Tibetan and Andean Patterns of Adaptation to High-Altitude Hypoxia

CYNTHIA M. BEALL[1]

Abstract Understanding the workings of the evolutionary process in contemporary humans requires linking the evolutionary history of traits with their current genetics and biology. Unusual environments provide natural experimental settings to investigate evolution and adaptation. The example of high-altitude hypoxia illustrates some of the progress and many of the remaining challenges for studies of evolution in contemporary populations. Current studies exemplify the frequently encountered problem of determining whether large, consistent population differences in mean values of a trait reflect genetic differences. In this review I describe 4 quantitative traits that provide evidence that indigenous populations of the Tibetan and Andean plateaus differ in their phenotypic adaptive responses to high-altitude hypoxia. These 4 traits are resting ventilation, hypoxic ventilatory response, oxygen saturation, and hemoglobin concentration. The Tibetan means of the first 2 traits were more than 0.5 standard deviation higher than the Aymara means, whereas the Tibetan means were more than 1 standard deviation lower than the Aymara means for the last 2 traits. Quantitative genetic analyses of within-population variance revealed significant genetic variance in all 4 traits in the Tibetan population but only in hypoxic ventilatory response and hemoglobin concentration in the Aymara population. A major gene for oxygen saturation was detected among the Tibetans. These findings are interpreted as indirect evidence of population genetic differences. It appears that the biological characteristics of sea-level humans did not constrain high-altitude colonists of the 2 plateaus to a single adaptive response. Instead, microevolutionary processes may have operated differently in the geographically separated Tibetan and Andean populations exposed to the same environmental stress. Knowledge of the genetic bases of these traits will be necessary to evaluate these inferences. Future research will likely be directed toward determining whether the population means reflect differences identified at the chromosomal level. Future

[1]Department of Anthropology, 238 Mather Memorial Building, Case Western Reserve University, Cleveland, OH 44106-7125.

Human Biology, February 2000, v. 72, no. 1, pp. 201–228.

KEY WORDS: HIGH ALTITUDE, TIBETAN, AYMARA, HERITABILITY, RESTING VENTILATION, HYPOXIC VENTILATORY RESPONSE, OXYGEN SATURATION, HEMOGLOBIN CONCENTRATION

research will also likely consider the biological pathways and environmental influences linking genotypes to phenotypes, the costs and benefits of the Tibetan and Andean patterns of adaptation, and the question of whether the observed phenotypes are indeed adaptations that enhance Darwinian fitness.

Human adaptability studies in physical anthropology analyze contemporary populations to understand the process of evolution and adaptation. The goal is to relate the ultimate evolutionary explanation for the existence of certain traits in a population with the proximate biological explanation for the expression of those traits in individuals. The example of human adaptation to the stress of high-altitude hypoxia illustrates some of the progress and many of the remaining challenges for studies of ongoing evolution. In particular, high-altitude studies encounter issues common to many such studies: interpreting population differences in quantitative traits in terms of genetic differences, even though the genetic bases of the traits are unknown and environmental factors are also known to influence the trait.

The purpose of this review is to describe adaptive phenotypes of indigenous populations on the Tibetan and Andean plateaus. Because both populations have long histories of high-altitude residence, natural selection has had the opportunity to increase the frequency of heritable traits that enhance fitness in their environment. I summarize evidence from 4 traits that demonstrates that indigenous Tibetan and Andean populations differ in their phenotypic adaptive responses to high-altitude hypoxia. I also describe knowledge of the heritable bases of these traits and then suggest fruitful directions for future research to relate these observations to the process of natural selection.

High-Altitude Hypoxia

The stress at high altitude is hypobaric hypoxia resulting from the lowered barometric pressure. It is unavoidable, unmodifiable, and uniform for everyone at any given altitude. Organisms at altitude must adapt to the stress of limited oxygen availability relative to sea level and still sustain aerobic metabolic processes. For example, at an altitude of 4,000 m (13,200 ft) the concentration of oxygen in 1 liter of inspired air is 21% oxygen, just as at sea level, but because of the lower barometric pressure, 1 liter of air at 4,000 m contains just 63% of the number of oxygen molecules at sea level. Nevertheless, oxygen-requiring physiological processes must be maintained. The homeostatic processes that enable oxygen delivery under that stress result from evolution by natural selection in the sea-level ancestral population, the high-altitude colonizing population, or both. Thus high-altitude environments

provide natural experimental settings to investigate human evolution and adaptation.

Research into adaptation to high-altitude hypoxia has used study designs contrasting sea-level natives at sea level, sea-level natives during high-altitude stays of varying duration, and indigenous natives at high altitude. The reasoning is that varying duration of exposure may elicit qualitatively or quantitatively different adaptive homeostatic responses. Of particular interest to evolutionary biologists is the possibility that natural selection has acted to produce genetically adapted high-altitude natives. The first wave of studies testing evolutionary hypotheses began in the 1960s and contrasted indigenous inhabitants of the Andean plateau with sea-level natives and migrants of European ancestry. The Andean highlanders had a long history of exposure and opportunity for natural selection and adaptation, whereas the Europeans did not. Thus, when highlanders differed from sea-level populations or their immediate descendents in ways that indicated better oxygen delivery, the inference was that natural selection had acted on the high-altitude population (Baker and Little 1976).

The second wave of studies testing evolutionary hypotheses began in the 1970s when indigenous populations of the Tibetan plateau and its environs became accessible. Those studies added a new dimension to the previous pairing of potentially selected and unselected populations. They added comparison of 2 populations with a long history of opportunity for natural selection and introduced the concept of testing the hypothesis that natural selection had acted on the same traits and with the same outcome in the 2 populations adapting to the same stress. Comparisons of these 3 types of populations—low-altitude natives with no evolutionary history of adapting to chronic hypoxia and 2 separate high-altitude native populations with long histories of exposure to chronic hypoxia—create a natural experiment in evolution (Harrison 1966). Data presented later indicate that the outcomes of this natural experiment are different.

Comparisons of mean values of many traits involved in oxygen transport demonstrate 1 pattern of adaptation among populations indigenous to the Tibetan plateau and another pattern among populations indigenous to the Andean plateau. These contrasts have raised the important question of whether the population differences in the mean values of adaptive traits are due to population genetic differences. The answer to that question is crucial to evolutionary interpretations of the population differences. If the different phenotypes reflect genetic differences, then the case for natural selection is strengthened. If they do not, then some other process causes the population contrast. As described later, identifying the genetic bases of the adaptive traits is just beginning.

Tibetan and Andean Patterns of High-Altitude Adaptation

The following description of the 2 patterns of adaptation is based primarily on data from a comparative study conducted by 1 set of investigators

(C.M. Beall and co-workers). It used the same recruitment processes and measurement and analytical techniques to compare large samples of Tibetan and Andean high-altitude natives living at the same altitude and under the same hypobaric stress. The study included 428 Tibetan highlanders of Tibetan ethnicity and the 608 Andean highlanders of Aymara ethnicity. The participants ranged from 9 to 94 years of age. The study communities were rural agropastoral village areas located at a median altitude of 4,000 m in the Tibet Autonomous Region of China and in Bolivia. The study design was selected to maximize comparability of data.

The comparative study investigated 4 oxygen transport traits widely reported in studies of high-altitude adaptation: resting ventilation, hypoxic ventilatory response, oxygen saturation of arterial hemoglobin (the percentage of hemoglobin molecules carrying oxygen, Sa_{O_2}), and hemoglobin concentration. These pulmonary and hematological traits are components of oxygen transport from the lungs to the tissue. They are thought to participate in the proximate biological processes of high-altitude adaptation because changes in these traits can offset hypoxic stress. The findings have been reported in detail elsewhere [resting ventilation and hypoxic ventilatory response by Beall, Brittenham et al. (1997); percentage of oxygen saturation of arterial hemoglobin by Beall, Strohl et al. (1997) and Beall et al. (1999); and hemoglobin concentration by Beall et al. (1998)]. The following discussion focuses on the Tibetan-Aymara study because of the comparability of the data and because of the analytical techniques employed. Many other recent studies contrast various populations and various traits at high altitude (Brutsaert et al. 1999; Chen et al. 1997; Ge et al. 1995; Ge, Qiuhong et al. 1994; Ge, Chen et al. 1994; Niermeyer et al. 1995; Sun et al. 1990; Zhuang et al. 1993, 1996).

Increased resting ventilation relative to sea level is an immediate component of sea-level natives' short-term adaptation to high altitude. It offsets ambient hypoxia somewhat by increasing the volume of air taken into the lungs per unit time. High resting ventilation is characteristic of Tibetan but not Aymara lifelong high-altitude adaptation (Beall, Brittenham et al. 1997). Figure 1 is a scatterplot comparing the Tibetans and Aymara on the basis of resting ventilation for males and females from early adolescence through old age. The 2 populations' data were plotted on the same scale to illustrate the quantitative and qualitative contrast. Tibetan resting ventilation was roughly 50% higher than Aymara resting ventilation. For example, male Tibetans had an average resting ventilation of 19.7 L/min compared with an average of 13.4 L/min for male Aymara.

