Altitude Illness—1976 Version

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AS more and more thousands of people easily and speedily reach high mountain ranges which previously were almost inaccessible, the incidence of high altitude illness has also increased. It is probable that somewhere between 0.5 and 5.0% of all persons going above 10,000 feet can expect symptoms, and it seems likely that between 100 and 200 persons die each year, needlessly. As Dr. Drummond Rennie put it so well, "Altitude sickness kills people, and because these are people who go up into the mountains, it kills the young, the fit, the enthusiastic, the audacious and hardworking, and it is killing them in ever increasing numbers. . . ."

Altitude illness has attracted more interest in mountaineering literature than in medical journals, where it is still considered a medical curiosity. Surprisingly few practicing doctors know anything about altitude illness—even most surprisingly, some who practice near the mountains. In contrast climbers are becoming more and more knowledgeable. Research into various aspects of altitude hypoxia has increased, and bits and pieces of data are falling together to make an emerging picture of what happens when man goes high. In this brief paper I will simply outline some of what we know about altitude illness today, along with concepts which are currently popular.

There is growing consensus that altitude illness is a single entity which can be manifest in several different forms or combinations. Until recently we spoke of acute mountain sickness (AMS), high altitude pulmonary edema (HAPE), cerebral (brain) edema (CE), and retinal hemorrhages (RH) thinking of them as separate entities although all were caused by oxygen lack. It has become clear that these rarely exist alone: the victim usually shows a great deal of one condition, and some of the others. We think today of altitude illness as a spectrum of clinical pathology rather than a set of individual diseases.

This is of much more than academic importance, because it means that an individual with pulmonary edema almost certainly has some brain edema too and often shows retinal hemorrhages as well. It is quite logical that many parts of the body should be affected, some more, some less, since oxygen cannot be stored except briefly in myoglobin—a special case —and since all living human tissues are totally dependent on oxygen for effectiveness and for their existence.

Start then with the realization that we are talking about different forms of a common problem: oxygen lack or hypoxia due to altitude causes altitude illness. Some prefer to speak of "altitude edema" since edema (swelling due to excess water) is an integral part of altitude illness. Although the signs and symptoms are widely known, they are worth listing briefly.

FORMS OF ALTITUDE ILLNESS

Acute Mountain Sickness (AMS)	Headache, weakness, nausea, vomiting, breathing and sleep disturbance
High Altitude Pulmonary Edema (HAPE)	Shortness of breath, weakness, cough, stupor, death
Cerebral Edema (CE)	Severe headache, vomiting, lethargy, stupor, coma, death
Retinal Hemorrhage (RH)	Rarely symptomatic; tiny hemorrhages in the back of eye

Few people know that Dr. T.H. Ravenhill clearly described these forms of altitude illness in 1913, calling them "normal puna," "cardiac puna," and "nervous puna." He was puzzled that persons with "cardiac puna"—which we call HAPE—had no evidence of heart disease. Since Ravenhill's time, many excellent case reports and review articles have appeared; some of these are shown in the appendix.

AMS is common, often beginning as low as 6000 feet in especially susceptible persons, and worsening as altitude increases. Headache, weakness, some shortness of breath, loss of appetite, vomiting, and disturbances of sleep usually begin within a few hours of arrival, are worst the next morning, and slowly improve. AMS is rarely serious although dehydration may need intravenous treatment, and usually disappears; it is very much like a bad hangover. Light activity, plenty of fluids, aspirin, time, and no upward progress are usually all that is needed. AMS should dictate slowing down or halting the climb, and the patient should be carefully watched for more serious developments, but AMS alone seldom forces descent. Like all forms of altitude illness it is minimized or prevented by taking time to go high, and its symptoms are lessened—for parties such as rescue groups which must go very high very fast—by taking Diamox in advance.

HAPE seldom occurs below 9000 feet, although a few deaths from HAPE have occurred even lower. Until recently we felt that HAPE did not begin until 24 or 72 hours after a too rapid ascent to dangerous altitude; today we feel that HAPE may begin subtly and insidiously within six or eight hours of arrival, in the form of interstitial edema (accumulation of water in the loose tissues which surround the alveolar air sacs).

