}$(torrs) n=6	26.1 ±1.5	24.3 ±0.7	(-1.8) ±0.9	25.0 ±1.0	23.3 ±1.1	(-1.7) ±0.9
SaO2 % n=6	78.2% ±2.9	82.5% ±2.2	(+4.3%) ±0.9	81.2% ±1.7	85.2% ±0.9	(+4.0%) ±1.3
PEF (lit/sec) n=6	.603 ±.044	.584 ±.049	(-.019) ±.014	.563 ±.034	.572 ±.098	(+.009) ±.015
FVC (liters) n=6	3.21 ±.11	3.20 ±.21	(-0.01) ±0.13	3.18 ±.31	3.12 ±.30	(-0.06) ±0.11

* For all data except PaO2, $p>.05$ for comparison of change over 24 hours between groups (Mann-Whitney Rank-Sum test).

** Mean PaO2 and PaCO2 values are for n=3 in the acetazolamide group and n=6 in the placebo group. All other mean values are for n=6.

+ $P_{ET}CO2$ was used for calculation of (A-a)DO2 in all subjects.

Figure 3. Change in (A-a)DO2: Acetazolamide Group

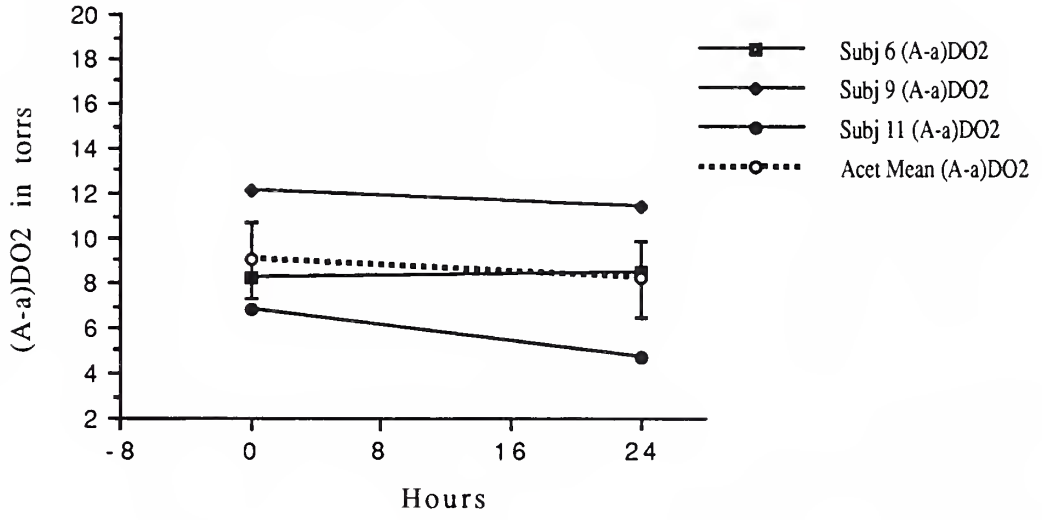
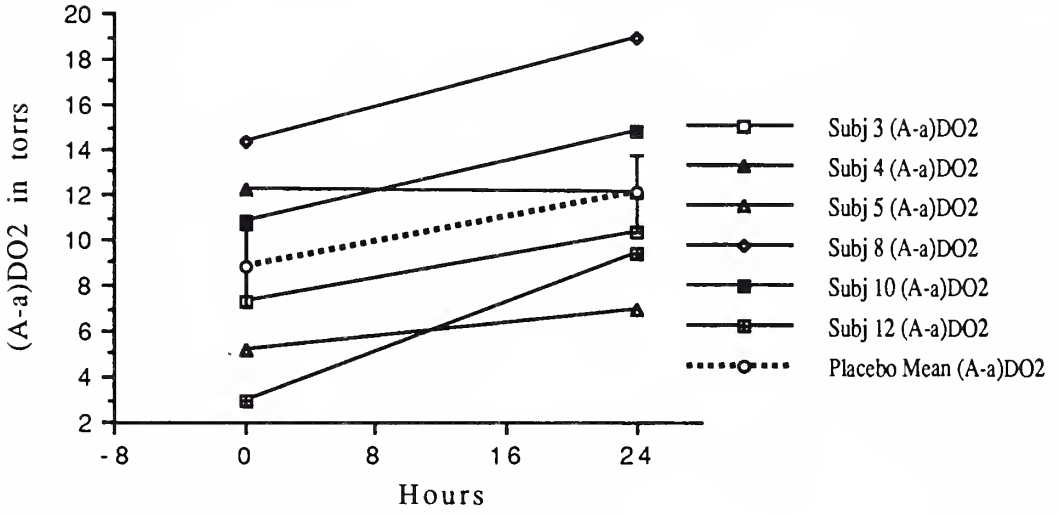


Figure 4. Change in (A-a)DO2: Placebo Group



Figures 3 and 4. Change in A-a gradient for O2 over 24 hours in the acetazolamide and placebo groups. For the acetazolamide group n=3, and for the placebo group n=6. Change in (A-a)DO2 over 24 hours is shown for each subject by the solid lines, and mean change in (A-a)DO2 over 24 hours is shown for each group by the dashed lines. Error bars indicate ± standard error for the mean at 0 hours and at 24 hours.

