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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Acute mountain sickness (AMS) is usually a benign and self-limited illness which befalls previously healthy individuals who ascend rapidly to high altitude without sufficient acclimatization. In its more severe forms AMS can progress to a life-threatening condition in which pulmonary or cerebral edema can occur singly or in concert. High altitude cerebral edema (HACE) is a little known clinical entity which manifests itself by a perplexing array of both generalized and localized neurological symptoms and signs. Furthermore, the development of HACE in climbers offers a unique experimental situation in which to examine the

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March 25, 1986

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Dear Dr. Cymmerman:

Here is a copy of Dr. Allan Hamilton's review of high altitude
cerebral edema submitted to Neurosurgery today. Please let me know if
there are any changes you feel would be necessary if it is accepted.

Sincerely,

Peter McL. Black, M.D., Ph.D.

PB:daa

HIGH ALTITUDE CEREBRAL EDEMA

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Running Title:
High Altitude Cerebral Edema

Abstract

Acute mountain sickness (AMS) is usually a benign and self-limited illness which befalls previously healthy individuals who ascend rapidly to high altitude without sufficient acclimatization. In its more severe forms AMS can progress to a life-threatening condition in which pulmonary or cerebral edema can occur singly or in concert. High altitude cerebral edema (HACE) is a little known clinical entity which manifests itself by a perplexing array of both generalized and localized neurological symptoms and signs. Furthermore, the development of HACE in climbers offers a unique experimental situation in which to examine the effects of hypoxia on the central nervous sytem. The epidemiology and clinical picture of HACE are reviewed. In addition, the pathology and predominant pathophysiological mechanisms postulated to explain HACE are examined and the present recommendations for prevention and treatment of this dangerous and unusual form of brain swelling are discussed. Keywords:

Key Words: acclimatization, acute mountain sickness, carbonic anhydrase inhibitors, cerebral edema, cytotoxic edema, decompression sickness, diuretics, high altitude, hypoxia, pulmonary edema, steroids, vasogenic edema.

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Introduction

Environments at high altitude have served as one of the most important and productive settings for exploring human physiological adaptation. Individuals who ascend rapidly to high elevations without adequate acclimatization are prone to suffer from a broad range of homeostatic disturbances which have been clinically described as acute mountain sickness (AMS). In its benign form AMS is distinguished by the onset of headache, fatigue, drowsiness, lassitude, dizziness, anorexia, nausea, vomiting and sleep disturbances; these symptoms usually start within 6 to 96 hours after arrival at high altitude and resolve with just rest and adequate hydration although occasionally the use of supplemental oxygen may be required (6,10,17,26,30,38,47,52,59). In its more severe form AMS can lead to a life-threatening condition in which the manifestations of high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE) can occur singly or in concert (6,10,12,26,28,30,36,47,51,52,59). The clinical presentation and pathophysiology of HAPE have been previously presented and reviewed elsewhere (16,29,31,51,53). This review will examine the epidemiology and clinical manifestations of HACE, discuss the pathology and pathophysiology of this unique form of cerebral edema as well as the methods for its prevention and treatment in visitors to high altitude.

Historical Background

Mankind has lived in areas of high altitude for as long as there exist historical records. Most of the Altiplano of South

America lies above 11,500 ft (3500 m) and the Tibetan plateaus begin at 10,000 ft (3000 m) and yet both terrains have been continuously inhabited by races well-adapted to living at these elevations for several millennia (27) although no permanent habitations have been found either now or in the archeological record above 17,000 ft. Marco Polo during his travels in the Far East is reported to have climbed over a high range of peaks, aptly named "the headache mountains" (27). Jose de Acosta was a Jesuit priest who accompanied the Conquistadores to Peru and gave us the first written description of acute mountain sickness when he arrived at an elevation of approximately 12,000 ft (3700m) in a mountain pass between what is now the city of Lima and that of Jauga:

"I therefore persuade myself that the element of air is there so subtle and delicate, as it is not proportionable with the breathing of man, which requires a more gross and temperate air, and I believe it is the cause that doth so much alter the stomach, and trouble all the disposition" (7).

It is Acosta who wrote of the mareo de las punas which literally means "seasickness of the desert places" and the term puna has come to mean altitude sickness in Peru.

In 1760 Horace de Saussure offered a monetary prize for the first ascent up Mt. Blanc, the highest peak in Europe, in the hopes that this might encourage guides to develop a route up the mountain so he could climb it. In 1786, a physician, Paccard, and a mountain guide, Balmat, claimed the prize and the next year de Saussure found himself on the summit where he wrote:

"I was constantly forced to interrupt my work and devote myself entirely to breathing...the kind of fatigue which results from the rarity of the air is absolutely unconquerable"(8).

In 1872, a member of the Alpine Club known only by her first name

of Joanne wrote in their journal:

"The lightness and great rarity of air in the Alps...cause
at certain altitudes very noticeable physiological phenomena such
as...nausea, drowsiness, panting, headache, fatigue, etc..."(33).

