

# High-Altitude Cerebral Edema Evaluated With Magnetic Resonance Imaging

## Clinical Correlation and Pathophysiology

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**Context.**—Because of its onset in generally remote environments, high-altitude cerebral edema (HACE) has received little scientific attention. Understanding the pathophysiology might have implications for prevention and treatment of both this disorder and the much more common acute mountain sickness.

**Objectives.**—To identify a clinical imaging correlate for HACE and determine whether the edema is primarily vasogenic or cytotoxic.

**Design.**—Case-comparison study.

**Setting.**—Community hospitals accessed by helicopter from mountains in Colorado and Alaska.

**Patients.**—A consecutive sample of 9 men with HACE, between 18 and 35 years old, 8 of whom also had pulmonary edema, were studied after evacuation from high-altitude locations; 5 were mountain climbers and 4 were skiers. The control group, matched for age, sex, and altitude exposure, consisted of 3 subjects with high-altitude pulmonary edema only and 3 who had been entirely well at altitude. Four patients with HACE were available for follow-up imaging after complete recovery.

**Main Outcome Measures.**—Magnetic resonance imaging (MRI) of the brain during acute, convalescent, and recovered phases of HACE, and once in controls, immediately after altitude exposure.

**Results.**—Seven of the 9 patients with HACE showed intense  $T_2$  signal in white matter areas, especially the splenium of the corpus callosum, and no gray matter abnormalities. Control subjects demonstrated no such abnormalities. All patients completely recovered; in the 4 available for follow-up MRI, the changes had resolved entirely.

**Conclusions.**—We conclude that HACE is characterized on MRI by reversible white matter edema, with a predilection for the splenium of the corpus callosum. This finding provides a clinical imaging correlate useful for diagnosis. It also suggests that the predominant mechanism is vasogenic (movement of fluid and protein out of the vascular compartment) and, thus, that the blood-brain barrier may be important in HACE.

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HIGH-ALTITUDE CEREBRAL edema (HACE) is a potentially fatal neurologic syndrome that develops over hours or days in persons with acute mountain sickness (AMS) or high-altitude pulmonary edema (HAPE).<sup>1-3</sup> This type of high-altitude illness typically presents with altered mental status, ataxia, and progressive neurologic deterioration and is considered to be the end stage of AMS. Although hypoxia is the triggering stimu-

lus, the exact pathophysiology of HACE, as well as AMS, is still not known. In the framework of the 2 general types of cerebral edema,<sup>4,5</sup> authors have postulated that HACE may be either cytotoxic (intracellular, due to cellular swelling),<sup>2,6</sup> vasogenic (extracellular, due to blood-brain barrier leakage),<sup>1,7,8</sup> or a combination of the 2.<sup>9</sup> The distinction has important implications not only for prevention and treatment but also for determining the direction of future research on the basic mechanisms of altitude illness. Brain edema found on autopsy has been so severe and global that it has not been helpful in elucidating the initial pathophysiology.<sup>1,10</sup> One brain biopsy done to exclude other diagnoses reported microscopic evidence of "edematous brain" without further distinction.<sup>1</sup> Work with a sheep model of altitude illness that showed extravasation of Evans blue dye in the brain suggested vasogenic edema.<sup>11</sup>

In vivo brain imaging, by localizing the edema earlier in the course of the illness, might offer new insights into the pathophysiology. Vasogenic edema preferentially spreads along white matter tracts, whereas cytotoxic edema affects both gray and white matter, especially the former.<sup>4,5,12,13</sup> Previous imaging studies were primarily with computed tomography (CT). Kobayashi et al<sup>14</sup> performed axial CT scans on 9 mountain climbers with HACE and neurologic signs. In 8 subjects, the CT scan revealed small ventricles and cisterns, disappearance of sulci, and a diffuse low-density appearance of the entire cerebrum, all of which resolved slowly on recovery. Levine et al<sup>15</sup> also reported diffuse low density on CT of the brain in 1 subject with AMS. Although confirming the presence of cerebral edema, the CT scans did not differentiate regional differences or help define mechanisms.