Figure 5. Change in PaO2: Acetazolamide Group

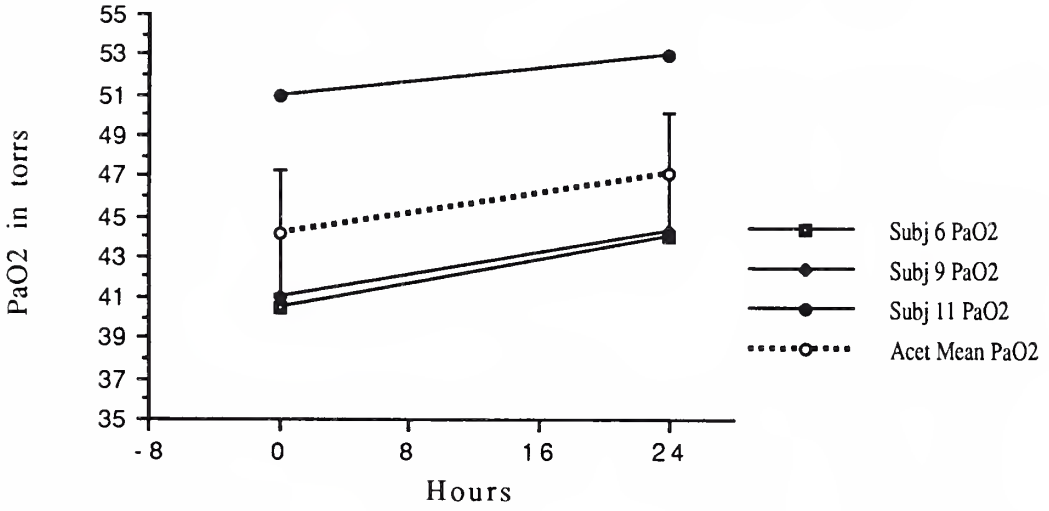
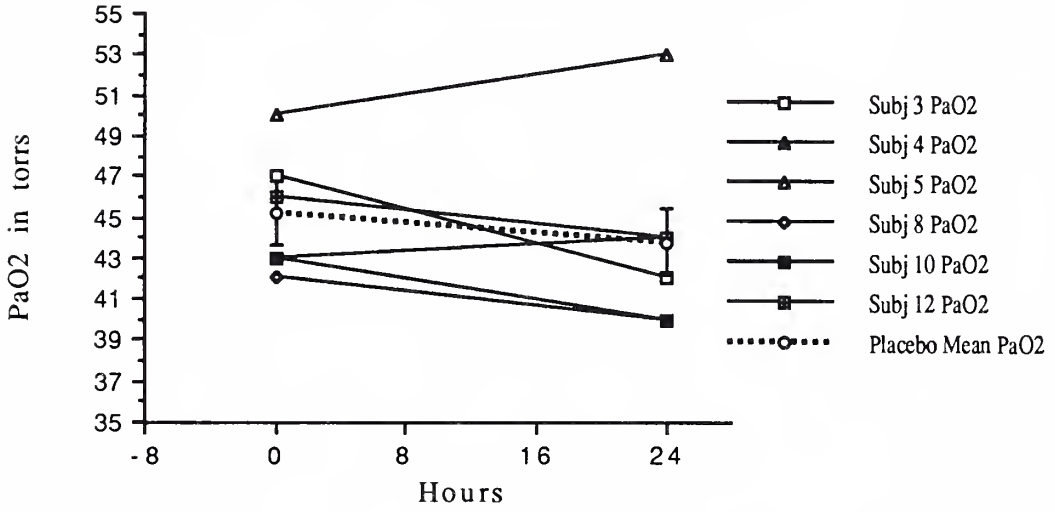


Figure 6. Change in PaO2: Placebo Group



Figures 5 and 6. Change in PaO2 over 24 hours in the acetazolamide and placebo groups. For the acetazolamide group n=3, and for the placebo group n=6. Change in PaO2 over 24 hours is shown for each subject by the solid lines, and mean change in PaO2 over 24 hours is shown for each group by the dashed lines. Error bars indicate ± standard error for the mean at 0 and 24 hours.

Correlation of Change in (A-a)DO2 and Change in Symptom Score:

For the acetazolamide and placebo groups combined, correlation between change in the symptom score and change in (A-a)DO2 over 24 hours was significant ($p<.005$, Figure 7). Acetazolamide was associated with a decrease in (A-a)DO2 and a greater improvement in symptom score, while placebo was associated with an increase in (A-a)DO2 and less of an improvement in symptomn score.

Figure 7. Change in (A-a)DO2 versus Change in AMS Symptom Score

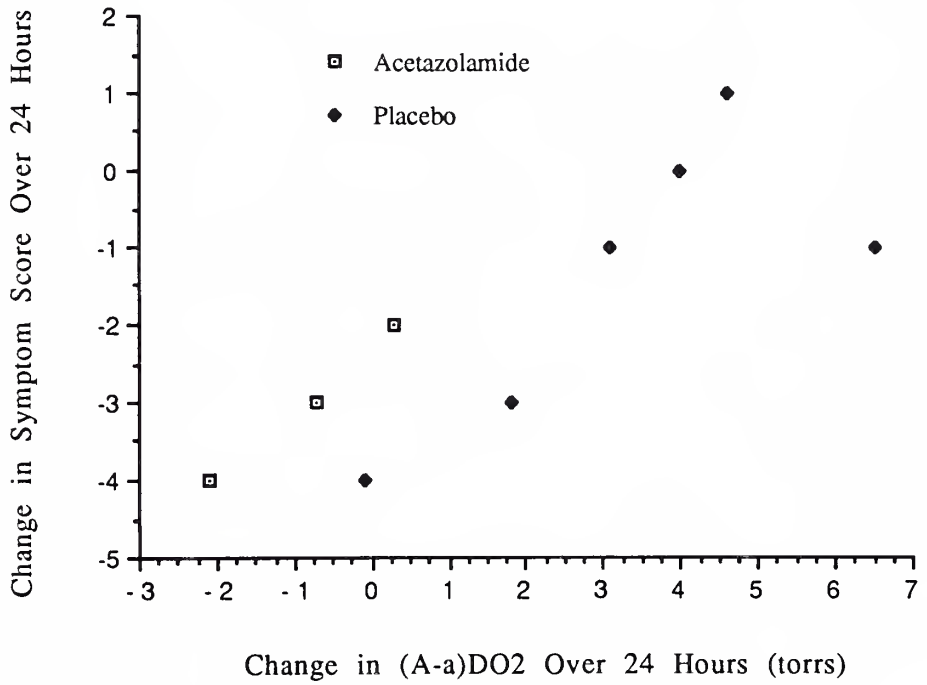


Figure 7. Change in AMS symptom score over 24 hours is plotted against change in A-a gradient for O2 over 24 hours using data from both the acetazolamide (n=3) and placebo (n=6) groups. Correlation between change in (A-a)DO2 and change in symptom score over 24 hours is significant at the $p<.005$ level (Spearman Rank Correlation Coefficient, $r_S=.87$).

Single Blind Crossover Data:

Data on single blind crossovers from placebo to acetazolamide are shown in Table 12 and Figures 8 & 9. In all three subjects (A-a)DO2 increased and PaO2 decreased with placebo, and in two of three subjects symptom score did not improve with placebo. This contrasts with acetazolamide-treatment which was associated with a narrowing of (A-a)DO2, an increase in PaO2, and an improvement in symptom score.

Table 12. Data for Crossovers from Placebo to Acetazolamide*

	PLACEBO			**ACETAZOLAMIDE**		
	AMS Symptom Score			AMS Symptom Score		
Subj**	0hrs	24hrs	Change	24hrs	48hrs	Change
#3x	5	4	(-1)	4	0	(-4)
#8x	2	3	(+1)	3	1	(-2)
#10x	2	2	(0)	2	0	(-2)
	(A-a)DO2 in torrs			(A-a)DO2 in Torrs		
Subj	0hrs	24hrs	Change	24hrs	48hrs	Change
#3x	7.3	10.4	(+3.1)	10.4	8.3	(-2.1)
#8x	14.3	18.9	(+4.6)	18.9	8.3	(-10.6)
#10x	10.8	14.8	(+4.0)	14.8	7.8	(-7.0)
	PaO2 in torrs			PaO2 in torrs		
Subj	0hrs	24hrs	Change	24hrs	48hrs	Change
#3x	47.0	42.0	(-5.0)	42.0	49.0	(+7.0)
#8x	42.0	40.0	(-2.0)	40.0	50.0	(+10.0)
#10x	43.0	40.0	(-3.0)	40.0	49.0	(+9.0)

* All subjects received placebo (0-24hrs) as part of the double blind study, then crossed over to acetazolamide (24-48hrs) in a single blind fashion (blinded to investigator).