In 1862 two British balloonists ascended to the height of

approximately 29,000 ft (8840 m) which is virtually as high as

the highest point on Earth, Mt. Everest. They very nearly died

from hypoxia before they could force the balloon to lower

altitudes in their last moments of consciousness. In the late

nineteenth century, Paul Bert performed a series of experiments

in a decompression chamber aimed at permitting balloonist to

conquer even loftier heights and discovered that the administration of

oxygen could prevent or abolish most of the symptoms of high

altitude, remarking in his notes:

"...the favorable effects of inhalation of oyxygen. Return
of strength and appetite, decrease of headache, restoration of
clear, calmness of mind...." (2)

IN 1854 Dr. Conrad Meyer-Ahrens of Leipzig published a

compendium of alpinist's woes and wrote:

"The principal symptoms (of altitude illness)...which occur
oftenest in man are: discomfort, distaste for food, especially
distaste for wine (however, the contrary has sometimes been
noted), intense thirst...., nausea, vomiting; accelerated and
panting respiration; dyspnea, acceleration of the pulse,
throbbing of the large arteries and temples, violent
palpitations, oppression, anxiety, asphyxia, vertigo, headache,
tending to syncope, unconquerable desire for sleep, muscular
fatigue...blunting of sensory perception and the intelligence,
impatience, irritability...finally, buzzing in the ears." (39)

Scarcely anything could be added even today to this list of ills that

constitute altitude sickness. Angelo Mosso, an Intalian

physiologist, developed the first high altitude research station

and in 1898 originally described periodic sleep disturbances associated with high elevation (44). Other studies performed in his decompression chamber showed that at a barometric pressure of 246 mm Hg (equivalent to the altitude of the summit of Mt. Everest) the composition of expired gas had a pO_2 of only 40 and a pCO_2 of 5 mm Hg. Because of these observations, he introduced the notion that diminished $pCOP_2$, or "acapnia," as he called it, might play a significant role in AMS (43).

IN 1913, T.H. Ravenhill described (47) his observations of mountain sickness in the Andes where he was stationed as a medical officer in one of the mining districts. He described "normal puna" which comprises the earliest, benign features of AMS. He also further identified "cardiac puna" in which the signs and symptoms were primarily cardiopulmonary in nature and correspond to what we term today HAPE. His last category was that of "nervous puna" in which neurological manifestations dominated the clinical picture and would be equivalent to HACE. Ravenhill was the first to comprehend clinically that it was dysfunction within these two organ systems which dominated the pathophysiology of severe AMS. In 1919 a British scientist named Joseph Barcroft spent 10 days in a "Glass House" in Cambridge, England in which the prcentage of oxygen was lowered to that found at 18,000 ft. By the sixth day, Barcroft was experiencing all the symptoms of AMS. During his "stay" at high altitude he demonstrated that there existed a diminished alveolar arterial

oxygen gradient by drawing arterial specimens from his radial artery and simultaneously determining the alveolar oxygen concentration in breath samples taken at end expiration. He irrevocably refuted with this data Haldane's then popular notion that oxygen could be secreted against a concentration gradient from the alveoli into the pulmonary capillaries and that such active secretion constituted the physiological basis for high altitude adaptation.

By the middle of the twentieth century Carlos Monge had published his classic work on chronic high altitude adaptation amongst the native populations of the Andes (41,42) to which Hurtado was to add a great wealth of physiological data on both human and animal subjects (32). In 1960 Charles Houston, who is one of the modern day American fathers of high altitude physiology, had described the first case of HAPE (25) in the English literature and Hultgren et al (31) described four more cases of HAPE within the next year. In 1960, Chiodi (5) first reported on a Peruvian patient suffering with severe AMS who experienced occipital headaches, altered consciousness and paresthesias and postulated that these manifestations reflected a cerebral form of high altitude illness. In 1964, Fitch described a similar form of mountain sickness with neurological manifestations in the English literature (12). The following year, large numbers of Indian troops were amassed along the mountainous borders between India and Pakistan during an outbreak in hostilities and Singh et al (51) evaluated nearly two thousand soldiers rapidly ascending to high altitude. They

first described neuropathological findings of cerebral edema and widespread petechial hemorrhages in two HAPE fatalities and later reported (52) neurological manifestations in 24 soldiers suffering from severe AMS at 18,000 ft. In 1975, Houston and Dickinson (28) presented a series of 12 patients with histories and clinical presentations suggestive of predominantly cerebral as opposed to pulmonary edema in the course of their illness at high elevations and coined the phrase "high altitude cerebral edema" or HACE.

Epidemiology

There are several limitations to be considered when trying to arrive at an understanding of the incidence of AMS. First, the true incidence cannot be known with certainty because the population at risk cannot be clearly identified (26) . Furthermore, until recently only small groups of exceptionally fit individuals (mostly mountaineers and soldiers) underwent acute, well-documented exposures to the highest altitudes for a period of several days and this limited the applicability of any statistical conclusions drawn from studies of such select groups to larger populations. In addition, observations made on individuals stricken with AMS were often performed only once they had been evacuated down from higher altitudes and their symptoms and signs might have already started to resolve. Finally, with multi-national expeditions entering high altitude regions, language difficulties often made precise interviewing impossible and valuable epidemiological information was missing (10). More recently, the popularity of mountaineering has surged in

conjunction with increased air travel permitting ever larger numbers of individuals with lesser degrees of physical fitness to ascend to high altitudes in very short periods of time thereby reducing the extent of acclimatization and increasing the likelihood that severe AMS may occur.

Hackett et al (22) examined 278 trekkers arriving at 14,000 ft (4,243m) on the route to the Mt. Everest Base Camp during a one month interval and placed the overall incidence of AMS at 53% and the that of severe, life-threatening AMS at 4.3% within this particular group. It is also important to distinguish between those individuals suffering primarily from pulmonary as opposed to cerebral manifestaions of AMS. As mentioned earlier, Singh et al (52) examined 1925 Indian soldiers at high altitude between 11,000 (3350 m) and 18,000 ft (5500 m) in their classic paper and found that the incidence of AMS varied widely from 1.01 to 83.3 per 1000. Furthermore, they identified 24 (1.2%) cases of HACE within this group and three patients within this group died from neurological complications. In his analysis of 39 cases of severe AMS between 1969 and 1978 at the general hospital in Kathmandu, Nepal, Dickinson found only 3 (7.5%) suffering from HAPE alone, 10 (26%) suffering with HACE alone and the remaining 26 (66%) have features of both forms (10). Within this series of severely stricken patients, 5 (12.8%) died from their illness. In a separate review of 12 cases of AMS in which the manifestations of HACE were predominant features in the clinical presentation, two fatalities reported (28).