The classical form of HAPE with its severe shortness of breath and weakness, the cough producing bloody sputum, and the bubbling lungs develops later, as the interstitial fluid seeps into the alveolar air sacs. The climber usually notices increasing fatigue, shortness of breath and cough; frothy then pink and often bloody sputum is coughed up. Usually there is little fever, the pulse is often fast, and vomiting or even diarrhea may occur. Curiously enough the patient may have a very severe headache or none at all. Often HAPE progresses swiftly, the climber becomes mentally confused and may even hallucinate. This suggests that CE is also present. Bubbling noises are heard in the chest, even from across the tent, and as one climber vividly described his companion, "he seemed to be drowning in his own juices." This indeed is exactly what happens.

As fluid accumulates, the oxygen becomes less effective—quite understandably because of the increasing barrier to the diffusion from alveolus to lung capillary. Once HAPE is diagnosed, or even strongly suspected, the party must start down. This is the only truly effective treatment. Rest in camp may help, but the party runs the risk of being unable to move because of weather at a time when the condition is worse. There is considerable debate about treatment: most physicians experienced in altitude believe that furosemide (Lasix) should be given by mouth or intravenously. This will squeeze fluid out of water logged tissues by causing a profuse flow of urine, and often relieves HAPE dramatically. However, no medicine, no amount of rest, no oxygen is a substitute for getting down. The party is taking a greater risk by delaying evacuation than by starting down at night or in dubious weather. Getting down even a few thousand feet is usually dramatic, unless the disease has gone too far, and then further descent to hospital care, oxygen under pressure, and more medication are necessary to save life.

HAPE can be mistaken for pneumonia and vice versa of course. However true bacterial or viral pneumonia is unusual on a climbing trip although it does occur. Think pneumonia last—get down. Other conditions have wrongly been called HAPE: pericarditis, coronary thrombosis, hyperventilation (which is quite common) or air in pleural cavity or mediastinum. These are uncommon medical problems which should be treated as HAPE is treated by descent to low altitude and competent medical care.

Brain edema (CE) has about the same time frame as HAPE although it often is slower to begin and is much less common. Full blown CE is uncommon below 12-13,000 feet. Characteristically the climber develops a severe and increasing headache, vomiting is common, he staggers like a drunk when walking, and until recently this was attributed to clumsy boots, slippery snow, uneven terrain. It is not these, the brain has accumulated water in the specific areas which control walking, and ataxia results. It is unusual for this clumsiness to affect hand or arm motions. Hallucinations begin: the climber sees weird sights such as bulldozers on

the summit, he hears voices, and believes that he has other companions nearby. Behavior becomes irrational and simple tasks impossible. Lethargy leads to stupor and the patient drifts into coma and may die. Even more urgently than HAPE, CE demands immediate descent. Intravenous steroids have been used quite often and there is anecdotal evidence that they work, but they are not effective in less than four to six hours. Other medical treatments to reduce brain swelling have not been used frequently enough to permit comment. Here again, once CE is suspected—descent is mandatory at once and under almost any conditions.

Retinal hemorrhages (RH) are common at altitude, probably occurring in 20 to 30% of all persons who climb above 14,000 feet. The more strenuous the exertion the more frequent the hemorrhage we believe. The climber rarely knows that he has a retinal hemorrhage, which is probably why they have not been observed until very recently. It is our impression that retinal hemorrhages disappear in two to six months leaving no after effects. This is supported by the fact that roughly 30% of all newborn infants have retinal hemorrhages which clear rapidly without residuals. Therefore retinal hemorrhages alone are not considered by most altitude wise doctors as cause for descent, or reason to not climb again. The really important question of whether or not retinal hemorrhages are indicative of hemorrhages elsewhere—for example in the brain—has not been settled. Nor is it likely to be for some time.