** After conclusion of the study subject 3x descended from 4200m. Subjects 8x and 10x eventually reached the summit.

Figure 8. Change in (A-a)DO2: Crossovers from Placebo to Acetazolamide

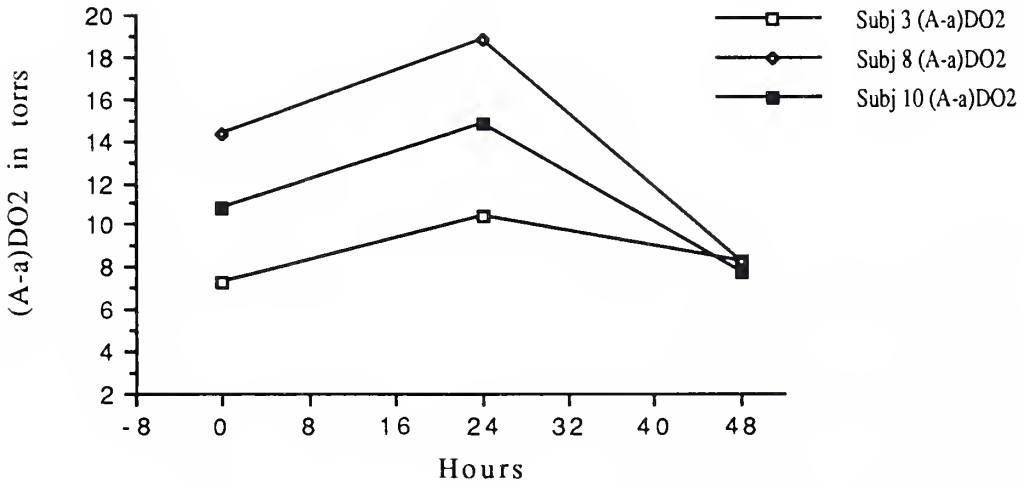


Figure 8. Change in (A-a)DO2 over 48 hours for crossovers from placebo to acetazolamide (n=3). (A-a)DO2 at 0 hours is baseline, (A-a)DO2 at 24 hours is after placebo, and (A-a)DO2 at 48 hours is after acetazolamide.

Figure 9. Change in PaO2: Crossovers from Placebo to Acetazolamide

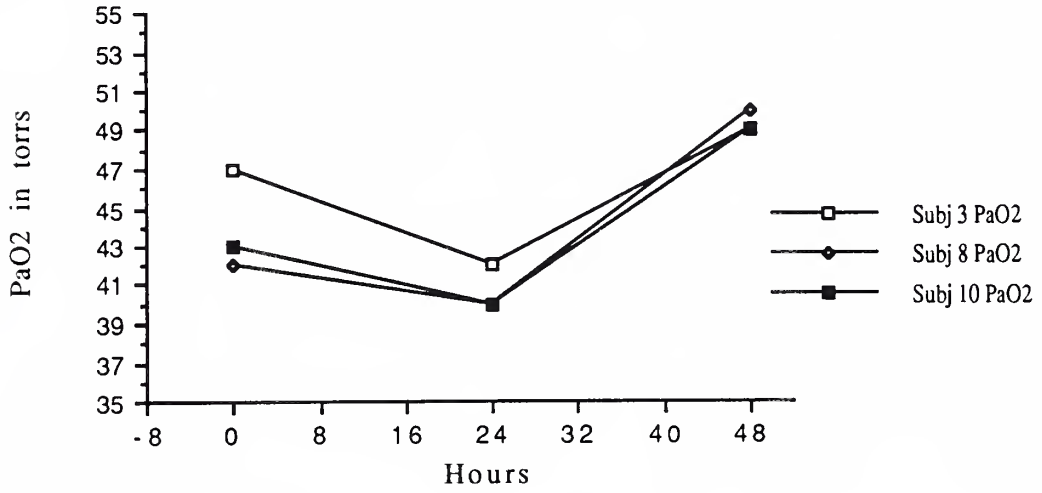


Figure 9. Change in PaO2 over 48 hours for crossovers from placebo to acetazolamide (n=3). PaO2 at 0 hours is baseline, PaO2 at 24 hours is after placebo, and PaO2 at 48 hours is after acetazolamide.

VI.E. DISCUSSION

In this study comparing acetazolamide to placebo in the treatment of 12 climbers with AMS at 4200m on Denali several observations were made: 1) Acetazolamide 250 mg administered in two doses eight hours apart was more effective than placebo in treating AMS; 2) Acetazolamide improved pulmonary gas exchange and PaO2 over 24 hours in AMS as compared to placebo; 3) A decrease in the A-a gradient over 24 hours correlated with a greater improvement in symptom score in the acetazolamide group, and an increase in the A-a gradient over 24 hours correlated with less of an improvement in symptom score in the placebo group. Therefore, acetazolamide is effective for the treatment of established cases of AMS, and is associated with an improvement in pulmonary gas exchange. Furthermore, the significant correlation between change in the A-a gradient and change in symptoms of AMS over 24 hours suggests that impaired pulmonary gas exchange contributes to the symptoms of AMS.

All subjects tolerated the study without complications, although subject 7 developed HAPE 24 hours after conclusion of the study and 40 hours after acetazolamide treatment. This indicates that acetazolamide at the dose used in this study is not completely effective in prophylaxis for HAPE.

Six of the 12 subjects in the study eventually reached the summit of Denali. Two of those who reached the summit received only placebo in the study and still had clinically defined AMS after 24 hours. Three subjects never made a summit attempt and descended from 4200m, and two of those did not have clinically defined AMS after completing the acetazolamide portion of the study. Therefore, AMS does not preclude summit success and acetazolamide treatment of AMS does not guarantee summit success.

Symptom Score Data:

Both the acetazolamide and placebo groups in this study showed improvement in symptom score over 24 hours. This was expected because AMS improves with time in most individuals if ascent is halted. The significant finding in this study, though, was that after 24 hours five out of six subjects in the acetazolamide group did not have AMS, whereas all six subjects in the placebo group still had clinically defined AMS. This indicates that acetazolamide speeds the process of acclimatization and shortens the period of symptomatic illness in AMS.

Although AMS symptom score after 24 hours was significantly different between groups ($p<.01$, Tables 7 & 8), the change in AMS symptom score over 24 hours was not significantly different between groups ($p>.05$, Tables 7 & 8). However, comparison of the mean

change in symptom score over 24 hours for the acetazolamide group (-2.8 $\pm$0.3) with the mean change for the placebo group (-1.3 $\pm$0.8), suggests that a larger sample size might have shown a significant difference in change of symptom score over 24 hours between groups.