Dickinson found his patients with severe AMS were derived from 15 different nationalities (including two native Nepalese sherpas) and ranged from the second to seventh decades in age (10). Hackett and his colleagues (21,22) found, however, that younger trekkers tended to be more susceptible to AMS than older ones even if differences in rate of ascent were taken into consideration. In both studies of AMS, a preponderance of males was found; 84.6% in Dickinson's paper and 71% in that of Hackett et al; this sex distribution undoubtedly reflects the larger numbers of males presently involved in trekking and mountaineering.

Altitude of onset of AMS is, to a large extent, dependent on the rate of ascent. AMS is rarely experienced below 6,560 ft (2000 m) but becomes increasingly common after 9,840 ft (3000 m) and death from HACE has been reported at altitudes as low as 8200 ft (2500 m) (26); 87% of the cases of severe AMS that were seen by Dickinson (14) occured between 10,000 ft (3050 m) and 18,000 ft (5500 m), which is roughly the same range of altitude in which Singh et al (52) reported their 24 cases of HACE.

Clinical Manifestations

A variety of schemes have been proposed to classify and categorize the wide spectrum of clinical manifestations of AMS (10,47,52,60). For the purposes of discussion in this review, the classification adapted by Dickinson (10) will be employed. Clinical manifestations grouped under the general term AMS are subdivided into those features which are clinically benign and generalized versus those features which are malignant and organ

specific. These maligant fe. tures are then subdivided into those

attributable to HAPE or HACE (see Table I).

The earliest signs of AMS are headache, nausea and vomiting,

anorexia, and sleep disturbances (60); other early and benign

signs of AMS which might be attributable to early cerebral edema

are loss of memory, tinnitus, irritability, emotional lability

and mood disturbances as well as dilatation of retinal veins and

retinal hemorrhages. Similar disturbances in mentation and

retinal vein morphology were described in earlier human studies

in decompression chambers and ascribed to increased intracranial

pressure (40). Of 840 Indian soldiers who were judged

incapacitated with symptoms and signs of early, benign AMS but

did not receive any medical treatment, the symptoms were in order

of decreasing frequency: headache, nausea, anorexia, dyspnea,

insomnia, muscular weakness, fullness or pain in the chest,

giddiness, vomiting, lethargy, thirst, indigestion, hysterical

outburst o: other behavior disturbances, decreased concentration,

fever, cough and peripheral edema (52). The onset of symptoms is

usually between one and three days after arrival at high altitude

(12,17,26,28,51,52,59). Singh et al (52) showed that only 38% of

patients were free of the symptoms and signs of AMS within 3 days

of their arrival; furthermore, 12.5% of affected soldiers still

remained incapacitated after 2 weeks of attempted acclimatization

and 1% were still not acclimatized at the end of 6 months.

Estimates as to the incidence of severe or malignant HACE

amongst those affected by high altitude sickness are quite

variable as discussed earlier. Of the 39 patients Dickinson studied with severe AMS, 92% had evidence of HACE as part of their clinical picture (10). As will be discussed in a later section, the mechanisms which may be involved in the pathophysiology of HACE are numerous and can have multiple and overlapping effects on the central nervous system. As a result of this, there is an enormous diversity in the clinical manifestations of HACE itself.

Observations of alpinists had suggested that severe deterioration of sensory, motor and higher cognitive functions occurred with increasing altitude and that at extreme altitude, the behavior of mountaineers might closely parallel that of patients with acute organic brain syndromes (37,57). Electroencephalographic recordings of subjects at sea level and subsequently at 11,480 ft (3500 m) showed increased levels of alpha-wave activity suggesting diffuse cortical depression (48). Reductions in arterial blood saturation down to 45% (such as have been shown to occur with exertion at extreme altitudes) lead to faulty judgement, behavioral changes and impaired motor function (57). Members of the 1981 American Medical Research Expedition to Everest underwent the administration of a battery of cognitive and neuropsychological tests 2 months prior to, within days immediately after, and one year after their ascent on Everest. The results of this study (57) showed that ascent to extreme altitudes was accompanied by significant deterioration of fine motor coordination, short-term and long-term memory, and language abilities (as determined by errors in reading, writing and spelling); in addition, the altitude attained by individual members was significantly related to the increase in so called

"aphasia errors." Furthermore, and perhaps more distressing, some of these cognitive deficits were still significantly demonstrable over a year after return to sea level.