Using magnetic resonance imaging (MRI), we sought to differentiate white from gray matter edema to identify the operant pathophysiologic mechanism. In addition, we hoped to find a reliable clinical imaging correlate that could be helpful in the diagnosis and assessment of HACE. We studied 9 consecutive patients with a clinical diagnosis of HACE, 8 of whom also had HAPE. Magnetic resonance imaging revealed characteristic changes (increased T<sub>2</sub> signal in the white matter, especially in the splenium of the corpus callosum, and no gray matter edema) in 7 of the 9 subjects. Control subjects had no such changes. Four subjects with repeat MRI after complete recovery showed total resolution of the abnormalities. Magnetic resonance imaging may provide a useful in vivo clinical imaging correlate for HACE, and the findings strongly suggest a predominantly vasogenic mechanism.

## METHODS

The study subjects were all patients admitted to 2 community hospitals during a 4-year period with the diagnosis of HACE. The authors (P.H.H. or P.R.Y.) cared for the study subjects. The control group consisted of 6 climbers without symptoms of HACE who had been climbing higher than 5000 m on Mt McKinley and who had MRI performed within 24 hours of returning to sea level. Three control subjects were entirely well at high altitude and 3 had developed HAPE. The control group matched the patient group for mean age, sex, and length of altitude exposure. Magnetic resonance images were obtained with either a GE 1.5-T Signa (Anchorage, Alaska) or a Siemens 1.0-T Magnetom (Denver, Colo). We were able to perform repeat MRI during recovery in 5 study patients and after complete recovery in 4 study patients.

## RESULTS

The Table presents the clinical and imaging data on our 9 patients. All were vigorous, healthy men aged 18 to 35 years (mean, 27.9 years). None had a history of significant medical problems and none were being treated for any acute illness. Previous high-altitude experience varied. Four had history of AMS but none had history of HACE or HAPE. Four developed HACE while skiing in Colorado and 5 while attempting to climb Mt McKinley (6194 m), also known by its Alaskan name, Denali. Eight received initial treatment in the field with oxygen, 5 received dexamethasone, 2 were given acetazolamide and nifedipine, and 1 was treated in a portable hyperbaric bag, which simulates descent. All 9 patients required hospitalization either in Denver (1610 m) or in Anchorage (sea level).

All subjects met the criteria for diagnosis of AMS as well as for HACE (all had mental status changes and/or ataxia in association with AMS).<sup>16</sup> Eight had clinical diagnosis of HAPE confirmed by radiographs. Respiratory alkalosis of varying degree was present in all patients and severe hypoxemia was present in the 8 with HAPE. Five patients had retinal hemorrhages and all had ataxic gait.

Hospital course varied considerably among patients. Average stay was 5.6 days, with a range of 1 to 15 days. Three patients required intubation. All recovered without evidence of permanent sequelae. Time to normal neurologic examination averaged 2.4 weeks, with a range of 1 day to 6 weeks. The imaging findings are presented in the Table and Figure 1 through Figure 6. The 3 most seriously ill patients (1, 4, and 9) had the most striking changes on MRI, but 2 moderately ill patients (6 and 7) had normal MRI findings. Time from onset of clinical cerebral edema to MRI varied from 16 to 132 hours (mean, 58 hours). Four patients with initial abnormal MRI results still had the abnormalities on repeat imaging performed between 3 and 11 days later, although they were clinically improved. These 4 subjects demonstrate that resolution of MRI findings can lag behind clinical improvement. Patients 1 and 4 had normal MRI findings at 6 weeks, and patients 2 and 9 had normal MRI findings on follow-up at 3 and 11 months, respectively. All control subjects had normal MRI results.

## COMMENT

Magnetic resonance imaging in 7 of 9 patients with HACE demonstrated strikingly increased T<sub>2</sub> signal in the corpus callosum, particularly in the splenium, with additional involvement in the centrum semiovale. The gray matter was normal. These abnormalities had resolved on subsequent MRI studies obtained in 4 patients, and all of the patients had complete clinical recovery. High-altitude controls, both healthy individuals and those with HAPE, did not show MRI abnormalities. This MRI pattern of reversible edema limited to white matter provides an imaging correlate for the syndrome of HACE and strongly suggests a predominantly vasogenic mechanism as the basis of the edema.

A potential problem of this study is the diagnosis of HACE. Although our patients' illnesses were consistent with HACE, other diagnoses must be considered. History, clinical course, and diagnostic evaluation, including brain MRI, excluded cerebrovascular events and brain trauma. Three patients presented with elevated temperature, but this is

common in HAPE, and brain infection was excluded in these 3 by negative cerebrospinal fluid cultures. The possibility of anoxic encephalopathy secondary to the pulmonary edema was excluded by lack of the typical gray-matter lesions on MRI and by clinical course. Vasculitis may cause white-matter MRI changes and was also considered in this group, perhaps secondary to sympathomimetic drug use. However, all subjects denied such drug use and toxicology findings were negative in all 5 patients tested. In summary, given the setting of acute ascent to high altitude, the reversibility of the syndrome, and the exclusion of other illnesses, we are reasonably certain of the clinical diagnosis of HACE.

