High-altitude (HA) exposure is a worldwide problem, with a relatively smaller population at risk in North America. The human population residing in the North American Rocky Mountains is sparse, with an average of four people per square kilometer (10 per square mile) and few cities with >50,000 people.

Globally, it is estimated that >140 million people live at a high altitude (HA), defined as >2,500 m (8,200 ft), and that countless others sojourn to the mountains for work, travel, and sport. The distribution of exposure to HA is worldwide, including 35 million in the Andes and >80 million in Asia, including China and central Asia. HA stress primarily is due to the hypoxia of low atmospheric pressure, but dry air, intense solar radiation, extreme cold, and exercise contribute to acute and chronic disorders. The acute disorders are acute mountain sickness (also known as soroche), HA cerebral edema, and HA pulmonary edema (HAPE). Of these, HAPE is highly correlated with acute pulmonary hypertension. The first chronic syndrome described in HA dwellers in Peru was chronic mountain sickness (Monge disease), which has a large component of relative hypoventilation and secondary erythrocytosis. The prevalence of chronic mountain sickness in HA dwellers ranges from 1.2% in native Tibetans to 5.6% in Chinese Han; 6% to 8% in male residents of La Paz, Bolivia; and 15.6% in the Andes. Subacute mountain sickness is an exaggerated pulmonary hypertensive response to HA hypoxia occurring over months, most often in infants and very young children. Chronic pulmonary hypertension with heart failure but without hypoventilation is seen in Asia. Not only does HA pulmonary hypertension exact health consequences for the millions affected, but also the mechanisms of disease relate to pulmonary hypertension associated with multiple other disorders. Genetic understanding of these disorders is in its infancy.

The highest elevation for an incorporated city in the United States is Leadville, Colorado (population 2,800), at 3,093 m (10,150 ft). Thus, the HA populations in the United States, including Alaska, are dwarfed by the populations in the Andes, Himalayas, and the Tian Shan mountain range of central Asia, which number in the tens of millions. Insights into the health effects and mechanisms of chronic HA dwelling originated in the Andes by Peruvian scientists. Important work on acute and subacute altitude disorders has been made by many other investigators, including studies...
on native dwellers and sojourners to Everest and multiple mountain regions throughout the world. Figure 1 shows the mean pulmonary artery pressure in healthy humans taken from cities around the world at different elevations and the associated arterial oxygen saturation ($\text{SaO}_2$).

The effect of HA on the heart and pulmonary circulation has been well reviewed recently, and a consensus statement on definitions of chronic and subacute HA diseases was published in 2005. Otherwise healthy HA natives have pulmonary hypertension, increased pulmonary arterial smooth muscle, right ventricular hypertrophy, and erythrocytosis. Decompensation at HA takes several forms, with variable contributions of hypoventilation, erythrocytosis, and remodeling of the pulmonary vascular bed. Hypoxic hypoxia is the invariant stimulus for HA disorders. Hypoxic pulmonary vasoconstriction is highly variable among animal species and individual humans and generally correlates with subsequent pulmonary hypertension in animals, although the correlation has never been adequately studied in humans. The mechanisms of hypoxic vasoconstriction are still incompletely understood, although redox stress leading to activation of intracellular calcium flux is clearly important. Remodeling of the pulmonary vascular bed is a separate process from acute hypoxic vasoconstriction, with activation of genes involved in growth, transformation, and structure. Of interest, HA dwellers fail to normalize pulmonary vascular pressures when exposed to oxygen, probably due to muscularization of the arterioles.