Current knowledge of the genetic bases for resting ventilation requires an indirect approach to identifying any population genetic differences. Such large differences in mean values of a biological trait are generally interpreted as evidence of population genetic differences after likely potential relevant environmental factors have been excluded. The logic is that both environmental and genetic factors influence the expression of traits and that control-

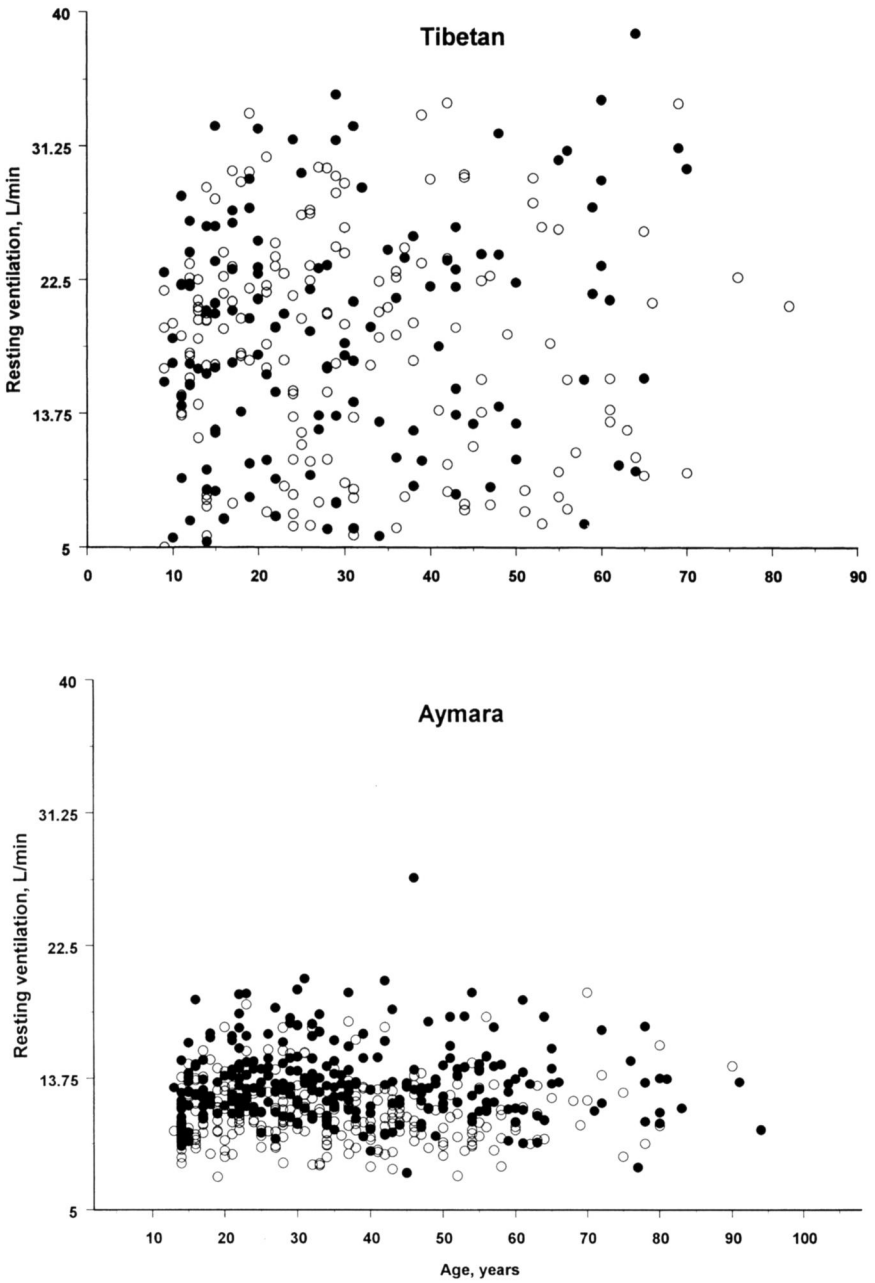

Figure 1. Scatterplot of resting ventilation with age comparing Tibetan and Aymara high-altitude natives at a median altitude of 4,000 m. Filled circles, males; open circles, females.

ling for environmental influences can reveal the influence of unknown genes. A shortcoming of this approach is the implicit assumption of genetic homogeneity at relevant loci in both samples and the explicit assumption that environmental sources of variation are known and uniform. Actually, many loci are polymorphic within populations and knowledge of environmental influences is incomplete. However, the indirect approach is an informative first step for analyzing quantitative traits. An informative second step is analysis of the variation within a population to determine whether variation is distributed consistently with known patterns of genetic inheritance.

Quantitative genetic techniques analyze the phenotypic variation within a population to detect the likelihood that genetic factors contribute to the variation. The approach can be applied to traits such as resting ventilation that are probably influenced by more than 1 unknown locus and allele and by individual characteristics such as age and sex and environmental factors such as cigarette-smoking behavior and household factors. Application to large data sets containing biological relatives allows the testing of hypotheses about the potential sources of phenotypic variance, including variance resulting from genetic factors, covariates, shared households, and random environmental factors.

A frequently reported summary value is the proportion of total phenotypic variance that is attributable to nonindependence resulting from biological relationships among individuals in the sample (Falconer 1989). This is reported as the heritability (h^2), calculated as the proportion of variance attributable to genetic relationships among individuals. One form of heritability is the residual heritability (residual h^2), calculated as the proportion of variance attributable to genetic relationships among individuals relative to the total variance minus the variance resulting from covariates such as age and sex. Theoretically, h^2 can assume values from 0 to 1, that is, from none to all of the variance being attributable to genetic factors. Heritability estimates are specific to the population from which the sample was drawn, just as estimates of the mean are specific to the population from which the sample was drawn.

Applying quantitative genetic analyses to the samples described in Figure 1 revealed significant genetic variance in resting ventilation in the Tibetan but not the Aymara sample. That is, a significant portion of the resting ventilation variance was attributable to biological kinship among individuals rather than to factors such as age, sex, body size, or household of residence (Beall, Brittenham et al. 1997). The residual h^2 for Tibetan resting ventilation was 32% compared with a statistically insignificant 6% for the Aymara. This difference in residual h^2 is indirect evidence of population genetic differences. One interpretation of the difference is that the Tibetan population with significant genetic variance may have alleles absent in the Aymara population without genetic variance. An alternative explanation is that the same alleles are expressed differently because of some unknown accentuating or dampening environmental factor.

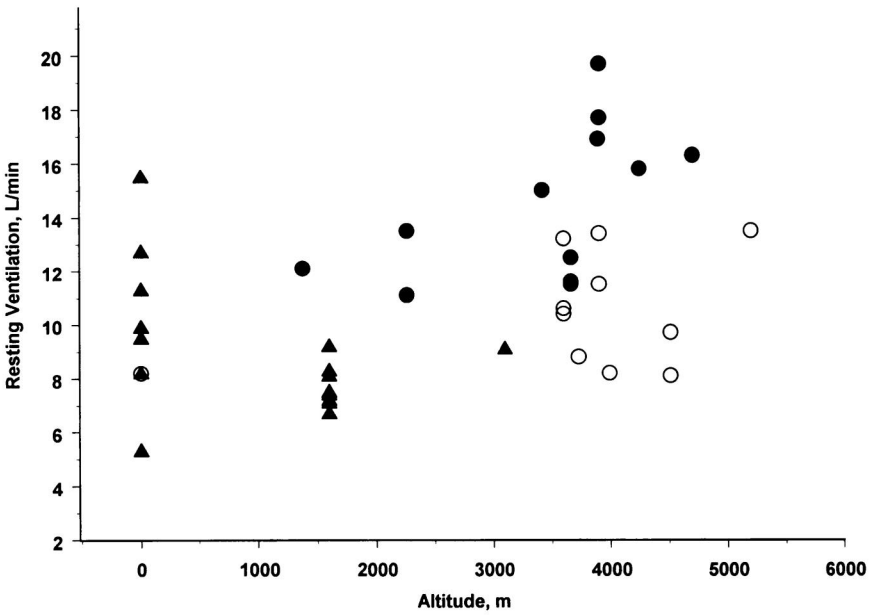

Figure 2. Scatterplot of published mean values of resting ventilation with altitude for samples of 10 or more natives or long-term residents with a mean age of 10 years or older. Filled circles, Tibetans; open circles, Andeans; filled triangles, Americans and Europeans.

Figure 2 puts these 2 samples into larger perspective with a scatterplot of published sample means of resting ventilation measured in indigenous Tibetan and Andean and long-term residents at a range of altitudes. It illustrates that the population contrasts found in the comparative study are consistent with other published findings. It also illustrates that, compared with sea-level samples from the United States and Europe (populations with no history of high-altitude residence), Tibetans have high resting ventilation. In contrast, Andean highlanders have low to normal resting ventilation. Tibetans tend to depart further from the unselected sea-level phenotype in a direction that appears advantageous in the high-altitude environment. Therefore Tibetans seem more likely to be genetically different from sea-level residents.

High Tibetan resting ventilation compared with sea-level values in combination with the presence of Tibetan intrapopulation genetic variance suggests that natural selection, either alone or in combination with random genetic drift, has acted in the past to increase the frequency of alleles resulting in a high resting ventilation. In contrast, the similarity of Aymara resting ventilation to sea-level values and the absence of Aymara genetic variance suggest that natural selection has not acted on resting ventilation because there was no heritable variation on which to act. The hypothesis would be strength-

ened if future studies of h^2 find no genetic variance in low-altitude populations. Nowadays, there is potential for natural selection on resting ventilation in the Tibetan but not the Aymara population because significant genetic variance is a prerequisite for natural selection (Falconer 1989).

One possible explanation for the Tibetan-Andean contrast in resting ventilation involves differences in the physiological control of ventilation. One measure of ventilatory control is assessed as the size of the reflexive increase in ventilation on exposure to hypoxia, a measure called the hypoxic ventilatory response (HVR). HVR is studied by experimentally inducing a standard hypoxic stress, usually a brief period of breathing air with a low oxygen concentration, and measuring the change in ventilation. HVR can be measured at any altitude; at high altitude the experimental hypoxia is added to the ambient hypoxia.

Figure 3 is a scatterplot comparing the Tibetan and Aymara samples on the basis of HVR. The *y*-axis units are liters of increase in ventilation per percentage decrease in oxygen saturation. Tibetan HVR was roughly double the Aymara HVR. For example, a 10% fall in the percentage of oxygen saturation of arterial hemoglobin resulted in an average 9.3 L/min increase in ventilation among Tibetan men compared with a 4.5 L/min increase among Aymara men. The residual h^2 of HVR in the Tibetan sample was 35% compared with just 22% in the Aymara sample. Although there is significant genetic variance in both samples, a larger proportion of the HVR variance is attributable to genetic factors in the Tibetan sample.