As more and more cases of altitude illness are carefully described, it is more and more clear that patients with HAPE have some CE as well, and that the difference between AMS and HAPE plus CE is only a matter of degree. Indeed some experienced researchers believe that AMS is actually caused by early brain edema.

Of course the majority of people who go to altitude carefully and slowly have only minor temporary discomfort. They adapt, they acclimatize. This process is an intricate one, and does not belong in this summary paper. However it does lead us to look at the response to altitude hypoxia as divided into two stages: some immediate reactions (deeper faster breathing, rapid bounding pulse, increased hemoglobin) seem clearly intended to bring more oxygen to the tissues despite less oxygen in the air. These are the "struggle for oxygen" responses defined by Barbashova. While these are providing temporary protection against hypoxia, other slowly evolving changes take place within the cells enabling them to use oxygen more effectively. These are the true adaptations. Some take days, others weeks, others a lifetime to perfect. As the cellular adaptations mature, the "struggle responses" decrease and disappear. In the fully acclimatized individual the "struggle responses" are minimal. By contrast, the patient with altitude illness shows strong struggle responses.

Meanwhile, while the cells are adapting, trouble develops. A current concept, particularly attractive although still only an hypothesis, may ex-

plain why hypoxia causes the type of reaction which we see. This concept or hypothesis runs as follows: lack of oxygen causes a change in the delicate membranes which enclose each living cell, a change which produces an increase of sodium within the cell, while potassium moves out. The increased sodium attracts water into the cell, and the cell swells. The extent and location of swollen cells dictate what signs and symptoms will result. The membrane change is attributed to a temporary breakdown in the "sodium pump" which depends upon adenosinetriphosphate (ATP) the fuel for most living processes, which is oxygen dependent.

It may be some time before we can prove or disprove this hypothesis, even though we know that most of the signs and symptoms of altitude illness are due to abnormal shifts of water and electrolytes.

There are obviously many other concurrent changes: certain hormones are increased while others decrease, the number of tiny capillaries increases, and the mass of a special form of hemoglobin (myoglobin) increases, enabling oxygen to be "temporarily stored." Circulating hemoglobin, after an immediate rise and fall again slowly rises; certain portions of the Krebs Cycle of metabolism within the cells change to enable more metabolism to occur without oxygen. Possibly the most significant change of all is a considerable increase in mitochondria—the tiny granules—which are called the true powerhouses of the cell.

In summary what do we know for sure? *First:* All forms of altitude illness are increasing in frequency and perhaps in severity, most probably because more people are going too high too fast. *Second:* Evidence is increasing to show that what we have until recently considered as separate diseases are in fact all part of a continuum of one disease, a disturbance of water and salt. *Third:* As yet there is no reliable way of predicting who will and who will not be taken with altitude illness, or which individuals, smitten once, may be smitten again. *Fourth:* No medicine is a proven preventive, although Diamox does help somewhat. *Fifth:* We do have a proven treatment: immediate rapid descent to safe altitude. Other treatment such as oxygen, steroids, aspirin, may help but is less and less valuable the longer the condition persists. *Sixth:* We cannot say for sure whether a person with one attack is more or less likely to have another. We cannot say for sure whether or not persons well acclimatized to high altitude, going down for a few days or weeks have a greater risk of altitude illness when they return to altitude, than do those going high for the first time.

We can say with a moderate degree of confidence that taking one day to climb each thousand feet will protect most people, but today we would start this slow rate of ascent at 7000 feet rather than 10,000 feet as was recommended earlier. A number of near fatal cases and deaths have occurred within a day of reaching 9500 feet from sea level.

Finally, we can say with great confidence that almost any one with

altitude illness who starts down early in the disease will recover rapidly and completely. As should be the case in all of medicine, prevention is the most important aspect in the management of altitude illness.

Selected Papers on High Altitude Illness

This is in no sense a complete bibliography, but a selection of some of the better, more authoritative publications of recent years on the subject of altitude illness in its various forms, and a few of the basic papers which give background. From references in most of the papers cited can be found almost all of the major publications in the field.