Houston and Dickinson compiled 12 cases of severe AMS in which the primary clinical problem was that of HACE (28). In eleven out of the twelve patients some details of the history and physical examination are available to us. Three patients exhibited emotional lability early on in their illness. Four out of twelve complained of decreasing ability to concentrate. One half of the patients eventually lost consciousness and became comatose during the course of their disease. Two patients experienced diplopia and two other patients displayed abnormal pupillary responses. Five out of the group of patients exhibited ataxia and four exhibited abnormal reflexes, including plantar extension (Babinski's sign). One patient exhibited meningismus while another displayed decerebrate rigidity. Gray et al (17) and Wilson (59) have commented on the development of ataxic gait in climbers, particularly those to whom furosemide has been administered either to prevent or treat AMS. Dickinson (10) has commented that tests for cerebellar ataxia were amongst the most sensitive in detecting early cases of HACE, confirming reports from others (17,59) that the cerebellum appeared to be particularly sensitive to high altitude hypoxia. Singh et al (52) studied 24 cases of HACE whose presentations included other neurological problems paralysis, hemiparesis and seizures. One particular patient exhibited unilateral palsies of the sixth and

seventh cranial nerves and underwent craniotomy for what was suspected to be a hitherto subclinical cerebral tumor. Biopsy revealed only edematous brain with no evidence of tumor. Dickinson (10) has reported on a Japanese climber who developed a gross, coarse 'hand flapping' that was indistinguishable from that seen in hepatic encephalopathy and resolved in a matter of days after descent.

Retinal hemorrhages were first described in 1968 in two individuals working on Mt. Logan at 17,500 ft (5300 m), one of who also exhibited papilledema and was semi-comatose (15). Singh et al (52) had reported finding engorgement of the retinal veins, blurring of the optic disk margins and frank papilledema (4 diopters) in four cases of HACE. In 1969 (15), 25 subjects underwent fundoscopic examination to detect retinal hemorrhages during the course of acclimatization at the Mt. Logan research station. Over one third of the subjects developed retinal hemorrhages; only one subject was symptomatically aware of the presence of the hemorrhages because it had occured in the region of macula and resulted in a scotoma. Marked hyperemia around the optic disk and increased diameter and tortuosity of retinal veins and arteries were noted in all subjects and these changes persisted throughout their stay at high altitude regardless of level of acclimatization achieved. Fluorescein injections did not demonstrate the presence of active capillary leakage nor was intraocular pressure elevated; mean retinal circulacion time was decreased by approximately 30% which parallels increases in cerebral blood flow measured by others at high altitude (52). No

was negative in all cases and normal respiratory excursions were
seen. CSF chemistries and cell counts were normal. Houston and
Dickinson (28) also reported that lumbar punctures were performed
on five of their twelve cases. Four of the five exhibited
elevated opening pressures greater than 200 mm of water; the
fifth had a normal opening pressure but had been vigorously
treated with diuretics prior to the assessment of CSF pressure.
CSF from one of the patients was reported as "bloody" in
appearance and a CSF cell count from a second patient showed a
leucocytosis suggestive of meningitis. Wilson (59) reported on a
climber suffering with decreased mentation, ataxic gait,
dymetria, blurred vision and retinal hemorrhages whose opening
pressure was 340 mm H_2O with normal CSF chemistries and cell
count. After resolution of HACE over 4 days and after evacuation
to lower altitude and treatment with steroids and diuretics, CSF
pressure was 85 mm H_2O. In 1960, Chiodi (5) described a patient
suffering with HACE who developed occipital headaches,
paresthesias, intermittent loss of consciousness and who went on
to develop nucchal rigidity and hyperreflexia. A lumbar puncture
was performed which revealed grossly hemorrhagic CSF. A
susbsequent cerebral angiogram was reported as normal. This is
the only case in the literature in which a patient suffering with
HACE has undergone cerebral arteriography to date.

   The issue as to whether any of these neurological deficits
are permanent sequelae from a vist to high altitude is a
significant issue not only for candidates of high altitude
expeditions but also in determining the vigor and rapidity with

...tion was found ... ... symptoms attributable to AMS ...l the prese...nce or absence of retinal hemorrhages. Houston and Dickinson (28) found retinal hemorrhages to be present in 7 out of t... ...heir 12 reviewed cases of HACE while papilledema was fo... ...varying degrees in 75% of the cases. The exact significance an... ...ognosis of these fundoscopic observations is debatable (6,15,18, 7,30,58). More recent studies (27) over the last decade seem to indicate that retinal hemorrhages occur in more than 50% of all persons going to high altitude, that they are rarely if ever symptomatic, that the incidence of papilledema as reported on the basis of direct ophthalmoscopy is not confirmed by stereo-pair photographs, and that almost all hemorrhages resolve without leaving permanent deficits. Weidman (18,58) has developed a classification system whereby retinal hemorrhages can be grouped according to their severity and the increasing likelhood of permanent visual impairment. Furthermore, he contends that the more serious retinal changes serve as one of the best indicators of how deleterious an effect high altitude hypoxia may be exerting on similar vascular beds in the brain and can therefore serve to identify individuals at risk for severe HACE.

Singh et al (52) performed lumbar punctures on 34 patients during and after their recovery from AMS and in all patients found the cerebrospinal fluid (CSF) pressure to be elevated by 60 to 210 mm of water during the illness as compared to when they had recovered. Queckenstedt's test (jugular venous compression)

which physicians initiate therapy for HACE and begin evacuation
of stricken individuals to lower altitudes. As we have already
seen, Townes et al (57) have demonstrated long-lasting cognitive.
dysfunction in high altitude climbers and several authors have
commented on permanent visual deficits from retinal hemorrhages
in the macular region (18,27,58). Dickinson (10) has reported on
two climbers suffering from HACE who remained unconscious for 6
weeks in one case and 3 weeks in another. Pines (46) has
described a case of a 39 year old climber who ascended rapidly to
18,500 f: (5600 m) and subsequently developed severe HACE with
loss of consciousness, absence of pupillary reactions, flaccidity
of all extremities and the presence of bilateral Babinski
responses. The climber was emergently evacuated to lower
altitudes and treated with steroids; 48 hrs later the patient had
regained consciousness but was left with slurred speech and
ataxia. Neurological examination a month later still showed
intellectual impairment, emotional lability and ataxia causing
the author to suggest that some neurological sequelae of HACE may
not resolve. Dickinson (10) cautions that cerebrovascular
accidents may occur in setting of individuals at high altitudes,
as has happened to one Sherpa and a physician on previous Everest
expeditions in the recent past, and that such a superimposing of
pathologies may confound the picture of transient and permanent
deficits. Finally, the recent trend in mountaineering towards
climbing Himalayan peaks without the aid of supplemental oxygen
has made the made it even more urgent that the issue of permanent

neurological sequelae from prolonged high altitude exposure be
resolved.