Another concern is whether white matter edema might be an incidental finding of high altitude. The fact that 3 asymptomatic climbers studied within 24 hours of returning from high altitude (6194 m) had no MRI abnormalities speaks against this, as does other work showing no increased T<sub>2</sub> signal intensity in 8 subjects with mild or absent AMS after simulated altitude exposure.<sup>17,18</sup> The brain edema does not seem related directly to HAPE or severe hypoxemia because 3 extremely hypoxic individuals with HAPE but without HACE also had normal MRI results. Although a greater number of control MRIs is desirable, we feel confident that our findings truly correlate with the diagnosed clinical illness.

A third concern is that 2 patients with HACE did not demonstrate the MRI abnormalities. The reason for this is not clear. Overall, all 5 high-altitude climbers, but only 2 of 4 skiers, had positive MRI results for HACE. Possible factors are that the climbers had all been at considerably higher altitude, their length of altitude exposure was longer, and their evacuation to low altitude was slower. In addition, the climbers were engaged in activities more likely to elevate cerebral capillary pressure, such as lifting and carrying heavy packs and pulling themselves up ropes. Duration and severity of symptoms and the treatment prior to MRI were similar in those with and without MRI changes. Because the MRI findings were not present in all cases, they are considered characteristic but not prerequisite for the diagnosis of HACE. Since resolution of MRI abnormalities lagged behind clinical improvement, their presence may help establish the diagnosis in a person recently recovered.

Our findings are consistent with other recent studies regarding imaging of AMS and HACE in the literature. Levine et al<sup>15</sup> found CT evidence of mildly decreased white matter density in the sickest of 6 subjects with AMS after a 48-hour simulated altitude exposure. Similarly,