Some Experiences of Mountain Sickness in the Andes, Ravenhill, T.H., Jour Trop Med and Hyg, 20, 313, Oct 15, 1913.
This appears to be the first definite description of acute mountain sickness, pulmonary edema, and cerebral edema due to altitude. The author describes his personal observations of numerous cases, and his puzzlement that some altitude residents do, while others do not, become ill on reascent to altitude after a brief stay at sea level. No references; a classic paper.

An Annotated Bibliography of Acute Mountain Sickness, Hall, W.H., U.S. Army Research Institute of Environmental Medicine, June 1964.
Twenty-two papers, selected from publications in the last seventy years, are carefully described. Only acute mountain sickness is included. Most of the classical reports are included.

Acute Mountain Sickness, Singh, I., Khanna, P.K., Srivastava, M.C., Lal, M., Roy, S.B., Subramanyan, C.S.V., New Engl Jour Med, 280, 175, 1969.
Clinical observations on 1925 individuals with various forms of acute mountain sickness in the Himalayan Sino-Indian war. Relationships between acute mountain sickness, cerebral and pulmonary edema and antidiuresis are discussed. Various treatments are evaluated.

Effect of Acetazolamide on Acute Mountain Sickness, Forwand, S.A., Lansdowne, M., Follansbee, J.N., and Hansen, J.E., New Engl Jour Med, 279, 839, 1968.
In a double blind study, either placebo or acetazolamide was given to forty-three subjects rapidly transported to 12,800 feet for five days. Significant reductions were observed in the most prominent symptoms of acute mountain sickness, but the mechanism of action was not identified.

A Hypothesis Regarding the Pathophysiology of Acute Mountain Sickness, Hansen, J.E., and Evans, W.O., Arch Env Health, 21, 666, 1970.
Acute mountain sickness is a syndrome of unknown etiology which occurs, after a time lag, following abrupt exposure to oxygen lack and which includes a characteristic spectrum of symptoms. The authors collected evidence to suggest that brain compression causes the symptoms of acute mountain sickness.

Acute Mountain Sickness: Increased Severity in Eucapnic Hypoxia, Maher, J.T., Cymerman, A., Reeves, J.T., Cruz, J.C., Denniston, J.C. and Grover, R.F., Aviation Space and Env Med, 826, June 1975.
In carefully controlled studies in the low-pressure chamber, arterial carbon dioxide levels were held constant by increasing carbon dioxide in ambient air at a simulated altitude of 4000 meters for four days, with ambient barometric pressure adjusted to maintain the same alveolar oxygen levels in both groups.

The benefits previously attributed to carbon dioxide are shown to be due to the hyperventilation which raised alveolar oxygen; in fact, when alveolar oxygen is the same, added carbon dioxide appears to aggravate symptoms.

Acute Pulmonary Edema of High Altitude, Houston, C.S., New Engl Jour Med, 263, 478, 1960.
A case of acute pulmonary edema occurring in a healthy skier at 12,000 feet is reported with brief reviews of four similar but less well documented cases among mountaineers. Though the mechanism was unknown, the combined effects of anoxia, cold, and exertion were suspected as causative. This early case report stimulated further studies.

High Altitude Pulmonary Edema, Hultgren, H.N., Spickard, W.B., Hellriegel, K., and Houston, C.S., Medicine, 40, 289, September 1961.
This early article reports eighteen patients with pulmonary edema at 12,000 feet in the Andes and thirteen suggestive cases occurring in mountaineers. The literature is reviewed and mechanisms examined. Fifteen of the eighteen persons studied in the Andes developed the condition after re-entry to altitude to which they were fully acclimatized, raising the possibility that such persons are more vulnerable.