Pathology

Necropsy findings (see Table II) from confirmed cases of
HACE are rare. Singh and his colleagues first reported in 1965 on
autopsy findings in 7 fatalities from HAPE and noted that
histopathological examinations of the two brains available for
study revealed congested, dilated capillaries throughout the
brain parenchyma (51). Many of the capillaries appeared to be
plugged with sludged erthrocytes and there were numerous,
widespread perivascular hemorrhages at such capillaries,
producing a typical so-called 'ring-and-ball' appearance. In the
largest clinical study of AMS to date, Singh et al (52) reported
that both autopsies in their 1969 series showed well developed
edema of the white matter and that both patients also had
evidence of pulmonary edema at post-mortem examination. As
mentioned earlier, a biopsy taken from one of their patients who
was suffering with very localizing signs of HACE also showed
brain edema. Houston and Dickinson (28) reported autopsy results
from the two fatalities in their series. In both cases multiple,
widespread petechial hemorrhages were noted throughout the brain.
One brain was avaliable from a climber who became comatose with
HACE at 18,000 ft (5480 m) and had been ill for almost a week prior to
evcuation and so had suffered from HACE for a relatively long
time before being evacuated. He subsequently died showed evidence
of several small intracerebr' hemorrhages and subarachnoid
hemorrhages. There were areas of focal degeneration noted at

sites of resolving petechial hemorrhages as well as areas of moderate focal edema at what were felt to be sites of more severe edema during the acute illness. Wilson (59) reports that autopsy in one his reported cases of death from AMS revealed a grossly edematous brain weighing 1610 gms and exhibiting flattened convolutions. Microscopic examination revealed widespread edema with occasional petechial hemorrhages found throughout the brain but more numerous in the regions of the thalamus and pons.

Pathophysiological mechanisms

It has long been observed that the symptoms and signs of AMS do not manifest themselves immediately upon arrival at high altitude but take between 12 and 96 hours to be exhibited; this time lag between arrival and onset of AMS argues against a direct, immediate relationship between AMS and hypoxia (52). Houston (26) has also points out that oxygen uptake itself is the same at sea level as at high altitude and is unaffected by acclimatization; he argues that hypoxia must then lead to AMS by its secondary effects on tissue function. Finally, anecdotal reports state that simply providing supplemental oxygen does not prevent or relieve the symptoms of AMS (28).

Hansen and Evan (24) first hypothesized that many of the symptoms of AMS corresponded to symptoms one might expect with "brain cell compression" and suggested that the neurological aspects of altitude sickness could be ascribed to early cerebral edema. Such a notion appeared to be supported not only by earlier experimental and clinical studies which had demonstrated that

hypoxia at high altitude produced brain swelling, headache and elevations in CSF pressures (13,40,45) but also by intra-operative observations which revealed swollen, edematous brain bulging through burr holes during trephining for relief of raised intracranial pressure in two severe cases of HACE (28).

Two pathophysiological theories contend at present as to the nature of the swelling involved in HACE. Lassen and his colleagues (55,36) contend that HACE is primarily an edema of the vasogenic type according to the classification of Fishman (11). In their view, high altitude brain swelling is caused by a vasodilatory response to hypoxia with subsequent increased cerebral blood flow and compromised autoregulation. There is evidence that cerebral blood flow is substantially elevated during the first few days after arrival at high altitude (50,52), suggesting that the vasodilatory effect of hypoxia is predominant over the vasoconstrictive stimulation of hypocapnia secondary to hyperventilation. Lassen and his coworkers further maintain that moderate hypertension attendant with strenous exercise, and especially isometric exercise, at high altitude then overwhelms the integrity of the blood brain barrier, leading to transcapilary and transarteriolar leakage and a vasogenic, multifocal cerebral edema ensues (36,55). They compare HACE to hypertensive encephalopathy and cite the similarity between hypertensive retinal hemorrhages and those seen at high altitudes.

This notion of vasogenic edema contrasts sharply with that of Houston and Dickinson (28) who theorize that HACE is caused by

massive hypoxic cell damage producing edema of the cytotoxic type as this is variety generally seen in the setting of experimental hypoxia studies (60). According to Fishman (11), cytotoxic edema in the setting of hypoxia would result from a failure of the cellular ATP-dependent sodium pump and soon sodium and water would accumulate within brain cells leading first to compromise of cellular functions and eventually to death of the affected brain cells. Fishman also points out that endothelial cells may be particularly affected by hypoxia, setting the stage for vascular disturbances superimposing themselves upon those occuring at the cellular level. Houston and Dickinson (28) cite necropsy findings of widespread edema along with multiple, diffuse petechial hemorrhages as evidence that such a series of hypoxia-mediated changes may be occuring in the brain during HACE. They also cite the findings of retinal vein engorgement during experimental hypoxia (13) and simulated high altitude (40) as evidence of a similar etiology for retinal hemorrhages in the setting of HACE.