Figure 4 compares the Tibetan and Aymara samples with published mean HVRs from samples of Tibetan and Andean natives and long-term residents at a range of altitudes. The wide range of variation in HVR at any altitude is noteworthy. Tibetan mean HVRs are generally in the middle of the range of HVRs reported for sea-level samples, whereas high-altitude Andean HVRs are at the bottom of or below the range.

Tibetans have mean HVR values similar to sea-level HVR values, and both Tibetan and sea-level populations have significant genetic variation in HVR (Moore et al. 1976; Saunders et al. 1976; Collins et al. 1978; Kawakami et al. 1981, 1984). These findings suggest that sea-level genetic variation has been maintained in the Tibetans, perhaps by stabilizing natural selection or perhaps because no evolutionary forces have acted to change allele frequency. In contrast, the low Aymara mean HVR compared to sea-level values and the relatively low genetic variance suggest that some of the sea-level genetic variation has been lost in the Andean population and that alleles for high genotypic mean values of HVR have been lost. It seems unlikely that natural selection would act against alleles for high HVR because the alternative low-HVR alleles would seem likely to exacerbate ambient hypoxia. This reasoning suggests that random genetic drift may have acted. Both populations retain a potential for natural selection on HVR because both have significant genetic variance.

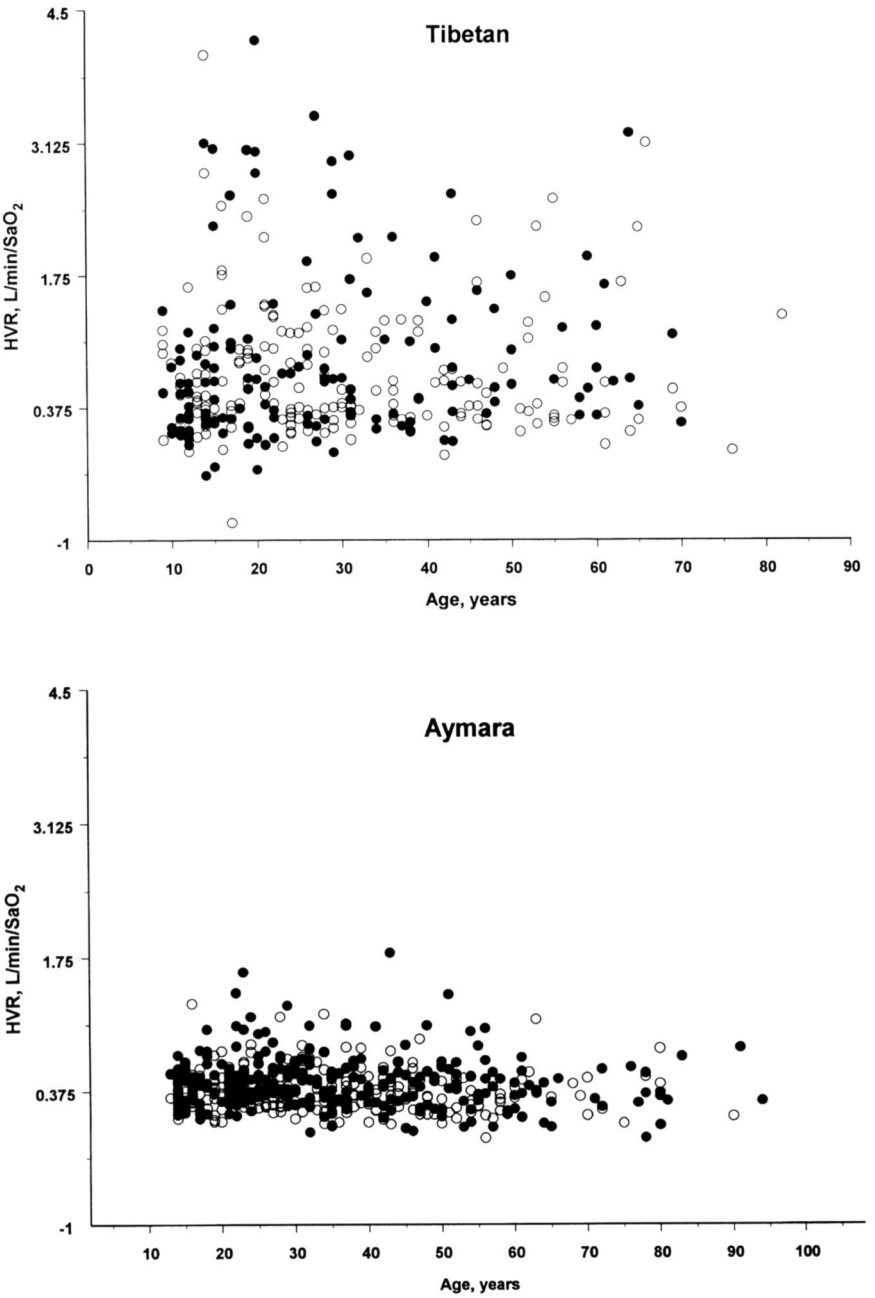

Figure 3. Scatterplot of hypoxic ventilatory response with age comparing Tibetan and Aymara high-altitude natives at a median altitude of 4,000 m. Filled circles, males; open circles, females.

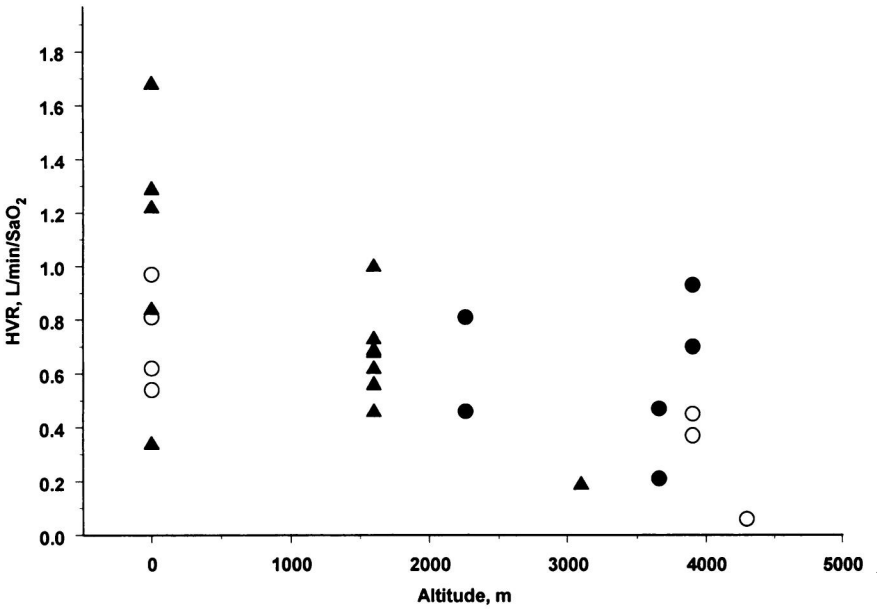

Figure 4. Scatterplot of published mean values of hypoxic ventilatory response with altitude for samples of 10 or more natives or long-term residents with a mean age of 10 years or older. Filled circles, Tibetans; open circles, Andeans; filled triangles, Americans and Europeans.

Higher Tibetan resting ventilation and HVR would seem likely to be more effective at offsetting the ambient hypoxia. This was assessed by measuring oxygen saturation (Sa_{O_2}), the percentage of hemoglobin carrying oxygen. Contrary to expectation, the Tibetan highlanders had lower Sa_{O_2} (i.e., greater arterial hypoxia) than the Aymara at the same altitude and with the same hypoxic stress (Figure 5). The average Sa_{O_2} of the Tibetan sample was 89% compared with 92% among the Aymara (Beall, Strohl et al. 1997; Beall et al. 1999). The 50% higher resting ventilation (bringing 50% more oxygen molecules into the lungs each minute) did not result in hemoglobin carrying more oxygen among the Tibetans.

The residual heritability of Sa_{O_2} in the Tibetan sample was 35%, and evidence for a major gene was detected using segregation analyses to identify the contribution of unknown genes with large effects (Beall, Strohl et al. 1997). A major gene is an inferred allele with a large quantitative effect at a segregating autosomal locus (Weiss 1993). The major gene for Sa_{O_2} is an autosomal dominant allele for 5–6% higher Sa_{O_2}. Figure 6 presents the observed phenotypic distributions in the sample and the theoretical distributions for each Sa_{O_2} genotype. Homozygotes for the recessive low-Sa_{O_2} allele (de-