High Altitude Pulmonary Edema, Singh, I., Kapila, C.C., Khanna, P.K., Nanda, R.B., and Rao, B.D.P., Lancet, 229, Jan 30, 1965.
Three hundred thirty-two Indian soldiers developed pulmonary edema at altitudes above 11,000 feet following rapid ascent. The condition occurred in 15.5% of persons reaching altitude for the first time, and in 13.0% of those returning after a stay at low altitude. Pulmonary edema, cerebral edema and acute mountain sickness are suggested to be various reactions to the same underlying physiologic response to hypoxia, and mechanisms are proposed. Treatment with aminophylline, atropine, morphine and digoxin is discussed; the latter apparently ineffective. Failure of oxygen to relieve hemoglobin desaturation is noted.

High Altitude Pulmonary Edema, Menon, N.D., New Engl Jour Med, 273, 66, July 8, 1965.
One hundred and one patients with proven high-altitude pulmonary edema were treated while still at 11,500 feet; digitalis and oxygen appeared to be more effective than either alone. Among troops taken rapidly to altitude the incidence appeared to be 5%

The Preterminal Arterioles in the Pulmonary Circulation of High Altitude Natives, Recavarren, S., Circulation 33, 177, February 1966.
Quoting the work of others, the author speculates that increased pulmonary artery muscularization correlates, in individuals fully acclimatized by long residence at altitude, with the susceptibility to pulmonary edema by increased capillary hydrostatic pressure, increased capillary permeability, and points out that normal lung capillary pressures have been observed after edema has appeared.

Pulmonary Edema of High Altitude, Viswanathan, R., Jain, S.K., and Subramanian, S., Amer Rev. of Resp Dis, 100, 342, 1969.
In a series of three reviews the authors examine the production of edema in animals, the clinical and hemodynamic features, and the pathogenesis, and conclude that the condition is due to an abnormal hypoxic response in susceptible individuals who manifest a genetically determined condition by greater than normal pre-capillary vascular resistance in lungs, leading to pulmonary artery hypertension. The mechanism whereby edema results is not explained.

Water Metabolism in Humans During Acute High Altitude Exposure, Krzywicki, H.J., Consolazio, F., Johnson, H.L., Nielsen, W.C., and Barnhart, R.A., Jour Appl Physiol, 30, 806, 1971.
Two groups of six men were studied before and after six days at 14,000 feet. Total body water was significantly decreased; extra-cellular water increased; and intra-cellular water decreased. Heavy physical exertion was performed before and during the altitude exposure; hypo-hydration and diuresis occurred, suggesting that water loss may have been an adaptive mechanism to acute altitude exposure. This report disagrees with the work of some others.

Hormonal and Electrolyte Response to Exposure to 17,500 Feet, Frayser, R., Rennie, I.D.B., Gray, G.W., and Houston, C.S., Jour Appl Physiol, 38, 636, April 1975.
Changes in cortisols, renin and aldosterone were found at day three after ascent to 17,500 feet, returning to normal on the fifth day. Sodium and potassium excretion was decreased. The changes observed are believed due to the stress and alkalosis of acute hypoxia, and return to normal as the body adapts. References and discussion of varying findings by other observers are included.

"State of the Art Review": Pathogenesis of Pulmonary Edema, Staub, N.C., Amer Rev Resp Dis, 109, 358, 1974.
A careful review of the development and pathology of various types of interstitial and alveolar edema, with extensive references and illustration of the various causes, including hypoxia.

Cerebral Form of High Altitude Illness, Houston, C.S., and Dickinson, J., The Lancet, 785, Oct 18, 1975.
Twelve cases of severe altitude illness in which neurological signs and symptoms dominated the clinical pictures are described. Two patients died and autopsy confirmed the presence of cerebral and pulmonary edema; other pathology was identified in several of the patients. The importance of early descent is emphasized.

Brain Edema, Fishman, R.A., New Engl Jour Med, 293, 706, Oct 2, 1975.
A brief, tightly written review of the various causes and pathophysiology of brain edema from various causes; management is discussed.

Acute High-Altitude Illness in Mountaineers and Problems of Rescue, Wilson, R., Annals of Internal Med, 78, 3, 421, March 1973.
Syndromes of acute mountain sickness share hypoxia as a cause, but expression of the illness varies. Cerebral edema causes headache, selective neurologic defect and coma and perhaps even pulmonary edema, although microthrombi in pulmonary capillaries are often seen and may be causal. Retinal hemorrhages frequently occur at high altitude. Acute mountain sickness is difficult to treat on a mountain, even with oxygen. Drugs are of uncertain usefulness; therefore immediate descent is important.