The efficacy of acetazolamide as compared to placebo in treating established cases of AMS in this study may be criticized because of an improvement with time bias in the acetazolamide group itself. Two aspects of the study minimize this bias. First, the number of nights spent at 4200m before inclusion in the study was similar for both the acetazolamide and placebo groups. Therefore, both the acetazolamide and placebo groups were equally likely to experience improvement in symptoms because of the natural history of AMS. Second, a more powerful controlling factor for improvement with time bias was present in the study design. Subjects started this study within 24 hours of onset of symptoms at 4200m, thus minimizing the chance of enrolling a subject in the study who was nearing the end of their course of AMS. This is ultimately more reliable in ensuring that subjects are not already improving when they enter the study. Symptoms of AMS may occur from several hours to several days after ascent to a higher altitude. Therefore, some individuals may experience symptoms upon arrival at 4200m, while other individuals may not experience symptoms until after sleeping one or two nights at 4200m. This makes time of onset of symptoms,

rather than the number of nights at 4200m, a more accurate parameter to follow the natural course of AMS.

The symptom score data in this study might also be criticized because of non-random assignment of subject 12 to the placebo group. In the study design a small number of subjects was anticipated, and allowance was made for subjects with a sulfa-drug allergy to participate as controls. Non-random assignment of subject 12 to the placebo group might have introduced bias in the symptom score data. Symptom scores rely on subjective criteria that might be reported differently by an individual more sensitive to the effects of drug therapy. However, data from physical measurements were probably not influenced by subject 12.

(A-a)DO2 and PaO2 Data:

The change in A-a gradient for O2 over 24 hours was significantly different between the acetazolamide and placebo groups in this study. The data suggest that this was due more to an increase in A-a gradient with placebo than to a decrease in A-a gradient with acetazolamide; the mean change in (A-a)DO2 in the placebo group over 24 hours was +3.3 $\pm$0.9 torr, whereas the mean change for the acetazolamide group was -0.8 $\pm$0.7 torr. Therefore, acetazolamide improved pulmonary gas exchange over 24 hours when compared to placebo in this study because it prevented the increase

in A-a gradient observed in the placebo group. Although two out of three subjects in the acetazolamide group decreased their A-a gradient over 24 hours, a larger sample size would have been required to further conclude that acetazolamide significantly decreased the A-a gradient. Further studies with larger sample sizes will need to confirm this.

Hackett has reported that some individuals with AMS have an increased A-a gradient with values of 15-16 torr, as opposed to healthy individuals with A-a gradients at altitude of approximately 7 torr (38). Some subjects in this study had elevated A-a gradients according to Hackett's parameters: subjects 8 and 10 with A-a gradients of 18.9 and 14.8 torr after 24 hours in the placebo group. However, the data in this study suggest a range of values for A-a gradient in individuals with AMS, rather than a group of "normal" values, and second group of "abnormal" values. Furthermore, AMS in the placebo group in this study was characterized by worsening gas exchange over 24 hours. It might be that impairment in pulmonary gas exchange in AMS is a continuum from normal to severe, and that worsening pulmonary gas exchange occurs over time in AMS.

The significant difference in change of (A-a)DO2 over 24 hours between acetazolamide and placebo may be questioned because the age difference between the placebo group and the acetazolamide group

may have influenced the data. The mean age of the placebo group (38.0 ± 5.8 SD) was older than the mean age of the acetazolamide group (29.5 ± 2.7 SD). Since ventilation perfusion mismatch and (A-a)DO2 increase with age, this may have biased comparisons between the acetazolamide and placebo groups. However, this study compares change in (A-a)DO2 rather than the absolute values of (A-a)DO2 for each subject. Still, stratifying the study for age would have been helpful.

The increase in PaO2 observed in the acetazolamide group and the decrease in PaO2 observed in the placebo group may have occurred for two reasons. First, a decrease in (A-a)DO2 with acetazolamide treatment may account for the increase in PaO2 in the acetazolamide group but, as discussed above, this cannot be confirmed by this study. An increase in (A-a) gradient was observed in the placebo group, however, and may have contributed to the decrease in PaO2 over 24 hours in the placebo group. Second, PaO2 will increase if minute ventilation is increased, even if (A-a)DO2 is unchanged. The increase in minute ventilation with acetazolamide therapy is well documented (57), and may have accounted for the increase in PaO2 in the acetazolamide-treated subjects in this study. Likewise, the decrease in PaO2 observed in the placebo group may have occurred because of relative hypoventilation known to occur in AMS (29,78). Direct measurements

of minute ventilation in this study would have been helpful in confirming a change in minute ventilation as a cause of the significant difference in change of PaO2 over 24 hours in the acetazolamide as compared to the placebo groups. Data on change in PaCO2 were not helpful in suggesting an increase in minute ventilation in the acetazolamide group, as the change in PaCO2 over 24 hours was not significantly different between groups.

Acetazolamide and Pulmonary Gas Exchange:

The increased baseline (A-a)DO2 observed in some individuals with AMS (38,78) is probably indicative of increased extravascular lung water with early interstitial edema. Increasing lung leak might also have contributed to the worsening pulmonary gas exchange in the placebo group observed in this study. Therefore, the improved pulmonary gas exchange over 24 hours in the acetazolamide as compared to the placebo group in this study might indicate decreased extravascular lung water in the acetazolamide-treated subjects. The diuretic effect of acetazolamide could explain this. Other studies using lasix in the treatment or prophylaxis of AMS, however, have shown conflicting results. Singh reported that lasix was effective in the treatment of AMS (76), but Gray observed severe AMS in subjects treated prophylactically upon air transport to 5400 m (21). In the latter study the authors speculated that

dehydration may have contributed to the increased severity of AMS in the subjects, and this has discouraged subsequent use of diuretics in North America. A study comparing acetazolamide with a mild diuretic in the treatment of AMS and their effect on (A-a)DO2 might help clarify two issues. First, whether diuresis is beneficial in the treatment of AMS. Second, whether a diuretic effect of acetazolamide is responsible for improvements in gas exchange as compared to placebo.

The increase in PaO2 in acetazolamide-treated subjects in this study also suggests a possible mechanism for improved pulmonary gas exchange. It might be that the increase in PaO2, due to increased minute ventilation known to occur with acetazolamide, indirectly improved those factors responsible for increased extravascular lung water. An increase in PaO2 might decrease hypoxic pulmonary vasoconstriction and pulmonary artery pressure, thereby reducing transudation of fluid from the pulmonary vascular bed to the interstitial space. This would result in improved pulmonary gas exchange and a further increase in PaO2.

Acetazolamide also might directly influence the pulmonary epithelium, vascular endothelium, or vascular smooth muscle, and influence factors that contribute to transudation of fluid to the interstitium. The presence of carbonic anhydrase in the pulmonary capillary endothelium is well established, and it also may be

present in alveolar epithelial cells (83). The full effects of inhibition of the different carbonic anhydrase isoenzymes at these various sites is not known.