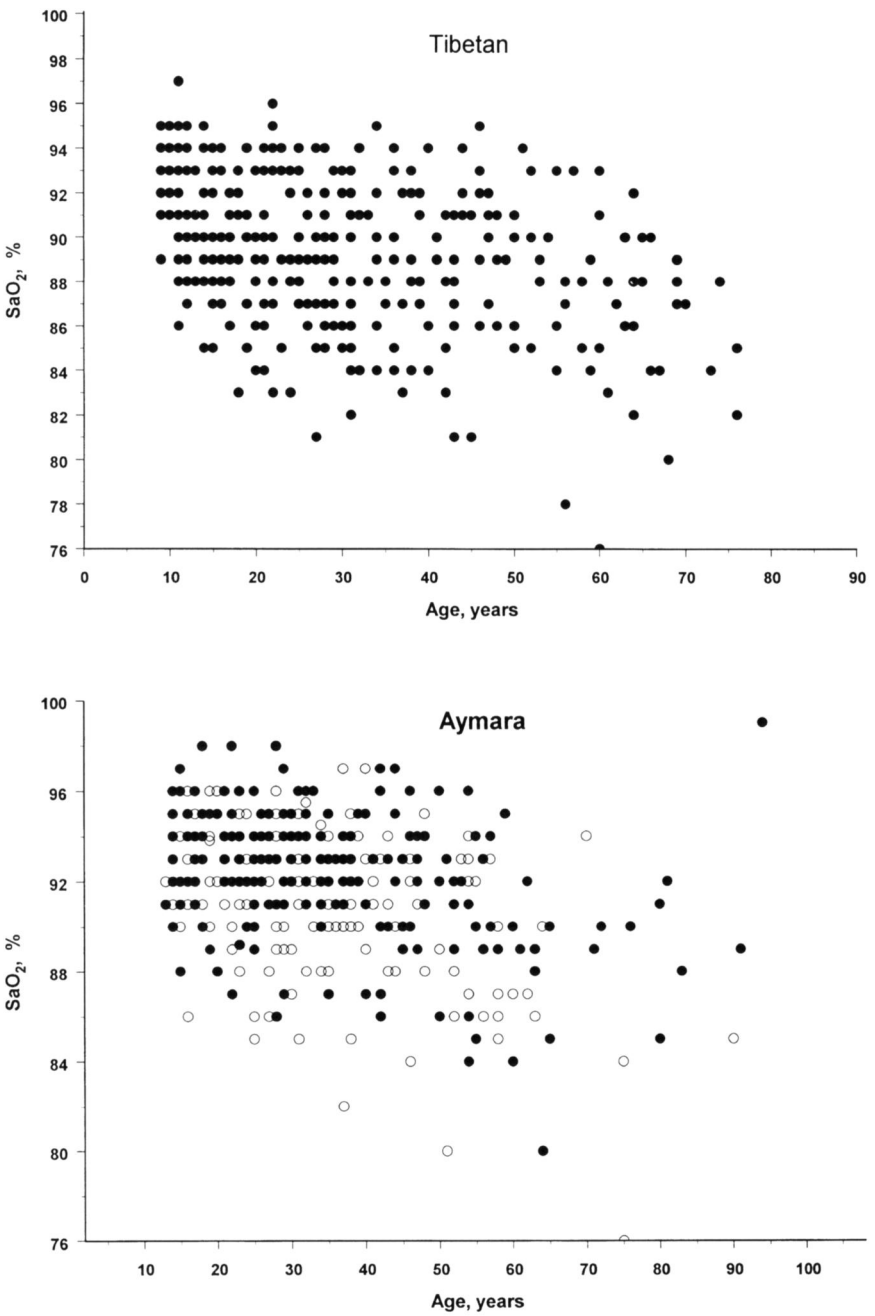

Figure 5. Scatterplot of percentage of oxygen saturation of arterial hemoglobin with age comparing Tibetan and Aymara high-altitude natives at a median altitude of 4,000 m. Filled circles, males; open circles, females. All Tibetans are denoted by filled circles because there were no sex differences in SaO_2 in that sample.

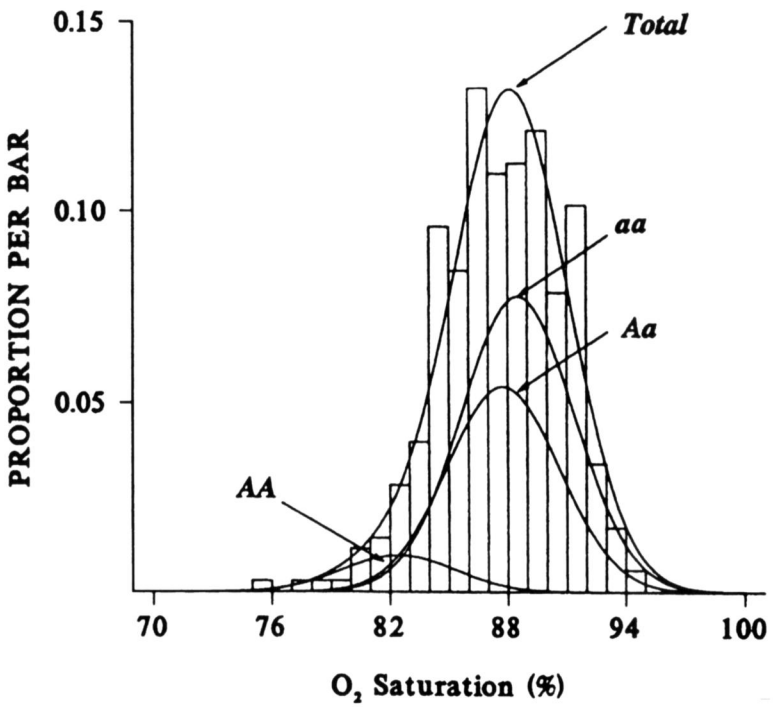

Figure 6. Observed Sa_{O_2} and theoretical genotypic distributions of 3 Sa_{O_2} genotypes in a Tibetan sample at 3,800–4,065 m [from Beall, Brittenham et al. (1997, p. 602); reprinted with permission].

noted *AA* in Figure 6) had a mean Sa_{O_2} of 82.6%, whereas heterozygotes (denoted *Aa*) and homozygotes (denoted *aa*) for the dominant high-Sa_{O_2} allele had means of 87.6% and 88.3%, respectively. This was the second Tibetan sample for which a major gene for Sa_{O_2} has been detected (Beall et al. 1994). The difference between the low and high Sa_{O_2} genotypic means was about the same in the 2 samples, which suggests that the same locus is involved. In contrast, there was no significant genetic variance in Sa_{O_2} in the Aymara sample (Beall et al. 1999).

Figure 7 plots published mean values of Sa_{O_2} measured in samples of indigenous Tibetan and Andean highlanders and long-term residents at a range of altitudes. It illustrates a general trend toward lower Sa_{O_2} at higher altitudes and the population contrast. The lower Sa_{O_2} at higher altitudes was expected because this measure is often used to quantify the physiological hypoxia resulting from exposure to ambient hypoxia. That is, this trait is used both as a measure of stress and as a measure of response. Unexpected was the nonrandom variation in arterial hypoxia within a population of individuals

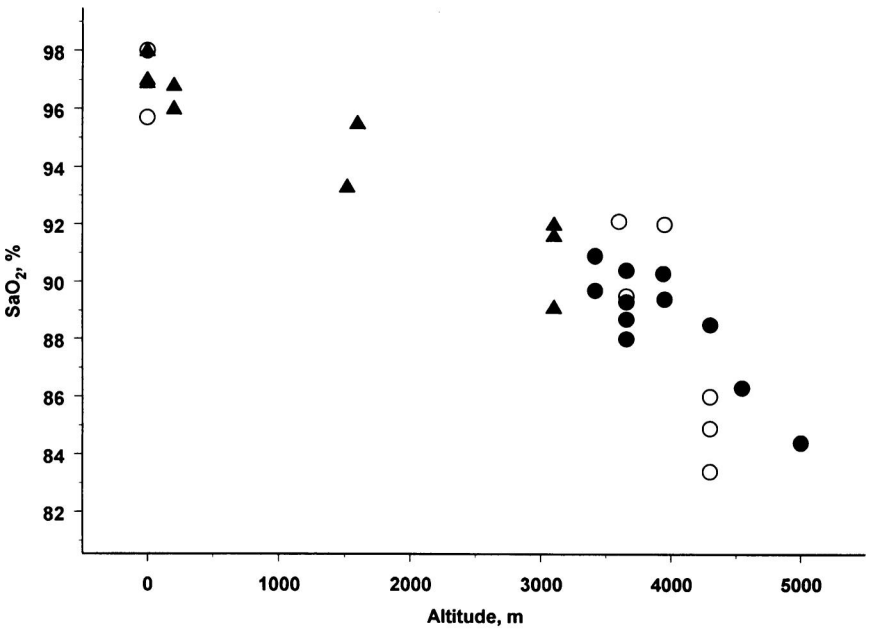

Figure 7. Scatterplot of published mean values of percentage of oxygen saturation of arterial hemoglobin with altitude for samples of 10 or more natives or long-term resident adults with a mean age of from 10 to 50 years of age and measured by pulse oximetry. Filled circles, Tibetans; open circles, Andeans; filled triangles, Americans and Europeans.

exposed to the same ambient hypoxia as in the case of the major gene. Also unexpected was the finding that Tibetan samples had lower mean Sa_{O_2} than their Andean counterparts up to about 4,000 m. However, at 4,300 m there were several low Andean mean values. They could reflect sample characteristics or could signal a reversal of a genuine population contrast. With respect to sample characteristics the sample at 4,300 m with the lowest Sa_{O_2} described women who had recently given birth (Moore et al. 1990), a subpopulation that may have particularly low Sa_{O_2}. In the Andean sample for the comparative study at 4,000 m women had lower Sa_{O_2} than men, and women who had given birth in the previous year had lower Sa_{O_2} than those who had not (Beall et al. 1999). This example further illustrates the challenges of comparing and interpreting population means. More samples from a range of high altitudes will be required to determine whether there is a consistent population contrast at various altitudes.

In the comparative study Tibetan mean Sa_{O_2} values departed further from sea-level values than Aymara means, and there was significant genetic variance in the Tibetans but not in the Aymara. These findings suggest that natural selection may be acting to increase the allele frequency for the higher

saturation allele in the Tibetan sample. The higher mean saturation of the Aymara was closer to sea-level values and reflects less arterial hypoxia. Thus the absence of Aymara genetic variance may be due to the past action of natural selection favoring an allele with a high genotypic mean that has now reached fixation.

The lower Sa_{O_2} of the Tibetans could be offset by higher hemoglobin concentration in order to achieve similar arterial oxygen content (a function of both Sa_{O_2} and hemoglobin concentration). However, this does not occur. Figure 8 illustrates that the Tibetans had a lower hemoglobin concentration than the Aymara. Tibetan males had a mean hemoglobin concentration of 15.6 g/dl compared with 19.2 g/dl for Aymara males. The Tibetan male and female means were virtually the same as those found at sea level in the United States (Beall et al. 1998). The residual h^2 of hemoglobin concentration was 64% in the Tibetan sample and 89% in the Aymara sample. These high residual h^2 values mean that both populations have a high potential for response to natural selection.