The prehistoric expansion of humans around the globe resulted in a variety of environmental selection pressures of which HA hypoxia is a prime example. Natural selection presumably favored individuals with genetic features in a variety of physiologic systems to adapt to hypoxia, and over time, these features were sustained in the population. The major impacts are on hypoxic vasoconstriction, pulmonary arterial remodeling, right ventricular function, hypoxic erythrocytosis, and ventilatory drives. Because the phenotypic penetrance associated with dysfunctional HA responses is low, the impact of genetic components may vary depending on genetic background, age, altitude, and length of exposure, masking insights into adaptation or maladaptation in natives and sojourners. For example, Tibetan newborns are reported to have higher $\text{SaO}_2$ at birth and during the first 4 months of life than Han newborns. Improved lung mechanics of the Ladakhi may be an important adaptation to the lifelong sustained increase in resting ventilation. Lack of smooth muscle in the small pulmonary arteries of Ladakhi men compared with age-matched lowlanders is correlated with better function in the hypoxic environment of HA. Hemoglobin concentration is lower in Himalayan than in Andean highlanders; the Tibetans are similar to sojourners with higher hypoxic ventilator responses compared with Andeans. Similarly, chronic mountain sickness (CMS) is rare in the Himalayas, whereas it is common in the Andes. The polygenic nature of the complex human response to HA hypoxia will require a better understanding of variants in pathophysiology to predict clear genotype-phenotype interactions. Although several candidate genes have been tested in this context, genetic understanding of these disorders still is in its infancy.

Genomic Variants and HA Syndromes

The association of HA disorders with polymorphisms in genes highlighted in this review includes
endothelial nitric oxide synthase (NOS3) \textsuperscript{21-24} β2-adrenergic receptor (ADRB2), \textsuperscript{25,26} angiotensin I-converting enzyme (ACE), \textsuperscript{27-33} bone morphogenetic protein receptor type 2 (BMPR2), activin receptor-like kinase 1 (ALK1), 5-hydroxytryptamine transporter (5-HTT) in humans, and hypoxia-inducible factor 1 (HIF-1α) in yak, a Himalayan animal.\textsuperscript{34-36} Variants of G94T (Glu298Asp), 4b/4a (a 27-base-pair variable number of tandem repeat in intron 4), −922A/G, and −786T/C polymorphisms of NOS3 contribute to varied nitric oxide (NO) levels in high-altitude pulmonary edema (HAPE).\textsuperscript{22} Overrepresentation of Asp and 4a alleles in patients with HAPE correlate with reduced NO levels, thereby associating with endothelial dysfunction and contributing to HAPE, whereas overrepresentation of Glu and 4b alleles are found in Ladakhi natives, thereby associating with elevated NO levels and HA adaptation (Fig 2).\textsuperscript{21,23} NOS3 variants associate with pulmonary artery pressure measurements in the Japanese but not in some European cohorts.\textsuperscript{37} A role of NO in the physiology of HA diseases has since been recognized\textsuperscript{38,39}, consequently, NO inhalation therapy has been introduced in the treatment of HAPE. It would be important to measure the pattern of the NOS3 variants in the population of the Andes and other HA populations so that the significance of NOS3 variants can be established (Fig 3).

The importance of β-receptors, with β2-subtype dominant (ADRB2), in lung smooth muscle cells has long been recognized. At HA, the role of ADRB2 in acclimatization is correlated with improved oxygen delivery.\textsuperscript{40} The prophylactic administration of salmeterol, a β2-adrenergic agonist, decreases the incidence of HAPE in susceptible individuals.\textsuperscript{41} Qadar Pasha and colleagues (unpublished data) systematically explored the possible role of single-nucleotide polymorphisms (SNPs) of this gene and associated haplotypes in combination with SNP variants. The haplotypes consisting of common SNPs 46A/G and 79C/G were associated with HAPE. A multidimensional reduction model depicting disease association through genotype-genotype and genotype-phenotype interaction included SNP 46A/G, 79C/G, and 523C/A as the best disease-predicting combination. The interaction values between any two polymorphisms are both positive and negative. The model showed best synergisms between 79G/T and −367C/T, 79G/T and 46G/A, 46G/A and 523C/A, and 46G/A and −654A/G (Fig 4). Further, although the global haplotype test showed significant association with HAPE, a moving-window analysis specifically revealed haplotype −367C/T_46A/G_79C/G significantly associating with HAPE. These SNPs also have been investigated in other HA populations; however, the results were not encouraging, and the tag SNPs in this gene could not be associated with acute mountain sickness susceptibility in the Nepalese.\textsuperscript{25} Thus, a role of ADRB2 variants in HA disorder susceptibility remains unclear.