Some authors suggest that there may be a neurogenic component to HAPE, and CNS dysfunction also may contribute to the increased extravascular lung water in AMS. Effects of acetazolamide on the brain, such as decreased production of CSF (75), may also influence the low grade pulmonary edema in AMS.

End Tidal CO2 and PaCO2 Data:

Surprisingly, no difference in change of $P_{ET}CO2$ or PaCO2 was observed between the acetazolamide and placebo groups. In the prophylaxis of AMS, acetazolamide increases minute ventilation and decreases PaCO2 (8,51,57), so it was expected that the PaCO2 of the treated group would be lower than that of the placebo group in this study. However, with the small sample sizes in this study Type II error must be considered. A larger sample size might show decreases in PE_TCO2 and PaCO2 with acetazolamide treatment as compared to placebo. As was mentioned above, it would have been helpful to measure minute ventilation directly. It also would have been helpful to observe whether acetazolamide decreased the arterial pH during this study, but the pH electrode on the blood gas machine was disabled.

It is important that PaCO2 did not increase in the acetazolamide group during this study. Swenson warns against acetazolamide treatment of AMS or HAPE because pulmonary dysfunction and relative hypoventilation in AMS may not allow ventilatory compensation for the respiratory acidosis secondary to RBC carbonic anhydrase inhibition (81). The doses of acetazolamide used in this study were slightly higher than the 5 mg/kg suggested to minimize RBC carbonic anhydrase inhibition, yet an increase in PaCO2 was not observed. However, RBC carbonic anhydrase inhibition may explain why no significant decrease in $P_{ET}CO2$ or PaCO2 were observed in the acetazolamide group as compared to the placebo group. RBC carbonic anhydrase inhibition in the acetazolamide group might have caused a respiratory acidosis (increase in PaCO2) that was then compensated for with increased ventilation so that over 24 hours no significant change in PaCO2 was observed.

Spirometry:

No significant change in PEF or FVC were observed between the acetazolamide and placebo treated groups in this study. Larson and colleagues observed an increase in FVC in climbers taking acetazolamide prophylactically for AMS during an ascent of Mt. Ranier, but the sample size in that study (n=30 in the acetazolamide group) was significantly larger than in this study

(57). A larger sample size in this study might have shown significant differences in change in spirometric data between the acetazolamide and placebo groups.

Change in (A-a)DO2 Versus Change in AMS Symptom Score:

In the acetazolamide and placebo groups combined, a significant correlation between change in A-a gradient for O2 and change in symptom score over 24 hours was observed in this study. Acetazolamide was associated with a decrease in A-a gradient and a greater improvement in AMS symptom score, and placebo was associated with an increase in A-a gradient and less of an improvement in symptom score. This suggests that impaired pulmonary gas exchange contributes to the symptoms of AMS. Although symptoms of AMS are more consistent with cerebral dysfunction, rather than pulmonary dysfunction, impaired pulmonary gas exchange may worsen cerebral hypoxia and thereby exacerbate AMS symptoms. Likewise, improving pulmonary gas exchange in AMS may improve cerebral hypoxia and improve AMS symptoms. In the acetazolamide-treated subjects in this study, improvement in gas exchange was associated with a greater improvement in symptoms of AMS. This suggests that acetazolamide improves the symptoms of AMS in part because it improves pulmonary gas exchange as compared to placebo.

Crossover Data:

Single blind crossovers (blinded to investigator) from placebo to acetazolamide in this study showed marked improvements with acetazolamide. All crossover subjects increased (A-a)DO2 and decreased PaO2 with placebo, and two out of three did not improve symptom score with placebo. In contrast, all crossover subjects decreased (A-a)DO2, increased PaO2, and improved symptom score with acetazolamide. These findings support the conclusions drawn from the double blind study data. However, the crossover data alone are not significant because the crossover subjects may have improved with time, and not because of acetazolamide treatment. It would have been helpful to study some placebo subjects over 48 hours for comparison with the crossover subjects. Other subjects completing the placebo portion of the study, though, were unwilling to continue as placebo to placebo crossovers. They either experienced relief of symptoms and continued climbing or they preferred to take acetazolamide rather than risk the chance of taking placebo for another 24 hours.

Acetazolamide Prophylaxis for HAPE:

Impaired gas exchange in AMS, presumably caused by increased extravascular lung water, may be a precursor to HAPE. The improvement in pulmonary gas exchange observed in the acetazolamide

treated subjects in this study, then, suggests that acetazolamide may be useful in the prophylaxis of HAPE. However, subject 7 offers a case study in the failure of acetazolamide as prophylaxis for HAPE.

On presentation subject 7's chief complaint was a pounding bitemporal headache somewhat relieved with analgesics. Additional complaints of insomnia and anorexia resulted in an AMS symptom score of 3. The subject had no pulmonary symptoms, but on physical exam he had a few right middle lobe rales and an SaO2 of 67%. Baseline (A-a)DO2 data were not obtained because of a venous blood sample. At 24 hours the subject reported sleeping better and eating better, but still complained of headache, and received a symptom score of 1. At 24 hours the right middle lobe rales were unchanged and the SaO2 was slightly improved at 73% (although the error of oximetry is $\pm$ 5% at this SaO2). One day after the conclusion of the study, the subject presented to the medical camp with markedly increased right sided rales, an SaO2 of 65%, and increased dyspnea, all consistent with HAPE. In addition to the two doses of acetazolamide 250 mg the subject had received as part of the study, he also reported taking another 250 mg of acetazolamide shortly before presenting with HAPE 48 hours after entering the study, and 40 hours after the last study dose of acetazolamide. The subject remained at 4400 m for another day, and

was treated with low flow oxygen overnight. He descended with a guide from his party the next day without complications.

Table 13. Progression from AMS to HAPE in Subject 7

	AMS		HAPE
	0 hours	24 hours	60 hours*
AMS Score	3	1	HAPE
SaO2%	67%	73%	73%
$P_{ET}CO2$	22.2	22.2	21.3
PaCO2	venous sample	25.7	28.9
PaO2		39.0	40.0
(A-a)DO2		14.1	17.6

(all values in torrs except SaO2 and symptom scores)

* Subject slept overnight on low flow oxygen.

Data on PaO2 and (A-a)DO2 were obtained on subject 7 at 24 and 60 hours after inclusion in this study, and surprisingly were not markedly different than arterial blood gases from other subjects in the study (Table 13). At 24 hours, PaO2 was 39.0 torr and (A-a)DO2 was 14.1 torr. At 60 hours, PaO2 was 40 torr and (A-a)DO2 was 17.6 torr. At 24 hours subject 7 had resolving AMS with a symptom score of 1 and some right middle lobe rales, and at 60 hours he had dyspnea at rest with diffuse right sided rales. Yet his PaO2 and (A-a)DO2 were not markedly different in contrast to

the change in his clinical presentation. Progression from AMS to HAPE in this case, then, was characterized by symptoms and not by objective measurements of PaO2 and (A-a)DO2.

