

ACUTE MOUNTAIN SICKNESS AND THE EDEMAS OF HIGH ALTITUDE: A COMMON PATHOGENESIS?

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Abstract. Within days of ascent to high altitude when symptoms of acute mountain sickness (AMS) are common, pulmonary and cerebral edema may also develop. Although peripheral edema of the hands, face or feet may also appear, its association with AMS is unclear. In addition, persons with high altitude pulmonary edema often report an antidiuresis. Hence, altitude sickness appears to result from abnormalities in the handling of body water. To test this hypothesis, we studied 102 men and women who were trekking in the Mount Everest region of Nepal. Most were seen both at low (1377 m) and at high (4243 m) altitude. Severity of AMS was measured by an established Symptom Score derived from a questionnaire and physical examination. Change in body water was inferred from change in body weight in less than 10 days. Peripheral edema was assessed separately by physical examination. AMS Symptom Score correlated directly with weight change; those who remained well lost weight, whereas increasing signs and symptoms of AMS occurred in those with increasing weight gain. The symptomatic subjects also developed peripheral edema and reported decreased urinary output.

These findings support the hypothesis that with rapid ascent to high altitude, abnormalities in the handling of body water, with antidiuresis, result in fluid retention (weight gain) manifest as peripheral, pulmonary, and/or cerebral edema.

Acute mountain sickness	High altitude
Cerebral edema	Peripheral edema
Fluid retention	Pulmonary edema

Life threatening pulmonary and cerebral edema may develop singly or together during the first week of high altitude exposure, when acute mountain sickness (AMS) is most common. Peripheral edema also occurs at high altitude, but was first described as trivial and not related to acute mountain sickness or to the other edemas of altitude (Lancet editorial, 1976). Subsequently, however, we reported 10 subjects with peripheral edema, eight of whom also had pulmonary and/or

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cerebral edema (Hackett and Rennie, 1977). The pathophysiology of these problems remains obscure. If pulmonary, cerebral and peripheral edema do indeed occur together (Hackett and Rennie, 1979), one might postulate a common abnormality of water homeostasis.

The 'normal' change in body water on ascent to altitude is controversial. Krzywicki *et al.* (1969) have reported a significant loss of weight in men who remained well at altitude, due not merely to loss of fat and protein, but to a loss of body water over and above that attributable to caloric deficit. Frayser *et al.* (1975) reported a drop in total body water. Hannon *et al.* (1969) reported a shift in water from the extra to the intracellular space, while total body water remained unaltered. They concluded from the literature that there was little evidence of body hypo-hydration. Janoski *et al.* (1969) reported a decrease in urine output at high altitude, but attributed this to a diminished water intake. None of these investigators related the observed fluid changes to symptoms of acute mountain sickness. Singh *et al.* (1969) concluded that subjects 'predisposed' to acute mountain sickness had an anti-diuresis, whereas 'immune' people passed urine freely. We, too, have previously reported increased frequency of urination in well subjects at altitude and decreased urine frequency in those with mountain sickness (Hackett and Rennie, 1979; Hackett *et al.*, 1976).

Williams *et al.* (1979) have recently shown peripheral edema in low altitude hill walkers, in the absence of any symptoms similar to acute mountain sickness or pulmonary or cerebral edema. Further, they suggest that the effects of altitude and exercise may be additive in producing the altitude edemas.

We wished, therefore, to determine whether an increase in total body water reflected as weight gain early during the course of altitude exposure is associated with the various edemas of altitude, as well as the less severe symptoms of acute mountain sickness. If so, this would be evidence that (a) fluid retention is an early common factor in their pathogenesis, and (b) that these clinical entities represent a spectrum of the same basic underlying pathophysiology.

Recently during an investigation in the Himalaya of Nepal, we examined approximately 100 trekkers both at low and high altitude, some of whom developed severe acute mountain sickness. In these subjects, the relationships between the various forms of edema, weight change, and symptoms gave support to the unifying concept of the pathogenesis of the various forms of high altitude illness which follows.

Methods

Two laboratories were staffed in Nepal during six weeks of the autumn season of 1978. One was at low altitude (Kathmandu, 1377 m) and the other at high altitude (Pheriche, 4243 m). We studied 102 subjects, all of whom were tourists who lived at low altitudes (below 1600 m) and were trekking to the Mount Everest region.