Adaptation to High Altitude, Lenfant, C., and Sullivan K., New Engl Jour Med, 284, 1298, June 10, 1971.
A concise and careful review of the process of acclimatization. Major emphasis is placed on changes in the oxygen transport mechanisms in response to altitude hypoxia. Many references.

Physiological Adjustments to Altitude Changes, Dill, D.B., Jour Am Med Assoc, 205, 123, Sept 9, 1968.
Physiological adaptation to high altitude involves rapid responses in respira-

tion and slower responses in nervous, muscular, and cardiovascular systems. An excellent criterion of adaptation is measurement of the capacity for supplying oxygen to tissues: the oxygen consumption (V_{O_2} maximum). Such measurements reveal four stages of response. At 10,000 feet stage 1 is reached in minutes; V_{O_2} max declines 10%. In one to three days, (stage 2), it declines another 10%; this is the stage of unpleasant subjective responses. In a few weeks, stage 3, performance approaches the level of stage 1. Red blood cell volume increases in stage 4, reaching its maximum after a year or more. Performance improves pari passu: eventually sea-level performance can be achieved at 13,200. Above 17,500 feet there is deterioration rather than adaptation.

Cellular Level of Adaptation, Barbashova, Z.I., Handbook of Physiology: Adaptation to Environment, Section 4, pp 37-54, 1964.
The writer suggests that two levels of adaptation to hypoxia occur: the immediate or "struggle for oxygen" responses of hyperventilation, increased cardiac output, increased hemoglobin, and slower adaptation of intracellular enzymes. As the latter mature, the former diminish. Acclimatized man shows few "struggle responses" and highly developed cellular adaptation.

Altitude, Migration, and Fertility in the Andes, Abelson, A.E., Baker, T.S., and Baker, P.T., Population Biology, 21(1), 12, 1974.
Using anthropological and sociological techniques Andean populations were examined to determine the impact upon fertility, live births, and infant mortality by altitude hypoxia and by migration from high to low or low to high altitude. Despite the complexity of such studies, evidence suggests that altitude decreases fertility, increases neonatal mortality and increases the probability of birth defects.

Retinal Hemorrhage at High Altitude, Frayser, R. Houston, C.S., Gray, G., Bryan, A.C., New Engl Jour Med, 282, 1183, 1970.
Nine out of twenty-five individuals taken to 17,500 feet were found to have retinal hemorrhage. Of seventeen of these persons who went up rapidly six had hemorrhage; of eight who climbed slowly to altitude, three showed hemorrhage. Incidence of retinal hemorrhage was unrelated to other symptoms of altitude sickness, but seemed to be reduced in the nine individuals premedicated with acetazolamide. This is the first report of retinal hemorrhage in healthy individuals exposed to high altitude hypoxia.

The Response of the Retinal Circulation to Altitude, Frayser, R., Houston, C.S., Gray, G., Bryan, A.C., and Rennie, I.D.B., Arch Int. Med, 127, 708, 1971.
Individuals taken rapidly or slowly to 17,500 feet showed increases in retinal blood flow of 89% over control values within two hours, and by 128% over control after four days. Retinal blood flow increased by 105% over control values in acclimatized subjects. Both arterioles and venules show increased diameter and tortuosity beginning a few hours after arrival at altitude.

Ocular Changes in Pulmonary Insufficiency, Spalter, H.F., and Bruce, G.M., Tr Am Acad Ophthal and Otol, 661, July 1964.
Changes in the ocular fundi in patients with hypoxia due to chronic pulmonary disease are described. The retinopathy (which included increased diameter and tortuosity of vessels, papilledema and hemorrhages) was attributed to carbon dioxide retention and resulting acidosis. Literature is reviewed and photographs presented.