ACE insertion/deletion (I/D) polymorphism in HA populations highlights the potential importance of the renin-angiotensin system. In a comparative study of 13 SNPs in HA dwellers and lowlanders, significant linkage disequilibrium was observed among SNPs in the native HA population. A large number of studies reported ACE I/D association with endurance,\textsuperscript{44} HA adaptation,\textsuperscript{30,39} oxygen saturation,\textsuperscript{30} and HAPE.\textsuperscript{27,31} The hypothesis initially was based on the concept of the renin-angiotensin system playing an important neurohumoral role in the maintenance of BP as well as electrolyte and fluid balance. The gene also plays a role in regulation of pulmonary vascular tone.\textsuperscript{32} Additionally, the ACE levels have been reported to be lower in acclimatized subjects.\textsuperscript{27,31,33}

Several studies have implicated the genes BMPR2, ALK1, and 5-HTT in the development of pulmonary arterial hypertension through receptor and/or transporter signaling, including cell proliferation and differentiation. Polymorphisms in the receptors

\textbf{Figure 2.} Schematic presentation of the pathway, involving NOS3/NO that defines health or disease. One or more variants of the NOS3 gene, such as at locus 894G/T, may regulate NO level. The hypothetical pathway depicts how either allele of the mentioned single-nucleotide polymorphism (SNP) influences NO level, which through a known cascade involving cGMP influences vasodilatation (health) or disease (high-altitude pulmonary edema [HAPE]).

NO = nitric oxide; cGMP = cyclic guanosine monophosphate; NOS = nitric oxide synthase; PAP = pulmonary artery pressure.

\textbf{Allele} \hspace{1cm} \textbf{NO} \hspace{1cm} \textbf{Allele} \hspace{1cm} \textbf{cGMP} \\
G894, 4b \hspace{1cm} ? \hspace{1cm} ? \hspace{1cm} T894, 4a

\textbf{Vasodilatation, health} \hspace{1cm} \textbf{Vasoconstriction, PAP, disease}
artery systolic pressure (PASP) between HAPE and high-altitude cerebral edema (HACE) was highlighted by Ghulam Mohammad, senior physician at associate with pulmonary hypertension. In Brisket disease in cattle, a form of HA pulmonary hypertension with right-sided heart failure, variants in \textit{BMPR2}, transforming growth-inhibiting factor, \textit{NOS3}, and nicotinamide adenine dinucleotide phosphate oxidase have been excluded as factors related to risk of disease.\textsuperscript{36} In addition, the \textit{ALK1} mutations are seen in the majority of patients with hereditary hemorrhagic telangiectasia associated with pulmonary arterial hypertension.\textsuperscript{45} Because pulmonary hypertension is a leading factor in the pathogenesis of HAPE, these genes also were examined for association with HAPE. Preliminary analysis in Indian sojourners has not revealed a significant association of polymorphisms of \textit{BMPR2}, \textit{ALK1}, and \textit{5-HTT} with HAPE.

**NEW CONSIDERATIONS FROM THE LEH SYMPOSIUM**

A recent symposium in Leh-Ladakh, India, “Recent Trends and Future Perspectives in High-Altitude Research,” was convened to discuss clinical and investigational themes on HA problems. The venue, Sonam Norboo Memorial (SNM) Hospital in Leh at 3,500 m (11,483 ft), was appropriately selected because of Leh’s large indigenous population and its popularity with a large number of sojourners from all parts of the world. The hospital treats an exceptionally high number of patients with various HA diseases and is among the few centers of the highland world that directly serves such patients.

The significance of clinical characteristics such as \textit{SaO_2}, pulse rate, chest radiography, and pulmonary artery systolic pressure (PASP) between HAPE and high-altitude cerebral edema (HACE) was highlighted by Ghulam Mohammad, senior physician at associate with pulmonary hypertension.

**Figure 3.** Global distribution of risk alleles of 894G/T and −786T/C polymorphism of NOS3. Distribution (%) of the risk alleles from different studies (\textsuperscript{†}Ahsan et al\textsuperscript{22}; \textsuperscript{*}Droma et al\textsuperscript{24}; **Droma et al\textsuperscript{40}; ¥Weiss et al\textsuperscript{41}) and its comparison with HapMap populations. CEU = Caucasian population; HapMap = haplotype mapping; HAPE-p = patients with HAPE; HAPE-r = controls with HAPE; HCB = Chinese population; JPT = Japanese population; and YRI = African population. See Figure 2 legend for expansion of other abbreviation.