All had been at altitudes above 2800 m for 10 days or less. Ninety-seven were seen at both low and high altitude. They were recruited in Kathmandu where they were fully informed of the purposes of the study and signed consent forms. Five who developed altitude illness were seen only at high altitude. At both altitudes, subjects were weighed without shoes, wearing light clothing, the scales having been calibrated with a known weight. A questionnaire (in English, German, French, or Japanese) was administered. On this questionnaire, the subjects gave a brief medical history, detailed their trekking itinerary, and answered yes or no to symptoms of acute mountain sickness. Responses were in each case verified by an investigator.

At high altitude, after the subjects had rested supine, the arterial oxygen saturation was measured with a Hewlett-Packard ear oximeter and a venous blood specimen was obtained. Hematocrit was determined by the microhematocrit technique. Serum and urine osmolality were measured with an osmometer (Advanced Instruments) and urine specific gravity was measured with a fractionometer. The presence or absence of peripheral edema was noted by the subjects on the questionnaire and its presence was confirmed by one of the investigators. Areas of edema included the hands, feet and ankles, and face. The frequency of urination at both high and low altitudes was also noted. Symptoms were weighted according to severity and a symptom score devised so that: one point was given each for headache, anorexia or nausea, and insomnia; 2 points each for vomiting or a severe headache not relieved by analgesics; and 3 points each for severe shortness of breath at rest, ataxia and severe lassitude (requiring assistance for walking, dressing and eating). This scoring system has been validated in previous studies (Hackett and Rennie, 1979; Hackett *et al.*, 1976). Peripheral edema was not included in symptom score. Pulmonary edema was diagnosed by the presence of severe tachypnea and dyspnea of rapid onset, pulmonary rales and an arterial oxygen saturation by ear oximeter of less than 80 per cent (at 4243 m the mean oxygen saturation is 86 per cent). The criteria for cerebral edema were severe lassitude, impaired consciousness, ataxia and papilledema. Statistical methods used were standard parametric and nonparametric analyses, including Spearman rank, 't'-tests, analysis of variance and Chi-square.

Results

The population of trekkers surveyed was similar in age and sex distribution to those examined in this area before (Hackett and Rennie, 1979; Hackett *et al.*, 1976), as was the incidence of acute mountain sickness. The mean age was 38.3 ± 12 (SD), range 18 to 63. Forty per cent were female. The symptom scores ranged from 0 (no symptoms) to 9 (table 1).

There was a direct correlation between symptom score at high altitude and change in body weight from low to high altitude (fig. 1) ($r_s = 0.9$; $P < 0.05$). Also, urinary frequency tended to decrease in subjects having increasing symptom score

TABLE 1
Measurements (mean \pm SEM) by symptom score in 102 persons seen at Pheriche, Nepal (4243 m)

Symptom score	N	Age (yrs)	% females	No. of females	Hct (%)	Osmolality		Urine sp. gr.
						Serum (M Osmole)	Urine	
0	30	44 \pm 2	26	8	46 \pm 1	295 \pm 2	721 \pm 42	1.018
1	26	36 \pm 2	38	10	46 \pm 1	294 \pm 1	681 \pm 65	1.016
2	25	33 \pm 2	48	12	46 \pm 1	293 \pm 1	681 \pm 66	1.016
3-5	13	38 \pm 3	61	8	45 \pm 1	293 \pm 2	647 \pm 67	1.016
6-9	8	42 \pm 4	38	3	49 \pm 2	297 \pm 2	737 \pm 82	1.019
Total	102	38 \pm 12 (SD)	40	41	(N = 7)	(N = 6)	(N = 5)	(N = 5)