Wohns (60) has reviewed Fishman's (11) pathophysiologic classification of vasogenic, cytotoxic and interstitial brain edema and its relationship to HACE. He argues that interstitial edema places little or no role in HACE as the clinical syndromes associated with this kind of edema, such as obstructive hydrocephalus or pseudotumor cerebri, bear little resemblance to the picture seen with AMS. Steroids, which have proven beneficial in the treatment of some cases of early AMS and severe HACE

(14,52), are of little benefit in the treatment of either interstital or cytotoxic edema (11) and this would seem to argue that vasogenic edema is playing some role in the pathophysiology of HACE. Wohns also cautions (60) that experimental models of hypoxia which initially may produce cytotoxic edema can also lead to confounding vasogenic swelling. Since this same phenomenon might also be occuring in the setting of HACE, one must be wary about drawing any conclusions about pathophysiological validity that are based upon therapeutic efficacy. It is quite feasible that the initial pathophysiological event in HACE is hypoxia-mediated compromise of the ATP-dependent sodium pump leading to brain cell dysfunction. Superimposed on these first cytotoxic changes may then follow vasogenically mediated events. Fishman points out that most patients with cerebral infarction--a hypoxic, cytotoxic event--go on to show signs of local vasogenic edema as evidenced by focally positive brain scans (11). As discussed earlier, many HACE patients do exhibit isolated neurological deficits suggesting well-localized anatomical disturbances. Many investigators have also reported (5,28,59) that their patients exhibited bloody CSF on lumbar puncture and at least one necropsy demonstrated both intracerebral and subarachnoid hemorrhage (28), supporting the view that localized disruption of the blood brain barrier is taking place in some instances of HACE. In addition, necropsy reports cite diffuse, localized petechial hemorrhages and the histological demonstration of 'ring-and-ball' hemorrhages, all arguing that some vasogenic component, namely

localized disruption of the blood brain barrier, must be at work
in the setting of HACE. Wohns has also pointed out that since
specific regions of the brain such as the pineal gland,
hypothalamus, pituitary gland, area postrema and choroid plexus
possess a fenetstrated endothelium and are therefore lacking an
intact blood-brain barrier such areas may be predisposed to edema
and thus rendered particularly sensitive to the effects of high
altitude (60). To date, necropsy findings have not addressed this
specific point although there is some physiological data to
suggest that there is impaired hypothalamo-pituitary function at
high altitudes with respect to anti-diuretic hormone secretion
(see below). Finally, although the relationship to retinal
hemorrhage remains conjectural (6,28), the fact that such
vascular disruption occurs within the eye at high altitude (15)
as frequently as now seems apparent would make it likely that
similar events may be taking place within the brain.

"Hohendiurese", or the diuresis of high altitude, was quite
a familiar phenomenon to early alpinists and had been clearly
documented in both real and simulated high altitude settings
(4,52). It was also noted that climbers who acclimatized well
experienced a marked diuresis for the first three or four days
upon arrival at high altitude while those who did not acclimatize
rapidly often exhibited oliguria and many developed symptoms of
AMS (9,19,52,). Singh et al (52) found that 118 soldiers
affected with symptoms of AMS within 6 to 96 hours after arrival
at high altitude showed oral fluid intakes exceeding urine output

by 1100 mls to 43 mls per day as opposed to a comparable group of soldiers who exhibited no symptoms of AMS and showed a urine output exceeding their oral intake of fluids by a range of 930 mls to 4700 mls per day. In addition, this same study revealed that improvement within the symptomatic group was preceeded by a similarly vigorous diuresis which persisted 2 to 10 days after the symptoms of AMS had resolved. It was postulated that such "hohendiurese" might be reflection of dimin_shed arginine vasopressin (AVP) secretion from the posterior lobe of the pituitary gland in the setting of hypoxia; furthermore, undiminished AVP secretion in the setting of AMS might then be amenable to treatment with diuretics before cerebral edema became advanced (52). Several clinical trials employing diuretics to prevent and treat AMS have been performed and the results will be discussed below. Hackett et al (20) observed that trekkers with HAPE exhibited higher levels of AVP than did unaffected trekkers. Jones et al (35) demonstrated reduced secretion of AVP in the setting of dehyration and serum hypertonicity in rats at high altitude. More recent studies (3) performed during the 1981 American Medical Research Expedition to Everest showed that prolonged exposure of humans to high altitude was also accompanied by impaired osmoregulation and that increases in serum tonicity failed to induce appropriate AVP secretion, suggesting that hypothalamic-posterior pituitary dysfunction does occur at extreme altitudes. Whether such suppression of AVP release plays a protective role in high altitude acclimatization and whether individuals susceptible to AMS demonstrate

persistent, "sea-level" release of AVP, as suugested by Hackett's preliminary data in HAPE patients (20), is a question that merits further investigation.

Finally, Sutton and Lassen (55) postulated that AMS and HAPE had a common underlying pathophysiological basis, namely increased flows in both the cerebral and pulmonary vascular beds both of which were damaged by hypertensive surges. In the pulmonic circuit, arterial hypertension would arise as the result of hypoxic vasoconstriction and dramatic elevations in pulmonary artery pressures are commonly seen in HAPE (49). In the cerebral vasculature, arterial surges are hypothesized to arise from both physical exertion and extreme cold at high altitudes. Wohns has suggested that HAPE may in fact be a variant of neurogenic pulmonary edema and occurs as a manifestation of hypothalamic dysfunction in HACE (60). Recent animal studies (61) have demonstrated that pre-treatment with diphenylhydantoin, an anticonvulsant, prevented the occurence of pulmonary edema in the setting of cerebral edema, supporting the notion of a neurogenic origin. While numerous cases of HAPE have occured without clinical evidence of HACE being present such overt neurological manifestations may only occur in a small majority of the most severely affected patients. On the other hand, nearly every necropsy to date of patients with neuropathological evidence of cerebral edema has demonstrated concomitant pulmonary edema.