Given this case, two contrasting conclusions could be made regarding acetazolamide prophylaxis for HAPE. Either acetazolamide was not effective in prophylaxis, or acetazolamide was effective and it was not until treatment was stopped that HAPE developed. The additional dose of acetazolamide given just before presentation with HAPE at 48 hours does not favor either conclusion. Pathophysiological events may have already occurred between 24 and 48 hours making the additional acetazolamide dose treatment rather than prophylaxis. However, Gray also reported a case of HAPE in a subject taking acetazolamide prophylactically for AMS (21) and concluded that acetazolamide was not effective in prophylaxis for HAPE.

Acetazolamide Prevention and Treatment of AMS:

Acetazolamide prevents AMS when taken prior to ascent (8,30,57), and this study shows that acetazolamide treats AMS when taken after symptoms occur. This requires a redefinition of appropriate use of acetazolamide during ascent to high altitude.

For abrupt ascent from sea level to very high altitude, such as may occur in air transport of rescue or military personnel,

prophylaxis for altitude illness is indicated. For more gradual ascent to altitude, however, prophylaxis is indicated only for individuals with a past history of AMS. This applies to the traveller flying from sea level to a ski resort in the Rocky Mountains who often misses the first day of skiing because of headache and lassitude, as well as to the high altitude climber who usually experiences AMS symptoms with ascents of 1000m in a single day. Recommended doses of acetazolamide are 125 to 250 mg twice daily beginning one day before ascent and continuing for the first day or two at altitude. A similar regimen should be used for reascent to higher altitudes.

For climbers at extreme altitude or making fast alpine style ascents, acetazolamide prophylaxis for AMS is also indicated. In these situations impaired coordination from CNS symptoms of AMS might endanger both the climber and his or her companions. Still, adequate acclimatization prior to a fast ascent or during a climb at extreme altitude is preferable to acetazolamide prophylaxis. The risk of serious altitude illness in a setting where rescue may be impossible makes adequate acclimatization essential.

For individuals without a past history of AMS acetazolamide need not be used prophylactically, but may be taken if symptoms occur. Doses of 125 to 250 mg twice daily continued for one or two days will speed acclimatization and relieve symptoms. If

symptoms do occur after ascent, and reascent to a higher altitude is anticipated later, then prophylactic therapy is indicated.

For individuals whose only symptom is disturbed sleep, low dose (125 mg) acetazolamide in the evening will result in decreased sleep periodic breathing, improved nocturnal arterial oxygen saturation, and more restful sleep. Doses of 125 mg appear to be effective in improving sleep and result in less side effects, such as nocturnal diuresis that may itself disturb sleep. Nocturnal headache also may be relieved with low dose acetazolamide and analgesics.

Acetazolamide is indicated for the treatment of AMS and may be used when symptoms occur, rather than for prophylaxis, by the individual without a consistent history of AMS on ascent to altitude. However, adequate acclimatization is preferable because it decreases the risk of more serious altitude illness. Likewise, acetazolamide therapy for AMS is not a substitute for descent. When symptoms of AMS do not improve or suggest progression to HAPE or HACE, descent may be lifesaving. The most useful treatment application of acetazolamide might be to relieve symptoms enough to make descent possible in more severe cases of AMS.

References

1. Anholm JD; Houston CS; Hyers TM. The relationship between acute mountain sickness and pulmonary ventilation at 2,835 meters (9,300 feet). Chest 1979;75(1):33-36.

2. Bailliart O; Raynaud J; Marotte H; Duran JC; Durand J. Common carotid blood flow measured by range gated doppler at high altitude (Abstract). In: Sutton JR, Houston CS, Coates G, Editors. Hypoxia. The tolerable limits Indianapolis, Indiana: Benchmark Press; 1988:382.

3. Bert P. Barometric pressure. Researches in experimental physiology. Translated by MA and FA Hitchcock. Columbus, Ohio: College Book Company; 1943.

4. Bouissou P; Richalet JP; Francois XG; Lartigue M; Lartigue M; Larmignat P; Devaux F; Dubray C; Keromes A. Effect of beta-adrenoceptor blockade on renin-aldosterone and alpha-ANF during exercise at altitude. J Appl Physiol 1989; 67(1):141-146.

5. Bradwell AR; Winterborn M; Wright AD; Forster PE; Dykes PW. Acetazolamide treatment of acute mountain sickness. Clin Sci 1988; 74: supp118: 62P.abstract.

6. Bradwell AR; Dykes PW; Coote JH; Forster PJ; Milles JJ; Chesner I; Richardson NV. Effect of acetazolamide on exercise performance and muscle mass at high altitude. Lancet 1986; 1(8488): 1001-1005.

7. Berthelsen P; Gothgen I; Husum B; Jacobsen E. Dissociation of renal and respiratory effects of acetazolamide in the critically ill. Br J Anaesth 1986;58:512-516.

8. Cain SM; Dunn JE. Low doses of acetazolamide to aid accommodation of men to altitude. J Appl Physiol 1965;21(2):1195-1200.

9. Cruz JC; Reeves JT; Grover RF; Maher JT; McCullough RE. Ventilatory acclimatization to high altitude is prevented by CO2 breathing. Respir 1980; 39:121-130.

10. Dempsey JA; Forster HV; Chosy LW; Hanson PG; Reddan WG. Regulation of CSF HCO3- during long term hypoxic hypocapnia in man. J Appl Physiol 1978; 44(2):175-182.

11. Dickinson JG. High altitude cerebral edema: Cerebral acute mountain sickness. Semin Respir Med 1983;5(2):151-158.

12. Dickinson JG; Heath J; Gosney J; Williams D. Altitude related deaths in seven trekkers in the Himalayas. Thorax 1983; 38:646-656.

13. Editorial. See Nuptse and Die. Lancet 1976; 2(7996):1177-1179.

14. Ellsworth AJ; Larson EB; Strickland D. A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. AM J Med 1987; 83:1024-1030.

15. Ferrazzini G; Maggiorini M; Kriemler S; Bartsch P; Oelz O. Successful treatment of acute mountain sickness with dexamethasone. Br Med J 1987; 294:1380-1382.

16. Fishman RA. Brain edema. N Engl J Med 1975; 293(14):706-711.

17. Forster PJ. Effect of different ascent profiles on performance at 4200m elevation. Aviat Space Environ Med 1985; 56:758-764.

18. Forster HV, Dempsey JA, Chosy LW. Incomplete compensation of CSF H+ in man during acclimatization to high altitude (4,300m). J Appl Physiol 1975; 38:1067-1072.

19. Glantz SA. Primer of Biostatistics 2nd ed. New York, NY: McGraw-Hill; 1987.

20. Gold WM; Boushey HA. Pulmonary function testing. In: Murray JF, Nadel JA, Editors. Textbook of Respiratory Medicine Philadelphia, PA: Saunders; 1988:654.