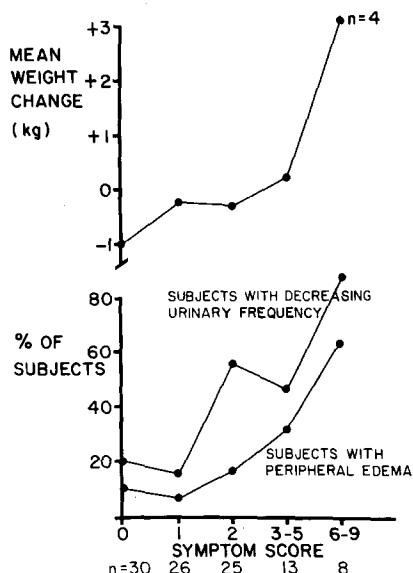


Fig. 1. *Upper*: Relationship of acute mountain sickness Symptom Score to weight change in 97 subjects ascending from 1377 m to 4243 m altitude in less than 10 days. Among 8 subjects with scores 6-9, weight change was available in only 4 ($n = 4$). Note weight loss with 0 symptoms, weight gain with increasing symptoms ($r_s = 0.9, P < 0.05$). *Lower*: With increasing Symptom Score, there is an increase in the percent of subjects reporting decreasing urinary frequency, and exhibiting peripheral edema ($r_s = 0.9, P < 0.05$).

(fig. 1) ($r_s = 0.9, P < 0.05$). Of the 17 subjects with edema, 14 had edema of the hands or face without lower extremity edema. One had edema of the feet alone, and two had edema of the feet or ankles in addition to edema of the hands or face.

There were eight persons with symptom scores of six or more (table 2). All eight required descent, three by helicopter, and seven had life-threatening acute mountain sickness. Five of the eight had peripheral edema and three had peripheral, pulmonary and cerebral edema together. All recovered, although five were hospitalized at Pheriche for treatment with oxygen, morphine, diuretics and intravenous fluids. Two were subsequently hospitalized in Kathmandu for seven days. Seven of the eight met our criteria for the presence of cerebral edema. All seven had gross ataxia and four of the seven had papilledema. In addition, four of the seven met our criteria for pulmonary edema. The one subject at Pheriche considered to have pulmonary edema, who was evacuated directly to a Kathmandu hospital, had a chest X-ray taken there on admission. Extensive infiltrates in the right lung were considered to be due to pulmonary edema. Arterial oxygen saturations by ear oximeter, obtained at Pheriche in three of the subjects breathing air and considered to have pulmonary edema, ranged from 40 to 50 per cent (table 2). The mean values of age, hematocrit, serum and urine osmolality and urine specific gravity are given for population grouped according to symptom score in table 1. There

TABLE 2
Measurements in persons with symptom score of 6 or greater

Age	Sex	Edema			Change in		Osmolality		Urine sp. gr.	Sa _O ₂
		Periph.	Cerebral	Pulm.	Wt (kg)	Hct (%)	Serum (mosmol)	Urine		
30	F	0	0	0	3.2	47	293	612	1.010	85
27	M	+	+	0	3.1	55	292	807	1.021	64
28	M	0	+	0	-	49	302	483	1.011	80
50	M	+	+	0	-	45	298	850	1.025	60
37	M	0	+	+	2.9	56	294	932	1.027	40
50	F	+	+	+	-	42	300	-	-	42
54	M	+	+	+	2.3	-	-	-	-	50
59	F	+	+	+	-	31	-	-	-	-

were no significant changes in these variables in the different symptom score groups.

Discussion

Our previous report suggested that persons who remain well probably lose weight at high altitude, but those with mild symptoms show less weight loss (Hackett *et al.*, 1976). Singh *et al.* (1969) reported that soldiers with a past history of altitude sickness developed symptoms and showed a reduced urine output on exposure to high altitude, and that subsequent improvement in symptoms was preceded by a diuresis. Soldiers who acclimatized well had a marked diuresis on ascent, but body weights were not measured. In the present study, we documented weight loss in subjects without symptoms, as well as increasing weight gain with increasing symptoms. In the most severely ill subjects who had the briefest exposure to high altitude, the weight gain was large. Further, reports of decreased urine output increased with increasing symptom score and paralleled the increase in body weight. Therefore, we concluded that fluid retention was related to development of acute mountain sickness.

The incidence of peripheral edema also increased with increasing symptom score and paralleled the increase in body weight, suggesting that peripheral edema was closely related to acute mountain sickness, and also to fluid retention. The higher values for symptom score reflected pulmonary and cerebral edema; for example, four of the eight most severely ill subjects had both forms of edema. Particularly striking were the three severely ill subjects with all three forms of edema. The close association of cerebral, pulmonary and peripheral edema with a gain in weight, and the circumstantial evidence that the weight gain reflected fluid retention, supported our hypothesis that all three forms of edema during acute high altitude

exposure share a common mechanism of pathogenesis, which involves fluid retention.