Patient Profile and History	Physical Findings (Low-Altitude Hospital Unless Otherwise Specified)	Hospital Course	Imaging
Patient 1: A 32-year-old male skier. Sea level to 2750 m on day 1. Day 2, experienced headache. Day 3, experienced dizziness and cough. Day 4, was agitated, weak, lethargic, dyspneic, confused, sent to hospital.	T: 38.4°C, RR: 40/min, HR: 110 beats/min, BP: 130/100 mm Hg. Agitated, thrashing about, disoriented. Bilateral retinal hemorrhages. (PaO <sub>2</sub> , 112) on 100% oxygen. EEG indicated bifrontal high amplitude slowing. CSF fluid stain and cultures were negative.	Intubated. Treated with diuretics, steroids, hyperventilation, and oxygen. Extubated after 4 days. Discharged after 15 days with cognitive impairment and motor apraxia. Complete recovery at 6 weeks, promoted at work.	CXR: Pulmonary edema. CT scan on day 1 indicated white matter low density. MRI on day 5 indicated increased T <sub>2</sub> signal white matter, mainly in corpus callosum and splenium (Figure 1 [A]). MRI on day 12 indicated same as day 6. MRI at 6 weeks normal (Figure 1[B]).
Patient 2: A 27-year-old male climber. Sea level to 5800 m in 8 days. Experienced headache, anorexia, malaise, and 1 hallucination; unable to walk; rescued 5 days later.	T: 37°C, RR: 18/min, HR: 88 beats/min, BP: 130/80 mm Hg. Alert, lucid. Bilateral retinal hemorrhages. Grossly wide-based spastic gait. Hyperreflexia of legs, bilateral ankle clonus.	Treated with gait training and strength exercises with rapid improvement. Discharged after 3 days with mild spastic ataxic gait. Three weeks later normal, back to work as letter carrier.	CXR normal. MRI on admission (3 hours after rescue) indicated increased T <sub>2</sub> signal of entire corpus callosum, especially for splenium (Figure 2). MRI was normal 3 months later.
Patient 3: A 26-year-old male climber. Sea level to 5800 m in 5 days. Day 5, experienced fatigue, headache, malaise, incoordination. Next day comatose. Responded to oxygen (awoke) but remained ataxic and confused. Treated with dexamethasone and oxygen, descent to 4300 m. Improved next day, evacuated to hospital.	At 4300 m, T: 35.5°C, RR: 60/min, HR: 112 beats/min, BP: 115/70 mm Hg. SaO <sub>2</sub> , 54%. Papilledema and rales. In hospital, confused and ataxic.	Spent 1 day in hospital, improved rapidly, discharged with minimal ataxia and clear lungs. Examination 1 week later indicated normal.	CXR: Pulmonary edema. MRI on admission indicated high T <sub>2</sub> signal in splenium (Figure 3).
Patient 4: An 18-year-old male skier. Sea level to 2750 m on day 1. Onset of "cold" on trip. Day 2, confused, lethargic. Day 3, progressive obtundation. Oxygen saturation was 50% at 2750 m.	At 2750 m, T: 38.7°C, RR: 30/min, HR: 108 beats/min, BP: 158/90 mm Hg. In hospital, combative, confused, retinal hemorrhages, rales, Babinski signs. CSF analysis normal. EEG indicated bilateral frontal slowing, posterior θ.	Intubated. Treated with hyperventilation, steroids, diuretics, and antibiotics. Extubated on day 4. Discharged on day 15 with mild cognitive dysfunction. Normal examination 1 week later. Normal EEG 3 weeks later.	CXR: Pulmonary edema. CT scan on day 1 indicated mild low density. MRI on day 2 indicated corpus callosum and splenium increased T <sub>2</sub> signal. CT on day 6 indicated marked diffuse edema. MRI on day 7 indicated periventricular and posterior corpus callosum white matter increased T <sub>2</sub> signal areas (Figure 4[A]). MRI on day 13 indicated as day 7, no enhancement with gadolinium contrast. MR I 3 weeks later was normal (Figure 4[B]).
Patient 5: A 35-year-old male climber. Sea level to 5250 m in 5 days. Headache, malaise, nausea, incoordination. On day 4 was found semiconscious at 5250 m. Treated with oxygen, acetazolamide, and dexamethasone. Descent to 4300 m; next day to sea-level hospital.	At 4300 m, RR: 28/min, HR: 112 beats/min, BP: 107/73 mm Hg, SaO <sub>2</sub> , 53%. In hospital, alert, lucid, no hemorrhages. Moderate ataxia, rales. SaO <sub>2</sub> , 92% on oxygen, 4 L/min.	Treated with oxygen and dexamethasone. Rapid improvement. Discharged after 5 days, ataxia resolved.	CXR: Mild pulmonary edema. MRI 14 hours after evacuation indicated increased T <sub>2</sub> signal in splenium.
Patient 6: A 26-year-old male skier. Sea level to 2800 m on day 1. Day 2, headache, malaise, anorexia, dyspnea. Day 3, found cyanotic, unresponsive, with pink frothy sputum and seizures. Given diazepam, furosemide, and oxygen.	T: 38.9°C, RR: 20/min, HR: 92 beats/min, BP: 110/76 mm Hg. SaO <sub>2</sub> , 80% on oxygen, 4 L/min. Confused, bilateral rales, fundi normal. EEG indicated normal. CSF and blood cultures were negative.	Intubated for 12 hours. Treated with oxygen, dexamethasone, and intravenous lactated ringers. Rapid recovery, discharged to home after 3.5 days, normal examination.	CXR: Pulmonary edema. CT scan on day 1 indicated normal. MRI on day 2 indicated normal.
Patient 7: A 28-year-old male skier. Sea level to 2750 m on day 1. Day 2, headache and nausea. Day 3, cough. Day 4, clumsy, disoriented. Given oxygen.	T: 37.2°C, BP: 180/90 mm Hg. Confused, dysarthric, ataxic, and hallucinating, with retinal hemorrhages and bilateral rales. EEG indicated abnormal, left frontal θ-Δ focus.	Treated with bed rest and oxygen. Discharged on day 4 mildly ataxic. Four weeks later had normal examination, EEG, and MRI. Grounded from flight duty for 1 year.	CXR: Pulmonary edema. MRI on days 2 and 4 indicated normal.
Patient 8: A 26-year-old male climber. Sea level to 5200 m in 7 days. Developed headache, dyspnea, cough, incoordination, confusion, and lethargy. Descended to 4300 m. Treated with acetazolamide, dexamethasone, aspirin, and oxygen.	At 4300 m, T: 37°C, HR: 110 beats/min, RR: 44/min, BP: 151/95 mm Hg, SaO <sub>2</sub> , 43%. At sea level, bilateral rales, ataxia, poor rapid alternating movements.	Treated with oxygen, intravenous fluids, and bed rest. Discharged after 2 days with slight ataxia and clear lungs. Examination 2 weeks later reported normal.	CXR: Pulmonary edema. CT on admission indicated slight attenuation on posterior white matter. MRI on admission indicated high T <sub>2</sub> signal in centrum semiovale and corpus callosum, especially on splenium (Figure 5). MRI 3 days later indicated no change.
Patient 9: A 33-year-old male climber. Sea level to 5200 m in 6 days. Dyspnea, cough, headache, nausea, confusion, lethargy, and incoordination. Removed to 4300 m and treated with oxygen, dexamethasone, nifedipine, and hyperbaric bag. Rapid recovery but persistent ataxia. SaO <sub>2</sub> , 56% at 4300 m.	T: 36°C, HR: 54 beats/min, RR: 18/min, BP: 110/64 mm Hg. Retinal hemorrhages, moderate ataxic gait. SaO <sub>2</sub> on room air, 97%.	Treated with steroids and bed rest. Discharged to home after 6.5 days with clear lungs and slight ataxia. Normal examination 1 week later.	CXR: Right perihilar interstitial edema. MRI indicated severe corpus callosum edema, splenium greater than genu, mild edema in centrum semiovale (Figure 6). Mild increased T <sub>2</sub> signal on brain stem. MRI 4 days later indicated no change, and 11 months later was normal.