21. Gray GW; Bryan AC; Frayser R; Houston CS; Rennie ID. Control of acute mountain sickness. Aero Med 1971; 42(1):81-84.

22. Groves BM; Reeves JT; Sutton JR; Wagner PD; Cymerman A; Malconian MK; Rock PB; Young PM; Houston CS. Operation Everest II: Elevated high altitude pulmonary resistance unresponsive to oxygen. J Appl Physiol 1987; 63(2):521-530.

23. Hackett PH. Carbon dioxide breathing and acute mountain sickness (Letter). Lancet 1989; 1(8632):272.

24. Hackett PH, Hornbein TF. Disorders of high altitude. In: Murray JF, Nadel JA, Editors. Textbook of Respiratory Medicine Philadelphia, PA: Saunders; 1988:1646-1663.

25. Hackett PH; Roach RC; Wood RA; Foutch RG; Meehan RT; Rennie D; Mills WJ. Dexamethasone for prevention and treatment of acute

mountain sickness. Aviat Space Environ Med 1988; 59:950-954.

26. Hackett PH; Rennie D. Acute mountain sickness. Semin Respir Med 1983; 5:132-140.

27. Hackett PH; Creagh CE; Grover RF; Honigman B; Houston CS. High altitude pulmonary edema in persons without the right pulmonary artery. N Engl J Med 1980; 302(19):1070-1073.

28. Hackett PH; Forsling ML; Milledge JS; Rennie ID. Release of vasopressin in man at altitude. Horm Metab Res 1978; 10:571.

29. Hackett PH; Rennie ID; Hofmeister SE; Grover RF; Grover EB; Reeves JT. Fluid retention and relative hypoventilation in acute mountain sickness. Respir 1982; 43:321-329.

30. Hackett PH; Rennie ID; Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. Lancet 1976; 2(7995): 1149-1154.

31. Hackett PH; Rennie ID. Rales, peripheral edema, retinal hemorrhage and acute mountain sickness. Am J Med 1979; 67:214-218.

32. Hackett PH; Roach RC; Schoene RB; Hollingshead F; Mills WJ. The Denali medical research project, 1982-1985. Am Alpine J 1986:129-137.

33. Hackett PH, Roach RC, Meehan RT, Rennie ID, Foutch R, Wood R, Mills JW J. Dexamethasone for prevention and treatment of acute mountain sickness (Abstract). In: Sutton JR, Houston CS, Coates G, Editors. Hypoxia. The tolerable limits Indianapolis, Indiana: Benchmark Press; 1988:384.

34. Hackett PH; Roach RC. Medical therapy of altitude illness. Ann Emerg Med 1987; 16(9):980-986.

35. Hackett PH, Roach RC, Sutton JR. Medical problems of high altitude. In: Auerbach P, Geehr E, Editors. Management of Wilderness and Environmental Emergencies St. Louis, MO: Mosby; 1988.

36. Hackett PH, Roach RC, Greene ER. Oxygenation, but not increased cerebral blood flow, improves high altitude headache (Abstract). In: Sutton JR, Coates G, Remmers JE, Editors. Hypoxia. The adaptations Philadelphia, PA: BC Dekker;1990.

37. Hackett PH; Roach RC; Harrison GL; Schoene RB; Mills JW J.

Respiratory stimulants and sleep periodic breathing at high altitude. Almitrine versus acetazolamide. Am Rev Respir Dis 1987; 135:896-898.

38. Hackett PH; Roach RC; Swenson ER; Mills JW J. Subclinical pulmonary edema in acute mountain sickness (Abstract). In: Sutton JR, Houston CS, Coates G, Editors. Hypoxia. The tolerable limits Indianapolis, Indiana: Benchmark Press; 1988:383.

39. Hackett PH; Swenson ER; Roach RC; Carter J; Mills JW J. 250mg acetazolamide intravenously does not increase cerebral blood flow at high altitude (Abstract). In: Sutton JR, Houston CS, Coates G, Editors. Hypoxia. The tolerable limits Indianapolis, Indiana: Benchmark Press; 1988:383.

40. Hamilton AJ; Cymerman A; Black M. High altitude cerebral edema. Neurosurgery 1986; 19(5):841-849.

41. Hannon JP; Chinn KS: Shields JL. Effects of acute high altitude exposure on body fluids. Fed Proc 1969; 28(3):1178-1184.

42. Hansen JE; Evans WO. A hypothesis regarding the pathophysiology of acute mountain sickness. Arch Environ Health 1970; 21:666-669.

43. Harvey TC; Raichle ME; Winterborn MH; Jensen J; Lassen NA; Richardson NV; Bradwell AR. Effect of carbon dioxide in acute mountain sickness: A rediscovery. Lancet 1988; 2(8612):639-641.

44. Heyes MP; Sutton JR. High altitude ills: A malady of water, electrolyte, and hormonal imbalance. Sem Respir Med 1983; 5(2): 207-212.

45. Houston CS. Acute pulmonary edema of high altitude. N Engl J Med 1960; 263(10):478-480.

46. Houston CS. Incidence of acute mountain sickness. Am Alpine J 1985; 27(59):162-165.

47. Houston CS. Going higher. The story of man and altitude Boston and Toronto: Little, Brown and Company; 1987.

48. Hultgren HN; Grover RF; Hartley LH. Abnormal circulatory responses to high altitude in subjects with a previous history of high altitude pulmonary edema. Circulation 1971; XLIV:759-770.

49. Johnson TS; Rock PB. Acute mountain sickness. N Engl J Med 1988; 319(13):841-845.

50. Johnson TS; Rock PB; Fulco CS; Trad LA; Spark RF; Maher JT. Prevention of acute mountain sickness by dexamithasone. N Engl J Med 1984; 310(11):683-686.

51. Kronenberg RS; Cain SM. Hastening respiratory acclimatization to altitude with benzolamide (CL 11,366). Aerospace Med 1968; 39:296-300.

52. Keys A; Hall FG; and Barron ES. The position of the oxygen dissociation curve of human blood at high altitude. Am J Physiol 1936; 115:292.

53. Keys A. The physiology of life at high altitude. Sci Monthly 1936; 43:289-312.

54. Koyama S; Kobayashi T; Kubo K; Fukushima M; Yagi H; Yoshimura K; Shibamoto T; Kusama S. The role of catecholamines in the genesis of high altitude pulmonary edema (HAPE) (Abstract). In: Sutton JR, Houston CS, Coates G, Editors. Hypoxia and cold New York, NY: Praeger; 1987:542.

55. Levine BD; Yoshimura K; Kobayashi T; Fukushima M; Shibamoto T; Ueda G. Dexamethasone in the treatment of acute mountain sickness. N Engl J Med 1989; 321(25):1707-1713.