Figure 9 summarizes published sample means for hemoglobin concentration among males from indigenous Tibetan and Andean samples and from long-term residents at a range of altitudes. (A single, large US national sample from the Third National Health and Examination Survey is plotted as the sea-level reference in this figure. Small clinical samples were plotted as the sea-level references in Figures 2, 4, and 7 because there were no national samples for those variables.) Tibetan highlanders consistently have lower hemoglobin concentration than their Andean counterparts. Tibetan samples as high as 4,000 m do not generally exhibit an increase over sea-level values, although they do so above 4,500 m. This demonstrates a capacity to respond hematologically to hypoxia when the hypoxic stimulus is sufficiently severe, although the response remains smaller than that of Andean highlanders at the same altitude.

Tibetans have a mean hemoglobin concentration similar to sea-level concentrations, and both populations have significant genetic variance (Perusse et al. 1987; Whitfield and Martin 1985). These findings suggest that sea-level genetic variation has been retained in the Tibetan population through stabilizing selection or because no evolutionary forces have acted to change allele frequency. In contrast, the Aymara have high hemoglobin concentration relative to sea level, a change in the direction of higher oxygen transport, and have high genetic variance. These findings suggest that directional selection and/or random genetic drift has acted to increase the frequency of alleles with high genotypic means.

Figure 10 summarizes and standardizes the Tibetan-Andean contrasts in mean values of the 4 oxygen transport variables. It plots the effect size of the 4 traits, calculated as the difference in the mean values of 20–29-year-old males divided by their pooled standard deviation. The effect sizes of resting ventilation and HVR are large and positive (Tibetan means are larger than

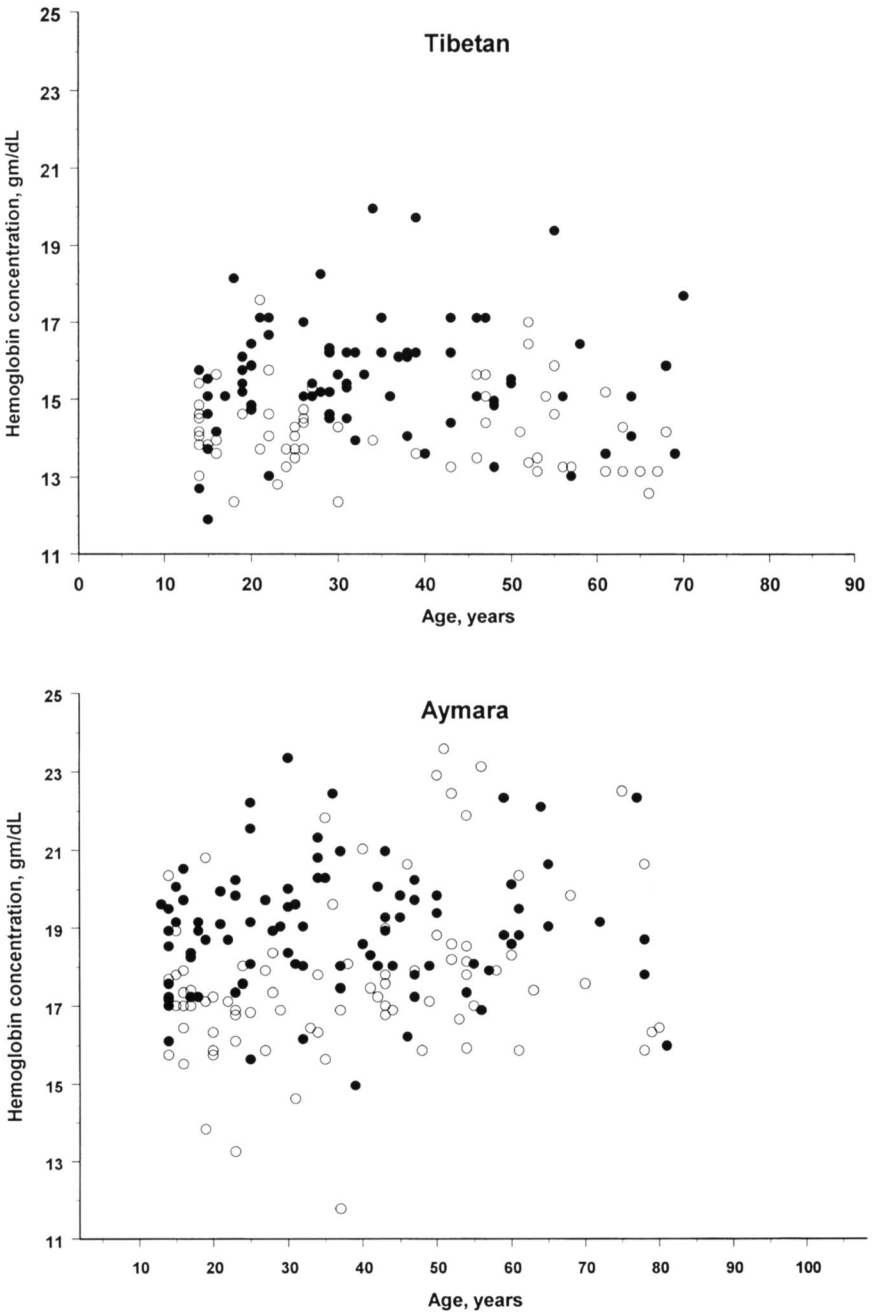

Figure 8. Scatterplot of hemoglobin concentration with age comparing Tibetan and Aymara high-altitude natives at a median altitude of 4,000 m. Filled circles, males; open circles, females.

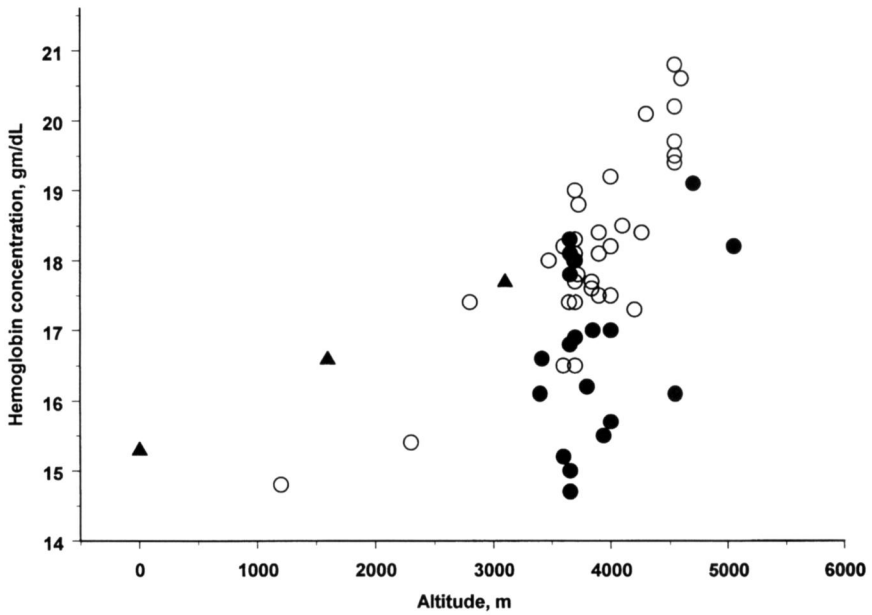

Figure 9. Scatterplot of published mean values of hemoglobin concentration with altitude for samples of 10 or more natives or long-term resident males with a mean age of 15 years or older. Filled circles, Tibetans; open circles, Andeans; filled triangles, Americans and Europeans.

Aymara means), and the effect sizes of Sao_2 and hemoglobin concentration are large and negative (Tibetan means are smaller than Aymara means).

Figure 11 summarizes the residual h^2 measures. Tibetans have significant residual h^2 for all 4 traits, whereas the Aymara have significant residual h^2 for HVR and hemoglobin concentration only. An inference of population genetic differences can be made for resting ventilation and Sao_2 because Tibetans have significant genetic variance and the Aymara do not and because there is a major gene for higher Sao_2 in the Tibetans. For HVR and hemoglobin concentration such an inference is uncertain because both populations have significant residual h^2. The population differences in the h^2 of these 2 traits could be due to different allele frequencies.

One explanation for the differences in h^2 is a difference in the number of alleles, in the allele frequencies, or in the number of gene loci. An alternative explanation is the existence of pleiotropy, a situation in which another locus or other loci influence the expression of genetic variance in the trait of interest. In this situation the internal environment resulting from 1 locus influences the expression of traits at another locus. For example, if there are alleles for high Sao_2 in the Aymara population, then they might influence the

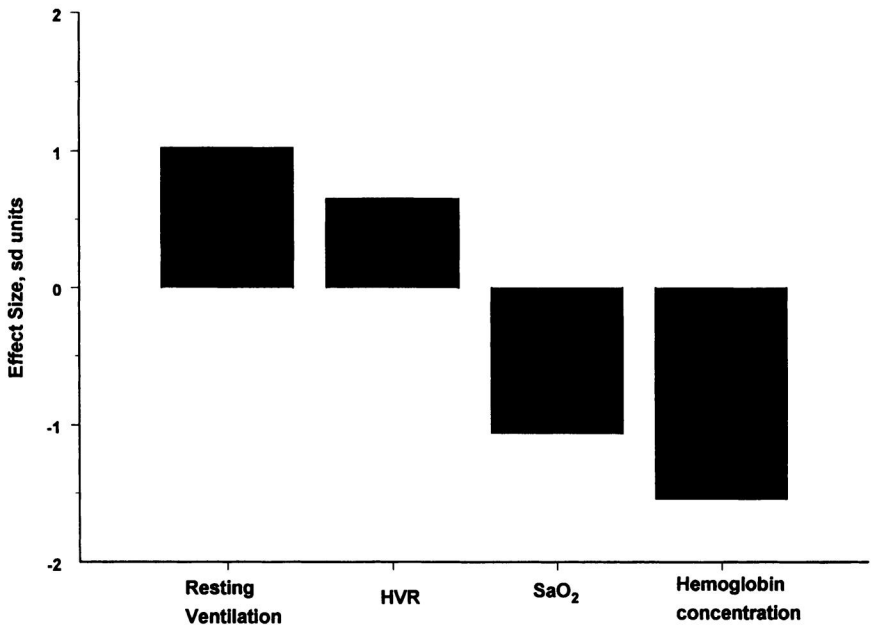

Figure 10. Effect size comparison of Tibetan and Aymara samples for 4 oxygen transport traits.

expression of resting ventilation and HVR alleles. No information on pleiotropy is available for these traits.