Prevention and Treatment of HACE

Given the abundance and divergence of pathophysiological

mechanisms postulated to play a role in the development, it is not suprising that a equally wide variety of preventive measures and therapies have been proposed and examined.

Since the deleterious effects of exposure to high altitude can be prevented or dramatically reduced by proper acclimatization, most protocols aimed at lessening the incidence and severity of AMS have been directed at determining the most effective rate of ascent to allow adequate acclimatization. With respect to mobilizing Indian soldiers safely to high altitudes, Singh et al (52) recommended a one week stay first at 8,000 ft (2400 m), a second week at 11,000 ft (3350 m) and a final week at 14,000 ft (4270 m) to provide adequate acclimatization for most subjects up to 18,000 ft (5500 m). Hackett (19) recommends acclimatizing for one extra day for every 3300 ft (1000m) of elevation gained above 10,000 ft (3000 m) and setting one's rate of ascent at 1000 ft (300 m) per day upward from 10,000 ft. He also warns against sudden transportation to an altitude greater than 10,000 ft. Hackett and Rennie (21) have shown that after widespread dissemination of clinical information about acclimatization within climbing circles in 1975, a statistically significant prolongation of ascent time could be demonstrated amongst trekkers arriving at Everest Base Camp at Pheriche, Nepal. Furthermore, they also showed that such acclimatization protocols had proven effective in lowering the incidence of AMS-related deaths amongst Himalayan trekkers from 5 in 1974 to zero in 1977 and reducing the number of emergent helicopter evacuation of AMS stricken climbers from 15 down to a single one over the

same period.

Because of the promising data reviewed above suggesting that inducing "Hohendiurese" might prevent the onset of symptoms of AMS, Singh et al undertook a study wherein 100 soldiers were treated with 80 mg of oral furosemide twice a day for two days after arrival at high altitude and compared to comparable controls. They found that the incidence of subjective symptoms of AMS was diminished by over half and the incidence of severe dyspnea was completely abolished.

From furosemide, other investigators turned their attention to acetazolamide, a milder diuretic which also had several theoretical benefits for high altitude acclimatization (17). First, acetazolamide is a carbonic anhydrase inhibitor and such enzyme inhibition would favor the creation of a metabolic acidosis to offset the hypoxic respiratory alkalosis of high altitude hyperventilation. In addition, acetazolamide is known to reduce the rate of cerebrospinal fluid formation and this might alleviate rises in intracranial pressure asociated with HACE. In 1968 Forwand et al (14) undertook a double-blind study in which 43 subjects received either placebo or acetazolamide for 32 hours prior to airlift to Mt. Evans, Colorado at an altitude of 12,800 ft (3900 m) and found that treated subjects experienced significantly fewer symptoms of AMS and exhibited a greater increase in ventilation and alveolar oxygen tension than the placebo-treated counterparts. Later, Gray et al (17) undertook a similar but smaller trial in which 6 subjects were given 250 mg

of acetazolamide twice a day for two days prior to ascent to 17,500 ft (5400 m) and four subjects were given placebo. All four subjects who recieved placebo were incapacitated with severe AMS although none had any evidence of pulmonary congestion. In contrast, the subjects pretreated with acetazolamide fared much better. Five of the six had mild symptoms of AMS, mostly nocturnal headache while the sixth became incapacitated and was later found to have a fever. Two of the acetazolamide-treated showed signs of pulmonary congestion and one was subsequently evacuated because of HAPE. Finally, acetazolamide seems to be more effective than traditional sedatives at relieving the insomnia that is often experienced by recent arrivals at high altitudes and accompanies AMS; sedatives may depress ventilatory drives during sleep and actually worsen arterial desaturation thereby making AMS more likely to occur (56).

Because many believe that the earliest symptoms of AMS are manifestations of vasogenic cerebral edema (see above), a small double-blind crossover study was recently performed (34) in which subjects were pretreated with dexamethasone and then remained in a hypobaric chamber for 42 hours while they were queried and examined for symptoms and signs of AMS. Subjects reported a significant decrease in both respiratory and cerebral symptoms, exhibited significantly narrower retinal artery diameters on serial fundoscopic examinations and demonstrated a higher urine output, thus supporting some of earlier anecdotal reports from Singh's group (52) of improved diuresis after steroid administration in AMS patients.

Treatment of HACE in the setting of AMS has involved a wide variety of therapeutic agents. In this regard, Singh and his colleagues stand unequaled for the breadth and scope of their therapeutic trails (52). Aspirin was administered at a dose of 0.6 gm three times a day for two days to 250 subjects with symptoms of AMS. While aspirin did relieve headache pain and promote sleep, it had no other significant effects on any of the other symptoms of AMS and produced a number of side-effects in the treated group, namely increased dyspnea, abdominal pain and hematemesis.