**Figure 4.** Interaction graph of the studied SNPs of B2-adrenergic receptor obtained through a multidimensional reduction model. Nodes and connections indicate the percentage of entropy in case-control status removed by each variable (main effect) and by each pairwise combination of attributes (interaction effect). The values indicate both a positive and a negative interaction between all the polymorphisms of the model. The model shows best synergisms between 79G/T and −367C/T, 79G/T and 46G/A, 46G/A and 523C/A, and 46G/A and −654A/G. No redundancy could be observed. See Figure 2 legend for expansion of the abbreviation.
have a fall in \( \text{Sao}_2 \) by >50% without the anticipated rise in PASP, which is expected once \( \text{Sao}_2 \) falls to <60%.

Tsering Norboo, senior physician at SNM Hospital, reported newly discovered CMS in a population of nomads \((n = 91)\) living at an altitude of 4,550 m (Korzok, Ladakh, India) (T. Norboo, personal communication). The CMS scoring in these subjects was 2% for severe; 7% for moderate, and 16% for mild. In addition, blurring of vision and occasional diplopia, a symptom not included in the international consensus scoring, were reported by 10% of subjects. Extreme HA native dwellers have a physiologic adaptation to HA in the form of enlarged carotid bodies and polycythemia with a rise in blood volume and a high FEV1 percent compared with lowlanders. Regional HA problems, such as pneumoconiosis, are found in the populations of the Indus belt in Ladakh, the Andes, and the Rocky Mountains, which complicate evaluation of HA disorders and add morbidity to the populations. Tashi Motup, MS, senior surgeon at SNM Hospital, has observed a higher incidence of duodenal ulcer perforation in lowland middle-aged male laborers working at HA than in natives. Further, splenic infarction, mesenteric artery thrombosis, and appendicular perforation appear to be more frequent in lowlanders working at HA. These interesting, yet unexplored observations beg prospective studies.

Very few reports are available on the use of anesthesia at altitude; to our knowledge, none are controlled. As reviewed by Firth and Pattinson, the cause of the many early chloroform deaths at altitude has not been clearly established. According to SNM Hospital anesthetists, more volume of gas is needed for anesthesia at HA (3,300 m [~11,000 ft]) presumably because of lower partial pressures, but recovery appears faster, suggesting that general anesthesia may be performed satisfactorily and safely at HA by experienced anesthetists. Hypoxemia can be rapidly worsened by depressed respiration in postoperative patients at HA, especially at night. Careful monitoring of oxygenation is indicated, and supplemental oxygen should be available during this period.

**Figure 5.** Correlation between \( \text{Sao}_2 \) (%) and pulse (rate/min). The regression lines depict correlation for patients with HAPE and controls with HAPE. The blood oxygen saturation negatively correlates with pulse rate, correlation constant \((R^2) = 0.02\) in controls and \(R^2 = 0.15\) in patients. \( \text{Sao}_2 \) = arterial oxygen saturation. See Figure 2 legend for expansion of other abbreviation.

**Future Directions**

More work on the mechanisms and inhibition of hypoxic vasoconstriction and chronic pulmonary hypertension is needed. If either or both responses could be chronically blocked at low cost with oral drugs, HA morbidity could be reduced for hundreds of thousands of affected HA natives and millions of sojourners. Further work to discover
genomic susceptibility is needed because signaling consequences of common polymorphisms can be overcome by appropriate pharmacological approaches in many cases. Identification of HA dwellers at risk for life-threatening subacute mountain sickness and CMS is important. The early detection of congenital heart disease is important especially because atrial septal defects can be closed and reduce late mortality. The management of general medical and surgical problems of HA natives and sojourners is a topic that deserves study and the development of consensus statements, especially with regard to the differential diagnoses of illnesses with overlapping features, including those of vascular occlusion such as mesenteric and splenic infarct, pulmonary embolism, and pneumonia. Work on genetic and genomic mechanisms will require international and intercontinental collaborative studies, including populations from the Andes and the Himalayas. Similarities and differences not only in adaptations but also in maladaptations would be revealed by differential studies.

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