The following scenario is advanced to explain the evolution of the Tibetan and Aymara contrasts. It assumes that there are population genetic differences resulting from natural selection on mean values for oxygen transport traits. Sea-level mammals, including sea-level humans, the ancestral population, have adaptations to the transient hypoxia encountered routinely at sea level. Sensors in a variety of cells detect hypoxia and initiate cell-specific homeostatic responses. A sensor in the carotid body detects transient falls in partial pressure of oxygen of arterial blood such as that which occurs when breathing slows during sleep (Gonzalez et al. 1994). It initiates an immediate HVR and restoration of normal oxygenation within seconds. A sensor in the kidney detects low arterial oxygen content of blood such as that caused by traumatic blood loss. It initiates an increase in erythropoietin production within hours and an increase in the number of hemoglobin-containing red blood cells within weeks (Bunn and Poyton 1996). These immediate (ventilatory) and delayed (hematological) responses are part of the evolutionary heritage taken to high altitude by visitors today and by the past colonizers of the 2 plateaus. Contemporary high-altitude visitors exhibit both the immediate increase in ventilation and the delayed increase in hemoglobin concentration

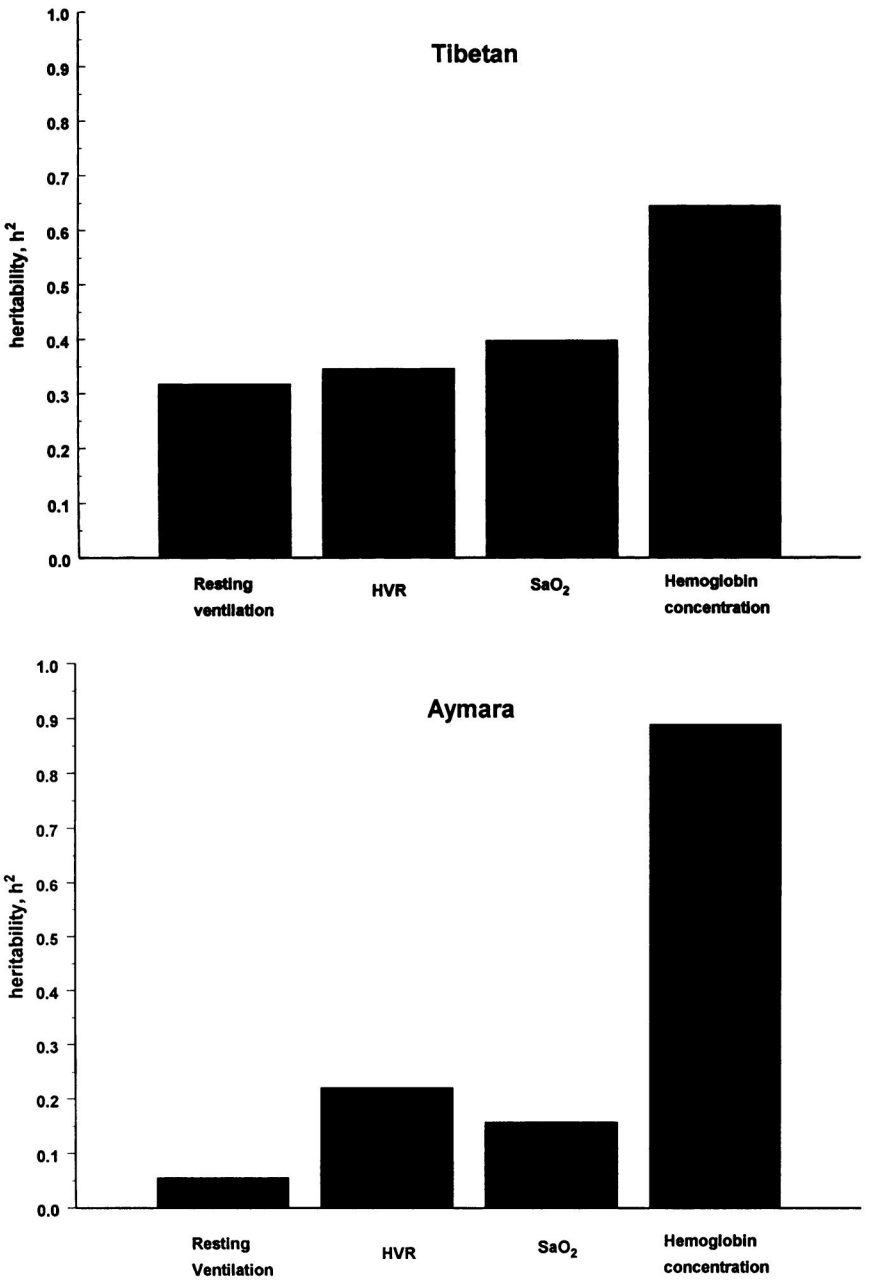

Figure 11. Comparison of Tibetan and Aymara heritability estimates for 4 oxygen transport traits.

(Ward et al. 1989). Among contemporary high-altitude natives with lifelong hypoxia at altitudes as high as 4,000 m, it appears that the Tibetan highlanders have retained the immediate ventilatory response but not the delayed hematological response. In contrast, it appears that across the range of altitudes surveyed the Andean highlanders have not retained the immediate ventilatory response but have retained the delayed hematological response. That is, the Tibetans continuously express the ventilatory response expected for an acute stress while the Aymara continuously express the hematological response expected for an acute stress.

This model will remain highly speculative until it is demonstrated that population genetic differences underlie the Tibetan-Andean phenotypic contrasts. Quantitative genetic analysis and segregation analysis provide intermediate results and information on the relative influence of genetics and environments *within* populations. Parallel comparative population analyses such as those described provide indirect evidence about the relative size of genetic and environmental influences in the 2 samples but no specific information on either and no information on population means.

Future Studies

Key to any ultimate explanation of the evolutionary processes and to any proximate explanation of the biological processes producing the Tibetan and Andean phenotypes is the identification of the relevant genetic loci. Without this knowledge statements about genetic differences cannot definitively exclude alternative explanations. The quantitative genetic analyses summarized here do not identify chromosomal locations, loci, and alleles. Thus 1 crucial line of future research to explain the existence of the Tibetan-Andean contrasts in mean values of the 4 oxygen transport traits should focus on using molecular genetic approaches to discover the underlying genetic factors identified by quantitative genetic analyses.

One approach is a candidate gene approach. This approach tests hypotheses that allelic variation in genes in known biochemical pathways is associated with phenotypic variation. Likely gene candidates might include those in the oxygen-regulated genetic cascade initiated by a transcription factor called the hypoxia inducible factor (HIF1) (Guillemin and Krasnow 1997). When a cell is exposed to hypoxia, HIF1 is manufactured and induces the transcription of many genes, including genes leading to ventilatory and hematological responses, depending on the type of cell. For example, in certain carotid body cells HIF1 induces the transcription of a gene for tyrosine hydroxylase (TH), a rate-limiting enzyme in the neural pathway leading to increased ventilation and the HVR. In certain kidney cells HIF1 induces the transcription of erythropoietin (EPO), a hormone that eventually causes an increase in hemoglobin concentration. These genetic pathways have been

investigated in the context of identifying the molecular patterns of response to hypoxia (Bunn and Poyton 1996; Czyzyk-Krzeska 1997) and linking them to systemic response (Guillemin and Krasnow 1997). In the context of the Tibetan-Andean contrast investigation of polymorphisms in genes in the HIF1 cascade is an important avenue of research. For example, the hypothesis of no population differences in HIF1 alleles is suggested by the finding that both populations respond to hypoxia. The hypothesis of population differences in the TH pathway and the EPO pathway is suggested by the population differences in mean values of HVR and hemoglobin concentration.

Another approach to identifying the underlying genetic factors is a genome scan. This approach may identify many loci, including those with unknown function, affecting the observed intrapopulation genetic variation. For example, a genome scan might look for the chromosomal location of the inferred major gene for Sao_2 detected in 2 Tibetan samples. As another example, Andean populations do not have elevated erythropoietin concentrations consistent with the elevation of hemoglobin concentration relative to sea level (Winslow et al. 1990). This suggests that another, presently unknown pathway regulates hemoglobin concentration in the Andean population. Such a locus might be identified by a genome scan.

Genetic research will likely include mtDNA studies and nuclear DNA studies because mtDNA codes for the synthesis of proteins with a major role in cellular energetics and oxygen use (Wallace 1995). All 3 genetic approaches—candidate gene, genome scan, and mtDNA—will probably be used to identify the loci and alleles underlying the genetic variance in these traits.