\*T indicates temperature; RR, respiratory rate; HR, heart rate; BP, blood pressure; PaO<sub>2</sub>, partial pressure of oxygen; EEG, electroencephalogram; CSF, cerebrospinal fluid; CXR, chest x-ray; CT, computed tomography; MRI, magnetic resonance imaging; SaO<sub>2</sub>, arterial oxygen saturation.

Matsuzawa et al<sup>17</sup> were able to detect slight increased T<sub>2</sub> signal of white matter in the sickest 4 of 7 subjects with AMS in a 24-hour simulated altitude experiment. Yamaguchi and colleagues<sup>19</sup> performed MRI on 4 patients with HAPE and neurologic symptoms and found only slightly increased T<sub>2</sub> signal, in contrast with the dramatic signal alterations in the current study. This is most likely because they studied the 2 subjects with cerebral edema only during recovery and the other 2 had only mild neurologic dysfunction. Follow-up studies were not performed in any of these studies; the changes were presumed to be transient. Slight increased T<sub>2</sub> signal of white matter in AMS and intense signal in HACE support the notion that the 2 illnesses reflect a continuum of the same pathophysiology.<sup>3</sup> However, only the advanced pathology of HACE provided the clear and unusual pattern of corpus callosum edema, the predilection for the splenium, and a useful clinical imaging correlate.

Our present findings are distinct from the white-matter hyperintense changes noted on MRI in subjects after climbs to extreme altitude without oxygen. Garrido et al<sup>20</sup> detected signal abnormalities in 7 of 26 subjects 1 month to 3 years after the most recent high-altitude exposure. There was no prior or subsequent imaging and no diagnoses could be established retrospectively. Although many subjects reported some neurologic symptoms, none apparently had HACE. The increased signals in this study and the subsequent investigation<sup>21</sup> were found in various deep white-matter tracts but not in the corpus callosum or splenium, and they were considered nonreversible. The mechanism of these changes is unknown. Although other MRI abnormalities may appear after extreme altitude exposure, our findings seem to be specific for acute HACE.

The finding that HACE is primarily manifested in the white matter *in vivo* has pathophysiologic implications. Reversible increased T<sub>2</sub> signal abnormality of white matter without gray matter involvement suggests a vasogenic type of cerebral edema as the predominant mechanism at this stage of the illness and at least a relative absence of cytotoxic edema.<sup>13</sup> Gray matter consists of tightly packed, tangled cellular structures, whereas white matter has an orderly network of extracellular channels, is less dense, and offers less resistance to invasion by edema fluid.<sup>5,12</sup> Vasogenic edema thus spreads preferentially through the white matter. In contrast, gray matter is more sensitive to imbalance of cellular energy demand and supply and, therefore, more susceptible to the cell swelling of cytotoxic edema. Also, cytotoxic edema most commonly displays morphologic changes