56. Larsen RF; Rock PB; Fulco CS; Edelman B; Young AJ; Cymerman A. Effect of spironolactone on acute mountain sickness. Aviat Space Environ Med 1986; 57:543-547.

57. Larson EB; Roach RC; Schoene RB; Hornbein TF. Acute mountain sickness and acetazolamide. Clinical efficacy and effect on ventilation. JAMA 1982; 288:328-332.

58. Maher JT; Cymerman A; Reeves JT; Cruz JC; Denniston JC; Grover RF. Acute mountain sickness: Increased severity in eucapnic hypoxia. Aviat Space Envir Med 1975; 46(6): 826-829.

59. Mathew L; Gopinathan PM; Purkayastha SS; Sen Gupta J. Chemoreceptor sensitivity in adaptation to high altitude. Aviat Space Environ Med 1983; 54(2):121-126.

60. Milledge JS; Catley DM. Angiotensin converting enzyme response to hypoxia in man: its role in altitude acclimatization. Clin Science 1984; 67:453-456.

61. Montgomery AB; Mills J; Luce JM. Incidence of acute mountain

sickness at intermediate altitudes. JAMA 1989; 261(5):732-734.

62. Moore LF. Altitude aggravated illness: Examples from pregnancy and prenatal life. Ann Emerg Med 1987; 16(9):965-973.

63. Moore LG; Harrison GL; McCullough RE; McCullough RG; Micco AJ; Tucker A; Weil JV; Reeves JT. Low acute hypoxic ventilatory response and hypoxic depression in acute altitude sickness. J Appl Physiol 1986; 60(4):1407-1412.

64. Olson LG; Hensley MJ; Saunders NA. Augmentation of ventilatory response to asphyxia by prochlorperazine in humans. J Appl Physiol 1982; 53(3):637-643.

65. Reeves JT; Groves BM; Sutton JR; Wagner PD; Cymerman A; Malconian MK; Rock PB; Young PM; Houston CS. Operation Everest II: Preservation of cardiac function at extreme altitude. J Appl Physiol 1987; 63(2):531-539.

66. Reeves JT; Halpin J; Cohn JE; Daoud F. Increased alveolar - arterial oxygen difference during simulated high - altitude exposure. J Appl Phys 1969; 27(5):658-661.

67. Rock PB; Johnson TS; Larsen RF; Fulco CS; Trad LA; Cymerman A. Dexamethasone as prophylaxis for acute mountain sickness. Effect of dose level. Chest 1989; 95(3):568-573.

68. Schoene RB. Control of ventilation in climbers at extreme altitude. J Appl Physiol 1982; 53(4):886-890.

69. Schoene RB. High altitude pulmonary edema: Pathophysiology and clinical review. Ann Emerg Med 1987; 16(9):987-992.

70. Schoene RB. Pulmonary edema at high altitude: Review, pathphysiology and update. Clin Chest Med 1985; 6(3):491-507.

71. Schoene RB; Hackett PH; Roach RC. Blunted hypoxic chemosensitivity at altitude and sea level in an elite high altitude climber (Abstract). In: Sutton JR, Houston CS, Coates G, Editors. Hypoxia and cold New York, NY: Praeger; 1987:532.

72. Schoene RB; Swenson ER; Pizzo CJ; Hackett PH; Roach RC; Mills JW J; Henderson WR J; Martin TR. The lung at high altitude: bronchoalveolar lavage in acute mountain sickness and high altitude pulmonary edema. J Appl Physiol 1988; 64(6): 2605-2613.

73. Schoene RB; Hornbein TF. High altitude adaptation. In: Murray

JF, Nadel JA. Textbook of respiratory medicine Philadelphia, PA: Saunders; 1988:1646-1664.

74. Schoene RB; Roach RC; Hackett PH; Harrison GL; Mills JW J. High altitude pulmonary edema and exercise at 4400 meters on Mt McKinley: Effect of expiratory positive airway pressure. Chest 1985; 87(3):330-333.

75. Senay LC; Tolbert DL. Effect of arginine vasopressin, acetazolamide and angiotensin II on CSF pressure at simulated altitude. Aviat Space Envir Med 1984; 55:370-376.

76. Singh I; Khanna PK; Srivastava MC; Lal M; Roy SB; Subramanyam CS. Acute mountain sickness. N Engl J Med 1969; 280(4):175-218.

77. Sophocles AM. High-altitude pulmonary edema in Vail, Colorado, 1975-1982. West J Med 1986; 144:569-573.

78. Sutton JR; Bryan AC; Gray GW; Horton ES; Rebuck AS; Woodley W; Rennie ID; Houston CS. Pulmonary gas exchange in acute mountain sickness. Aviat Space Environ Med 1976; 47(10):1032-1037.

79. Sutton JR; Ersley AJ; Caro J; Young PM; Cymerman A; Houston CS. Increased erythropoietin and hemoglobin with exposure to extreme altitude (Abstract). In: Sutton JR, Houston CS, Coates G, Editors. Hypoxia. The tolerable limits Indianapolis, Indiana: Benchmark Press; 1988:376.

80. Sutton FR; Houston CS; Marsell AL; McFadden MD; Hackett PH. Effect of acetazolamide on hypoxemia during sleep at high altitude. N Engl J Med 1979; 301(24):1329-1331.

81. Swenson ER; Maren TH. Acute mountain sickness (Letter). N Engl J Med 1989; 320(22):1492-1493.

82. Swenson ER; Leatham LK; Roach RC; Schoene RB; Mills WF; Hackett PH. The effects of benzolamide on sea level ventilatory drives and periodic breathing and oxygen desaturation during sleep at high altitude. Am Rev Resp Dis 1986; 133:A201.

83. Swenson ER. The respiratory aspects of carbonic anhydrase. Ann New York Acad Sci 1984; 429:547-560.

84. Tojima H; Kunitomo F; Okita S; Yuguchi Y; Tatsumi K; Kimura H; Kuriyama T; Watanabe S; Honda Y. Difference in the effects of acetazolamide and ammonium chloride acidosis on ventilatory responses to CO2 and hypoxia in humans. Jpn J Physiol 1986; 36:511-

521.

85. Wagner PD; Sutton JR; Reeves JT; Cymerman A; Groves BM; Malconian MK. Operation Everest II: Pulmonary gas exchange during a simulated ascent of Mt. Everest. J Appl Physiol 1987; 63(6):2348-2359.

86. Weil JV; Byrne-Quinn E; Sodal IE; Friesen WO; Underhill B; Filley GF. Hypoxic ventilatory drive in normal man. J Clin Invest 1970; 49(6):1061-1072.

86. West JB. Respiratory Physiology - the essentials Baltimore, MD; Williams and Wilkins; 1985:113-127.

88. Wassermann K; Hansen JE; Sue DE; Whipp BJ. Principles of Exercise Testing and Interpretation. Lea and Febiger, Philadelphia, PA; 1987:253-262.

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