Knowledge of the genetic loci and their allelic variants in sea-level populations and in the 2 high-altitude populations will provide input for a second line of research: developing population genetic models of evolutionary change from the sea-level ancestral population. Such models will require information on allele frequencies in ancestral populations, the strength of natural selection, and the operation of other microevolutionary processes such as random genetic drift. In addition, knowledge of the length of time of occupation of the Tibetan and Andean plateaus will be essential for any such evolutionary models. Currently, there are no chronometric dates for the likely earliest inhabitants of the Tibetan plateau. Numerous undated archeological sites with ancient looking stone tools have been used to claim great antiquity of habitation there [e.g., (Niermeyer et al. (1995, p. 1,248) state "approximately 25,000 years"]. However, the earliest chronometrically dated site is a village site on the eastern Qinghai-Tibetan plateau, estimated to date to 7,000 years B.P. (Chang 1986). It is not known whether there were earlier hunter-gatherers or pastoral inhabitants there. In contrast, the length of habitation of the Andean plateau is better documented. There is evidence of habitation of the Andean plateau by hunters and gatherers after 11,000 years B.P. (Dillehay 1999).

This question of the natural history of the Tibetan-Andean contrast is crucial to evaluating alternative evolutionary interpretations of the population contrasts. For example, some interpretations assert that Tibetans are better adapted to high-altitude hypoxia than Andean highlanders because Tibetans have been living at altitude for longer and have been subject to natural selection for longer (Moore et al. 1992; Zhuang et al. 1993). As mentioned, the current chronometric data do not support this. The genus *Homo* has a longer prehistory in Asia than in the New World (Klein 1999). However, that is not evidence that the Asian high-altitude plateau has been occupied for longer than the Andean plateau. An alternative but not mutually exclusive hypothesis is that there were chance differences in the low-altitude ancestral populations providing the high-altitude colonists. Nuclear and mitochondrial DNA evidence suggests that present-day Tibetans and native Americans had an ancestral population in northern Asia in the general area of present-day Mongolia (Torroni et al. 1994; Chu et al. 1998; Crawford 1998). If this is the case, then during the migration south to the Tibetan plateau and east to the New World (South America and the Andean plateau), descendent populations may have accumulated genetic variability not found in the ancestral populations. Subsequent drift, mutation, and natural selection may have all contributed to form different founding gene pools that in turn resulted in the contrasting Tibetan and Andean phenotypes.

Future research should also focus on relating genotypes to phenotypes at different stages of the life cycle. Studies integrating the molecular genetic investigations with the physiological pathways should be designed to provide a proximate explanation for the development of 1 adaptive phenotype rather than another. Such studies will need to identify the environmental factors causing intrapopulation variance in order to understand the relationship between genotypes and phenotypes.

A different line of future research should focus on analyses of the costs and benefits of the 2 patterns of adaptation. A cost of the Andean pattern is increased risk of chronic mountain sickness (CMS), a loss of adaptation characterized by further pathological decreases in ventilation, HVR, and Sa_{O_2} and an increase in hemoglobin concentration (Ward et al. 1989). Studies will be needed to identify the risk factors and natural history of CMS by addressing questions such as whether the risk of CMS has a genetic component and whether certain ranges or combinations of these phenotypes have higher risk of developing CMS. CMS may be a cost of a beneficial high mean hemoglobin concentration. If so, then the situation would be analogous to that of some populations adapting to the stress of endemic *falciparum* malaria: There is the simultaneous cost of homozygotes for sickle cell hemoglobin and benefit of heterozygotes for sickle cell and normal hemoglobin (Wiesenfeld 1967). An unexplored potential cost of the Andean pattern is the paradoxical finding that arterial oxygen content is higher than at sea level, despite the ambient hypoxia. The arterial oxygen content may be calculated as $1.39 \times$ (hemo-

globin concentration in g/dl) × Sa_{O_2}%/100 (West 1985). The mean arterial oxygen content of the Andean men in the sample was 24.4 ± 2.9 (SD) ml O_2/100 ml blood (n = 62) compared with 21.2 ml O_2/100 ml blood (n = 10) at sea level (Altman and Ditmer 1972–1974) and 19.2 ± 1.7 ml O_2/100 ml blood (n = 68) for the Tibetan men in the sample. A potential cost of more oxygen in the blood is greater oxidative damage to proteins (Berlett and Stadtman 1997). Still another potential cost to Andean highlanders is a high need for iron to sustain the high hemoglobin concentration.

The costs of the Tibetan pattern of adaptation should also be considered. A potential cost of the generally lower mean Sa_{O_2} and mean hemoglobin concentration that result is the risk of low arterial oxygen content for some individuals. They may have poorer function under conditions requiring elevated oxygen delivery, such as exercise. In addition, the severe hypoxia required to initiate a hematological response to hypoxia might result in a less vigorous response to and perhaps a longer time to recover from blood loss resulting from trauma and childbirth. Still another potential cost is the energetic cost of maintaining high ventilation.

Despite these different patterns, there has been a long-term survival benefit for both high-altitude populations, and in that sense both the Tibetans and the Aymara are well adapted. Nevertheless, we can consider the hypothesis that 1 population has benefited more. For example, the question, Are Tibetans better adapted? was answered in the affirmative in a study of 5 Tibetan men that reported on their oxygen transport characteristics and compared them with newcomers to altitude and Andean natives (Moore et al. 1992). Although the small sample size is inadequate for testing such a broad generalization, the question of relative benefit could be addressed with appropriately designed, large comparative studies.

Another approach to identifying benefits would be to ask whether survival and reproduction are linked to variance in any of these traits. The high h^2 of hemoglobin concentration in both the Tibetan and the Aymara populations coupled with the large difference in population means suggests that studies identifying optimal hemoglobin phenotypes could be informative (Tufts et al. 1985). Tests of the hypothesis that the major gene for Sa_{O_2} in Tibetan populations is associated with higher survival and reproduction are underway.

A final issue is whether any of these phenotypic characteristics are actually adaptations—traits that have evolved to enable humans to survive at high altitude. These traits correspond with altitude in 1 or both populations, as illustrated in Figures 2, 4, 7, and 9. However, evidence is not yet available to demonstrate that natural selection has occurred and that individuals with phenotypes characteristic of a particular population at a particular altitude have higher Darwinian fitness than those with other phenotypes. An alternative hypothesis is that these traits exemplify evolutionary quirks—traits selected for in sea-level ancestors that are simply chronically expressed in

chronically hypoxic populations (Nesse and Williams 1994). Another alternative hypothesis is that these traits exemplify exaptations—ancestral traits whose current function differs from the ancestral function (Gould and Vrba 1982).

Summary

These findings demonstrate that there is no single human adaptive response to lifelong high-altitude hypoxic stress. Although the universal problem at high altitude is delivering enough oxygen to maintain aerobic metabolism under conditions of reduced oxygen availability, the solution to that problem is different for Tibetan and Andean high-altitude natives. There is evidence of 2 patterns of oxygen transport traits in these populations from 2 geographic areas with long, separate histories of high-altitude residence. Intermediate steps have been taken to provide indirect evidence of a genetic basis of the 2 patterns. Future research should be designed to provide direct evidence of the genetic loci and alleles underlying these traits, to determine the history of any population differences, to develop an understanding of the biological processes leading from genotype to phenotype, to consider costs and benefits of the 2 patterns, and to explicitly test hypotheses about adaptation.

Received 7 June 1999; revision received 17 September 1999.

Literature Cited

Adams, W.H., and S.M. Shresta. 1974. Hemoglobin levels, vitamin B12, and folate status in a Himalayan village. *Am. J. Clin. Nutr.* 27:217–219.

Adams, W.H., and L.J. Strang. 1975. Hemoglobin levels in persons of Tibetan ancestry living at high altitude (38,952). *Proc. Soc. Exp. Biol. Med.* 149:1036–1039.

Altman, P.L., and D.S. Ditmer, eds. 1972–1974. *Biology Data Book,* 2d ed., vol. 3. Bethesda, MD: Federation of American Societies for Experimental Biology.

Antezana, A.-M., J.-P. Richalet, I. Noriega et al. 1995. Hormonal changes in normal and polychythemic high-altitude natives. *J. Appl. Physiol.* 79(3):795–800.

Arnaud, J., J.C. Quilici, and G. Riviere. 1981. High-altitude hemotology: Quechua-Aymara comparisons. *Ann. Hum. Biol.* 8(6):573–578.

Baker, P.T., and M.A. Little. 1976. *Man in the Andes: A Multidisciplinary Study of High-Altitude Quechua.* US/IBP Synthesis Series 1. Stroudsburg, PA: Dowden, Hutchinson, and Ross.

Banchero, N., F. Sime, D. Penaloza et al. 1966. Pulmonary pressure, cardiac output, and arterial oxygen saturation during exercise at high altitude and at sea level. *Circulation* 33:249–262.

Beall, C.M., and M.C. Goldstein. 1990. Hemoglobin concentration, percent oxygen saturation, and arterial oxygen content of Tibetan nomads at 4,850 to 5,450 m. In *Hypoxia: The*

Adaptations, J.R. Sutton, G. Coates, and J.E. Remmers, eds. Toronto, Canada: B.C. Decker, 59–65.

Beall, C.M., and A.B. Reichsman. 1984. Hemoglobin levels in a Himalayan high-altitude population. *Am. J. Phys. Anthropol.* 63:301–306.

Beall, C.M., M.C. Goldstein, and the Tibetan Academy of Social Sciences. 1987. Hemoglobin concentration of pastoral nomads permanently resident at 4,850–5,450 meters in Tibet. *Am. J. Phys. Anthropol.* 73:433–438.

Beall, C.M., L.A. Almasy, J. Blangero et al. 1999. Percent of oxygen saturation of arterial hemoglobin of Bolivian Aymara at 3900–4000 m. *Am. J. Phys. Anthropol.* 108:41–51.

Beall, C.M., J. Blangero, S. Williams-Blangero et al. 1994. A major gene for percent of oxygen saturation of arterial hemoglobin in Tibetan highlanders. *Am. J. Phys. Anthropol.* 95:271–276.

Beall, C.M., G.M. Brittenham, F. Macuaga et al. 1990. Variation in hemoglobin concentration among samples of high-altitude natives in the Andes and the Himalayas. *Am. J. Hum. Biol.* 2(6):639–651.