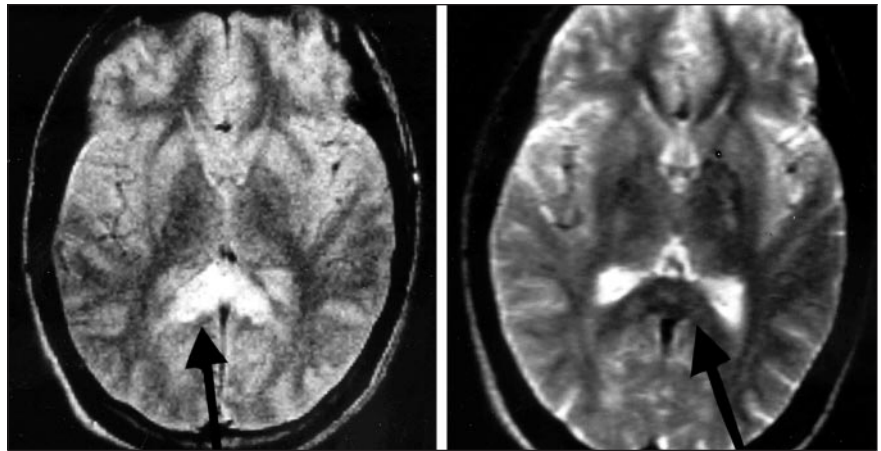


Figure 1.—Left, Axial proton-weighted magnetic resonance image for patient 1, with arrow demonstrating pronounced increased signal (edema) in splenium of corpus callosum. Right, Similar level axial T<sub>2</sub>-weighted magnetic resonance image of the same patient 6 weeks later, with no residual abnormal signal.

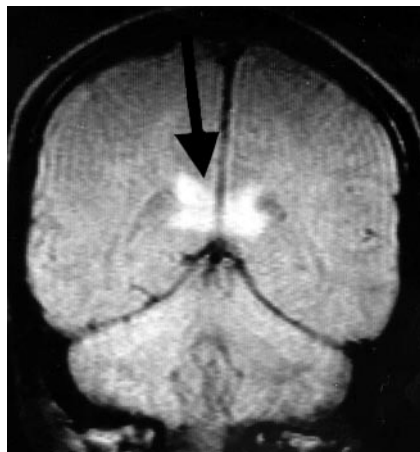


Figure 2.—Patient 2, 3 hours after helicopter rescue from 5550 m altitude. Coronal image demonstrates pronounced increased signals in splenium in this proton-weighted magnetic resonance image. Cerebrospinal fluid is gray, splenium (arrow) is white (edematous).

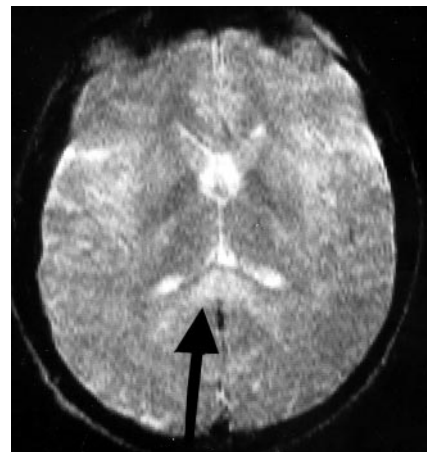


Figure 3.—Axial T<sub>2</sub>-weighted magnetic resonance image of patient 3 showing increased signal in splenium.

on T<sub>1</sub>-weighted images,<sup>22</sup> which we did not observe in gray or white matter. Thus, the presence of reversible white-matter changes and absence of gray-matter changes both support the conclusion of a vasogenic edema.

The remarkable predilection for the splenium and corpus callosum in our MRI images is puzzling. This is in contrast with the classic teaching of resistance to flow of fluid in the corpus callosum because of its thickly packed fibers.<sup>23</sup> However, because edema is seen in the corpus callosum in certain situations, this is merely a relative resistance. With the increased availability and use of MRI, more reports of edema of the corpus callosum and splenium are appearing.<sup>24,25</sup> Additionally, recent measurements indicate that the degree of water movement (or accumulation) depends much on orientation of the myelin fibers.<sup>26</sup> Flow along the axons is much less impeded than across them and the

very high signals seen in our MRIs may indicate accumulation of water parallel to the axons. Another possibility is that the edema is caused by increased vascular permeability in the corpus callosum itself. Because of the short arterioles and relative lack of pressure drop along the vessels, the unique vascular anatomy of the corpus callosum that provides relative protection from hypoperfusion and ischemia<sup>23,27</sup> may render it more susceptible to edema in the setting of hypoxic cerebral vasodilatation at high altitude.<sup>7</sup> However, these suggestions are very speculative. The fact that the signals are on T<sub>2</sub>-weighted images, reversible, and only in white matter indicate this is a vasogenic edema. An explanation for this relatively unusual location of water in the brain may yield important insights into the mechanisms of AMS and HACE. Development of an animal model evincing a similar edema pattern should be a high priority for further investigation.