The distribution of the peripheral edema was not that of the dependent type which accompanies right heart failure with its attendant high venous pressure; there is little known of cerebral venous pressure in the cerebral edema of altitude. It seems unlikely that the edema which occurs in various locations in the body at high altitude results from raised venous pressure. In some of the severely ill subjects with peripheral edema, the absence of distended neck veins and their dehydrated appearance in conjunction with high blood hematocrits, concentrated urine, and high serum osmolalities (table 1) all pointed to a reduction rather than an increase in intravascular volume.

In reviewing the pathophysiology of acute mountain sickness, Hansen and Evans (1970) proposed that when man goes to high altitude, the shift of water from the intravascular space to the intracellular space, in combination with increased cerebral blood flow, causes a shift of fluid into the brain resulting in cerebral edema, which produces the symptoms of acute mountain sickness. The results of the present study suggest that this concept of acute mountain sickness should be broadened to include the pulmonary circulation and the peripheral systemic circulation. The 'illness' can then be viewed as a general problem of water handling by the body, leading to abnormal water retention manifest as a net increase in body weight of as much as 3 kg. However, this retained fluid is not distributed homogeneously throughout the body, but rather appears in one or more target areas determined by individual, local, or environmental factors. Sutton and Hansen (1979) postulated that edema would appear in regions subjected to increased microvascular pressure and flow. Thus, cerebral vasodilatation combined with systemic hypertension would favor cerebral edema, whereas increased pulmonary blood flow (exercise) combined with pulmonary hypertension would favor pulmonary edema. Similarly, cutaneous vasodilatation combined with exercise and hypoxia could explain the six impressive cases of peripheral edema which occurred while climbing a 4100 m peak in tropical Borneo; resolution of the edema was accompanied by diuresis on descent (Sheridan and Sheridan, 1970). Whether prolonged exercise *per se*, as suggested by Williams *et al.* (1979), added to the effects of hypoxia in producing edema is unknown, but should be explored.

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References

- Editorial (1976). See Nuptse and die. *Lancet* 2: 117–119.
- Frayser, R., I. D. Rennie, G. W. Gray and C. S. Houston (1975). Hormonal and electrolyte response to exposure to 17,500 feet. *J. Appl. Physiol.* 38: 636–642.
- Hackett, P. H., D. Rennie and H. D. Levine (1976). The incidence, importance and prophylaxis of acute mountain sickness. *Lancet* 2: 1149–1155.
- Hackett, P. and D. Rennie (1977). Acute mountain sickness. *Lancet* 1: 491–492.
- Hackett, P. H. and D. Rennie (1979). Rales, peripheral edema, retinal hemorrhage and acute mountain sickness. *Am. J. Med.* 67: 214–218.
- Hannon, J. P., K. S. K. Chinn and J. L. Shields (1969). Effects of acute high-altitude exposure on body fluids. *Fed. Proc.* 28: 1178–1184.
- Hansen, J. E. and W. O. Evans (1970). A hypothesis regarding the pathophysiology of acute mountain sickness. *Arch. Environ. Health*, pp. 666–669.
- Janoski, A. H., B. K. Whitten, J. L. Shields and J. P. Hannon (1969). Electrolyte patterns and regulation in man during acute exposure to high altitude. *Fed. Proc.* 18: 1185–1189.
- Krzywicki, H. J., C. F. Consolazio, L. O. Matoush, H. L. Johnson and R. A. Barnhart (1969). Body composition changes during exposure to altitude. *Fed. Proc.* 28: 1190–1194.
- Sheridan, J. W. and R. Sheridan (1970). Tropical high-altitude peripheral oedema. *Lancet* 1: 242.
- Singh, I., P. K. Khanna, M. C. Srivastava, M. Lal, S. B. Roy and C. S. V. Subramanyam (1969). Acute mountain sickness. *N. Engl. J. Med.* 280: 175–184.
- Sutton, J. R. and N. Lassen (1979). Pathophysiology of acute mountain sickness and high altitude pulmonary oedema: an hypothesis. *Bull. Eur. Physiopathol.* 15: 1045–1052.
- Williams, E. S., M. P. Ward, J. S. Milledge, W. R. Withey, M. W. J. Older and M. L. Forsling (1979). Effect of the exercise of seven consecutive days hillwalking on fluid homeostasis. *Clin. Sci.* 56: 305–316.