As early as 1919, Haldane and his colleagues had suggested that the symptoms seen in AMS might be related to the ventilatory alkalosis and that administration of ammonium chloride might prove beneficial in hastening acclimatization (23). Barron et al (1) administered ammonium chloride to 6 out of 12 climbers ascending to 15,500 ft (4725 m) and found that although the treated subjects exhibited lower carbon dioxide and increased oxygen concentration in expired alveolar air there was no significant difference in the symptoms of AMS experienced by either group. More recently, Singh's group (52) administered 2 gms ammonium chloride orally for 3 days to 30 subjects with AMS in the hopes that some of their symptoms might be due to the early respiratory alkalosis seen upon arrival at high altitude. Unfortunately 23 out of the 30 subjects felt worse after treatment. Since it was postulated that hypokalemic alkalosis might occur during acclimatization, Singh et al (52) also treated

30 patients with daily potassium supplements but found no significant improvement.

Returning to the notion of inducing "hohendiurese" with furosemide, Singh and his colleagues (52) treated 446 cases of AMS with a usual dose of 80 mg of furosemide every 12 hours for two days or until an adequate level of urine output occured. The therapy was described as effective although actual data in support of furosemide treatment was derived from a prophylactic trail of furosemide described above rather than an actual therapeutic trail. Forty-two cases of malignant AMS with predominantly pulmonary mainfestations were treated with furosemide alone and forty-two cases were treated with a combination of morphine and furosemide therapy. The latter group demonstrated a more effective diuresis although no clinical data was presented to determine if one group fared better clinically. Nineteen out of 24 cases of severe HACE were treated with furosemide and betamethasone. Although again no quantitative clinical data was provided, Singh et al reported that patients improved rapidly with such combination therapy and presented one illustracive case where administration of steroids was followed by prompt diuresis, a fall in CSF pressure and resolution of papilledema (52).

Anecdotal reports wherein patients suffering from severe HACE received steroid therapy and subsequently improved and recovered without neurologic defict abound (10,28,46,52,59,). It is exceedingly difficult to differentiate the effects of descent to lower altitude and other therapies which were concomitant with

the administration of steroids. Wilson reports on one climber severely affected with HACE and still exhibiting slow mentation, wide-based ataxic gait, and dysmetria upon his evacuation to a hospital at sea level and who was treated solely with dexamethasone with full recovery within approximately a week's time (59).

The use of furosemide in the treatment of HACE is potentially hazardous since almost all climbers at high altitude are volume contracted from dehydration, increased insensible respiratory losses, vomiting and poor fluid intake (59). Gray et al (17) administered furosemide to five subjects suffering from severe AMS. Three of the treated individuals developed severe ataxia of gait, another became incapable of standing and the last member of this group lapsed into coma and required emergent evacuation. The investigators reported that volume depletion was clinically evident in this group with two patients becoming hypotensive and tachycardic. Four out of the five subjects developed concomitant retinal hemorrhages. Wilson (59) also reported a patient who exhibited ataxic gait after furosemide administration. Singh et al, however, in the largest single study of furosemide in the treatment of HACE reported no subsequent ataxia (52) although many of their patients with HACE also received steroids concomitant with diuretic therapy and this may have altered the clinical results.

Finally, the best treatment for AMS (see Table III) still remains prevention by slow, deliberate ascent to high altitude.

Acetazolamide seems to alleviate some of the early symptoms of AMS. In cases of severe AMS with evidence of cerebral edema, oxygen therapy should be instituted. The stricken individual should be promptly evacuated to lower altitude and steroid therapy is probably useful at least initially. The use of diuretics and morphine should probably be conservatively employed for cases where there is clinical evidence of pulmonary congestion.

Acknowledgements:

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Table I: Clinical Features of Acute Mountain Sickness (AMS)
[Modified from Dickinson (14)]

Early, Benign AMS: Systemic Generalized Features

Headache   Chest discomfort or fullness
Nausea, vomiting   Peripheral edema
Vertigo, insomnia   Retinal hemorrhages
Generalized fatigue   Anorexia
Irritability   Mental slowness
Tinnitus

Malignant Features of AMS constituting High Altitude Pulmonary Edema (HAPE)

Dyspnea at rest   Cyanosis
Cough   Basal crepitations
Sputum production (frothy)   Tachypnea
Hemoptysis   Tachycardia

Malignant of AMS constituting High Altitude Cerebral Edema (HACE)

Common features:

Severe headache   Altered level of consciousness
Vomiting   Hypo- or hyperreflexia
Impaired sensory, motor functions Ataxia
Impaired long, short term memory   Papilledema
Extensor plantar responses

Less Common features:

Hallucinations   Blurred vision
Scotoma   Speech difficulty
Urinary incontinence   Cranial nerve palsies
Hemiparesis   Rigidity or flaccidity
Paresthesias, dysesthesias   Convulsions
Visual field defects   Tremor
Pupillary changes   Meningismus

Table II: Pathologic Features Of
High Altitude Cerebral Edema (HACE)

Edema of white matter
Widespread petchial hemorrhages (perivascular 'ring and ball')
Sludging of erythrocyes in capillaries
? intracerebral hemorrhages
? preponderance of thalamic and pontine hemorrhages
? subarachnoid hemorhages

Table III: Prevention and Management of HACE

Prevention

slow acclimatization [adapted from Hackett (28)]
  Rules of thumb: Start walking at 10,000 ft (3,000 m)
                 1000 ft (300 m) of ascent per day
                 1 night of aclimatization for every 3000 ft
(1000m) gained above 10,000ft (3000m)
Acetazolamide

Management

Early AMS:

Analgesics for headache
Hydration
Rest
Supplemental Oxygen
Acetazolamide

Severe HACE:

Avoid sedatives or analgesics
Emergent evacuation to lower altitude (on foot if necessary)
Supplemental oxygen
Steroids
? Morphine if concomitant HAPE present
? Diuretics if HAPE present