Further evidence for the concept of vasogenic edema is based on important

clinical observations. Acute mountain sickness, the early form of HACE, is effectively prevented and treated by steroids<sup>15,28,29</sup> and, anecdotally, steroids are also beneficial when given early in the course of HACE.<sup>1,30</sup> It is well known that vasogenic edema responds to steroids whereas cytotoxic brain edema does not.<sup>5</sup> The slow resolution of edema is also consistent with a vasogenic mechanism because removal of extravasated proteins is primarily by the relatively slow process of astrocyte pinocytosis.<sup>12,31</sup> Furthermore, a predominantly vasogenic edema tends to leave the brain tissue well preserved after resolution, as is demonstrated in HACE by the usual complete clinical recovery and normalization of MRI. Cytotoxic edema, in contrast, is generally not so benign.<sup>12</sup>

The actual mechanism of this vasogenic edema is still unclear. By definition, vasogenic edema results from opening of the blood-brain barrier. A complete discussion of the blood-brain barrier and

vasogenic edema is beyond the scope of this article. Recent excellent reviews are available<sup>32</sup> and the summary by Krasney<sup>11</sup> with respect to AMS, HACE, and the blood-brain barrier is of particular interest. A few facts are worth mentioning for the purposes of our discussion. Some researchers have proposed that hypoxic vasodilatation results in a failure of autoregulation,<sup>1,7,8</sup> a hypothesis that has not yet been directly tested. Their view is that increased cerebral capillary hydrostatic pressure, not necessarily with systemic hypertension, may result in blood-brain barrier opening and outflow of fluid along white-matter tracts. Indeed, a number of clinical conditions exhibiting vasogenic edema on MRI are thought to share this mechanism. These include hypertensive encephalopathy, toxemia of pregnancy, seizures, acute intermittent porphyria, cyclosporine toxic effects, and migraine.<sup>33-35</sup> Hypoxic cerebral vasodilatation on ascent to high altitude is well documented but whether this in itself ex-

plains vasogenic edema is doubtful. All persons at high altitude have cerebral vasodilatation and those with AMS or HACE are not appreciably different in this regard than those who are well.<sup>36</sup> Whether regional changes in autoregulation, cerebral blood flow, and cerebral capillary pressure are sufficient to produce vasogenic edema remains unanswered.

The animal model of AMS and HACE developed by Krasney<sup>37</sup> also supports the vasogenic hypothesis but suggests additional mechanisms. In animals that became ill, Krasney found increased wet-dry brain tissue ratio and extravasation of Evans blue dye, confirming leak of the blood-brain barrier, in conjunction with increased cerebral blood flow and elevated brain capillary pressures, without systemic hypertension. However, further experiments disclosed that brain edema from large increases in capillary hydrostatic pressure induced by carbon dioxide breathing or nitroglycerin was much less than that resulting from hypoxic edema, suggesting that another factor than capillary hydrostatic pressure must be in play.<sup>11</sup> This other important factor is the conductance or permeability of the blood-brain barrier itself and, primarily, the role of the cerebral endothelium.<sup>31</sup> A quite complex regulatory mechanism, the blood-brain barrier is influenced by many factors, including adrenergic and cholinergic systems, neurotransmitters and neuromodulators, cyclic nucleotides, nitric oxide, histamine, and cytokines and other factors released by white cell-endothelial interaction.<sup>11,31,38</sup> All of these are candidates for being altered by hypoxia<sup>39</sup> and some, like atrial natriuretic peptide, norepinephrine, and eicosanoids, are known to be altered in AMS.<sup>40,41</sup> In addition, the beneficial effect of steroids in altitude illness might likely be due to an effect on blood-brain barrier permeability. Dexameth-

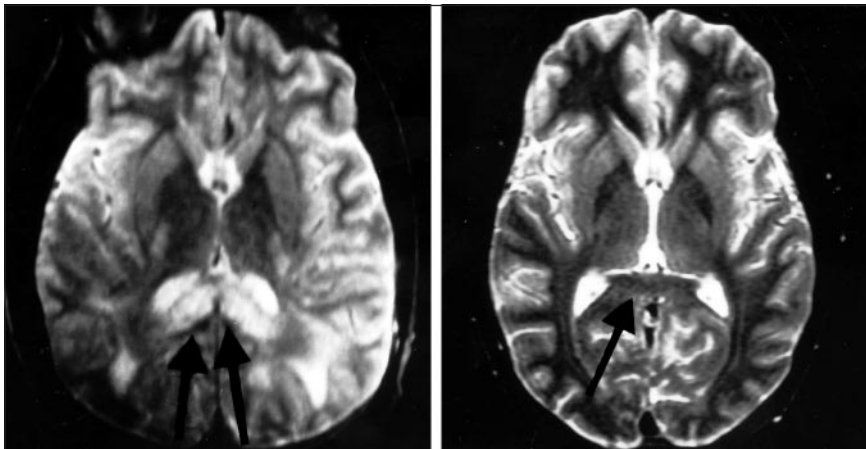


Figure 4.—Left, Axial T<sub>2</sub>-weighted magnetic resonance image of patient 4 showing markedly increased signal in corpus callosum (arrows), including both the genu and the splenium, as well as increased signal of periventricular and subcortical white matter. Right, Axial T<sub>2</sub>-weighted magnetic resonance image of the same patient 5 weeks after original presentation, demonstrating no residual abnormality in splenium (arrow).

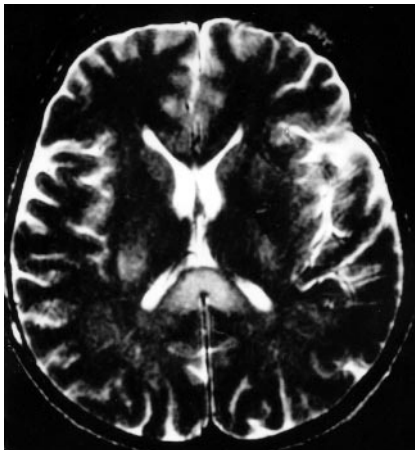


Figure 5.—Axial T<sub>2</sub>-weighted magnetic resonance image of patient 8 showing markedly increased signal in splenium and centrum semiovale.

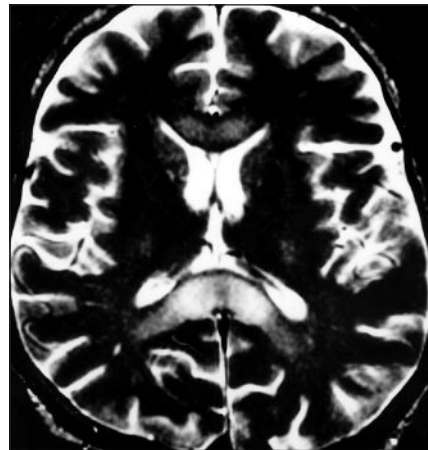


Figure 6.—Left, Axial T<sub>2</sub>-weighted magnetic resonance image of patient 9 demonstrating high signal in splenium and mild increased signal in centrum semiovale. Right, Axial T<sub>2</sub>-weighted magnetic resonance image of the same patient demonstrating complete resolution of abnormal signals 11 months later.

asone is known to suppress lipid peroxidation as well as block vascular endothelial growth factor and therefore angiogenesis, both of which actions make the barrier less permeable.<sup>11,31,42</sup> Dexamethasone also prevents the increased permeability of cultured endothelial cell monolayers that are subjected to hypoxia.<sup>43</sup> Of course, increased blood-brain barrier permeability and capillary hydrostatic pressure may be working in concert; flux of fluid is greatly influenced by hydrostatic pressure in the presence of an opening of the blood-brain barrier.<sup>12</sup>

Our findings do not exclude an element of intracellular edema as well but

strongly suggest that vasogenic edema is the major operant factor in the pathophysiology of HACE, at least in the phase in which it becomes clinically evident. As Klatzo<sup>4,12</sup> has described, progressive extracellular vasogenic edema, by increasing intercapillary distances, will affect the energy requirements of the cells, eventually rendering them ischemic and leading them to swell, thus contributing to a further increase in intracranial pressure. This cytotoxic mechanism, traditionally invoked to explain HACE,<sup>2</sup> likely becomes operant only at this late stage. Successful treatment must begin while the condition is

still reversible, before onset of neuronal damage. The next focus of research into AMS and HACE should be on the role of the blood-brain barrier.

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