Beall, C.M., G.M. Brittenham, K.P. Strohl et al. 1998. Hemoglobin concentration of high-altitude Tibetans and Bolivian Aymara. *Am. J. Phys. Anthropol.* 106:385–400.

Beall, C.M., G.M. Brittenham, K.P. Strohl et al. 1997. Ventilation and hypoxic ventilatory response of Tibetan and Aymara high-altitude natives. *Am. J. Phys. Anthropol.* 104:427–447.

Beall, C.M., K. Strohl, J. Blangero et al. 1997. Quantitative genetic analysis of arterial oxygen saturation in Tibetan highlanders. *Hum. Biol.* 69(5):597–604.

Beall, C.M., K.P. Strohl, B. Gothe et al. 1992. Respiratory and hematological adaptations of young and older Aymara men native to 3600 m. *Am. J. Hum. Biol.* 4(1):17–26.

Berlett, B.S., and E.R. Stadtman. 1997. Protein oxidation in aging, disease, and oxidative stress. *J. Biol. Chem.* 272(33):20,313–20,316.

Bharadwaj, H., A.P. Singh, and M.S. Malhotra. 1973. Body composition of the high-altitude natives of Ladakh: A comparison with sea-level residents. *Hum. Biol.* 45(3):423–434.

Brutsaert, T.D., R. Soria, E. Caceres et al. 1999. Effect of developmental and ancestral high-altitude exposure on chest morphology and pulmonary function in Andean and European/North American natives. *Am. J. Hum. Biol.* 11(3):383–398.

Bunn, H.F., and R.O. Poyton. 1996. Oxygen sensing and molecular adaptation to hypoxia. *Physiol. Rev.* 76(5):839–885.

Chang, K.-C. 1986. *The Archeology of Ancient China,* 4th ed. New Haven, CT: Yale University Press.

Chen, Q.-H., R.-L. Ge, X.-Z. Wang et al. 1997. Exercise performance of Tibetan and Han adolescents at altitudes of 3,417 and 4,300 m. *J. Appl. Physiol.* 83(2):661–667.

Chiodi, H. 1957. Respiratory adaptations to chronic high-altitude hypoxia. *J. Appl. Physiol.* 10(1):81–87.

Chu, J.H., W. Huang, S.Q. Kuang et al. 1998. Genetic relationship of populations in China. *Proc. Natl. Acad. Sci. USA* 95:11,763–11,768.

Collins, D.D., C.H. Scoggin, C.W. Zwillich et al. 1978. Hereditary aspects of decreased hypoxic response. *J. Clin. Invest.* 62:105–110.

Cosio, G. 1972. Caracteristicas hematicas y cardiopulmonares del minero andino. *Bol. Of. Sanit. Panam.* 72(June):547–557.

Crawford, M. 1998. *The Origin of Native Americans: Evidence from Anthropological Genetics.* Cambridge, England: Cambridge University Press.

Cudkowicz, L., H. Spielvogel, and G. Zubieta. 1972. Respiratory studies in women at high altitude (3,600 m or 12,200 ft and 5,200 m or 17,200 ft). *Respiration* 29:393–426.

Curran, L.S., J. Zhuang, T. Droma et al. 1995. Hypoxic ventilatory responses in Tibetan residents of 4400 m compared with 3658 m. *Resp. Physiol.* 100:223–230.

Curran, L.S., J. Zhuang, S.F. Sun et al. 1997. Ventilation and hypoxic ventilatory responsiveness in Chinese-Tibetan residents at 3,658 m. *J. Appl. Physiol.* 83(6):2098–2104.

Czyzyk-Krzeska, M.F. 1997. Molecular aspects of oxygen sensing in physiological adaptation to hypoxia. *Resp. Physiol.* 110:99–111.

Decker, M.J., P.L. Hoekje, and K.P. Strohl. 1989. Ambulatory monitoring of arterial oxygen saturation. *Chest* 95(4):717–722.

Dillehay, T.D. 1999. The late Pleiostocene cultures of South America. *Evol. Anthropol.* 7(6):206–216.

Falconer, D.S. 1989. *Introduction to Quantitative Genetics,* 3d ed. New York: Longman Scientific and Technical.

Filuk, R.B., D.J. Berezanski, and N.R. Anthonisen. 1988. Depression of hypoxic ventilatory response in humans by somatostatin. *J. Appl. Physiol.* 65(3):1050–1054.

Frisancho, A.R., and L.P. Greksa. 1989. Developmental responses in the acquisition of functional adaptation to high altitude. In *Human Population Biology: A Transdisciplinary Science,* M.A. Little and J.D. Haas, eds. New York: Oxford University Press, 203–228.

Frisancho, A.R., T. Velasquez, and J. Sanchez. 1975. Possible adaptive significance of small body size in the attainment of aerobic capacity among high-altitude Quechua natives. In *Biosocial Interrelations in Population Adaptation,* E.S. Watts, F.E. Johnston, and G.W. Lasker, eds. The Hague, The Netherlands: Mouton, 55–64.

Garruto, R.M. 1976. Hematology. In *Man in the Andes: A Multidisciplinary Study of High-Altitude Quechua,* P.T. Baker and M.A. Little, eds. Stroudsburg, PA: Dowden, Hutchinson, and Ross.

Garruto, R.M., and J.S. Dutt. 1983. Lack of prominent compensatory polycythemia in traditional native Andeans living at 4,200 meters. *Am. J. Phys. Anthropol.* 61:355–366.

Ge, R., G. He Lun, Q. Chen et al. 1995. Comparisons of oxygen transport between Tibetan and Han residents at moderate altitude. *Wilderness Environ. Med.* 6:391–400.

Ge, R., C. Qiuhong, H. Lungao et al. 1994. Characteristics of hypoxic ventilatory response in Tibetan living at moderate and high altitudes. *Chin. J. Tuberculosis Resp. Dis.* 17(6):364–366, 388.

Ge, R.-L., Q.-H. Chen, L.-H. Wang et al. 1994. Higher exercise performance and lower $\dot{V}O_{2max}$ in Tibetan than Han residents at 4,700 m altitude. *J. Appl. Physiol.* 77:684–691.

Georgopoulos, D., S.G. Holtby, D. Berezanski et al. 1989. Aminophylline effects on ventilatory response to hypoxia and hyperoxia in normal adults. *J. Appl. Physiol.* 67(3):1150–1156.

Glomb, W.B., C.L. Marcus, T.G. Keens et al. 1992. Hypercapnic and hypoxic ventilatory and cardiac responses in school-aged siblings of sudden infant death syndrome victims. *J. Pediatr.* 121:391–397.

Gonzalez, C., L. Almaraz, A. Obeso et al. 1994. Carotid body chemoreceptors: From natural stimuli to sensory discharges. *Physiol. Rev.* 74(6):829–898.

Gould, S.J., and E.S. Vrba. 1982. Exaptation: A missing term in the science of form. *Paleobiology* 8:4–15.

Guillemin, K., and M.A. Krasnow. 1997. The hypoxic response: Huffing and HIFing. *Cell* 89:9–12.

Guleria, J.S., J.N. Pande, P.K. Sethi et al. 1971. Pulmonary diffusing capacity at high altitude. *J. Appl. Physiol.* 31(4):536–543.

Hackett, P.H., J.T. Reeves, C.D. Reeves et al. 1980. Control of breathing in Sherpas at low and high altitude. *J. Appl. Physiol.* 49(3):374–379.

Harrison, G.A. 1966. Human adaptability with reference to the IBP proposals for high-altitude research. In *The Biology of Human Adaptability,* P.T. Baker and J.S. Weiner, eds. Oxford, England: Clarendon Press, 509–519.

Huang, S.Y., J.K. Alexander, R.F. Grover et al. 1984. Increased metabolism contributes to increased resting ventilation at high altitude. *Resp. Physiol.* 57:377–385.

Huang, S.Y., S. Sun, T. Droma et al. 1992. Internal carotid arterial flow velocity during exercise in Tibetan and Han residents of Lhasa (3,658 m). *J. Appl. Physiol.* 73(6):2638–2642.

Huang, S.Y., D.P. White, N.J. Douglas et al. 1984. Respiratory function in normal Chinese: Comparison with Caucasians. *Respiration* 46:265–271.

Huang, Z.R., S.C. Zhu, Z.F. Ba, and X.C. Hu. 1981. Ventilatory control in Tibetan highlanders. In *Geological and Ecological Studies of Qinghai-Xizang Plateau,* D.S. Liu, ed. New York: Gordon and Breach, 1363–1369.

Hultgren, H.N., J. Kelly, and H. Miller. 1965. Pulmonary circulation in acclimatized man at high altitude. *J. Appl. Physiol.* 20(2):233–238.

Hurtado, A. 1964. Animals in high altitudes: Resident man. In *Handbook of Physiology,* sec. 4, *Adaptation to the Environment,* D.B. Dill, ed. Washington, DC: American Physiological Society, 843–859.

Hurtado, A., C. Merino, and E. Delgado. 1945. Influence of anoxemia on the hemopoietic activity. *Arch. Intern. Med.* 75:284–324.

Kawakami, Y., H. Yamamoto, T. Yoshikawa et al. 1984. Chemical and behavioral control of breathing in adult twins. *Am. Rev. Resp. Dis.* 129:703–707.

Kawakami, Y., T. Yoshikawa, A. Shida et al. 1981. Relationships between hypoxic and hypercapnic ventilatory responses in man. *Jpn. J. Physiol.* 31:357–368.

Klein, R.G. 1999. *The Human Career: Human Biological and Cultural Origins,* 2d ed. Chicago, IL: University of Chicago Press.

Kryger, M., J. Weil, and R. Grover. 1978. Chronic mountain polycythemia: A disorder of the regulation of breathing during sleep? *Chest* 73(2):303–304.

Kryger, M., R. McCullough, R. Doekel et al. 1978. Excessive polycythemia of high altitude: Role of ventilatory drive and lung disease. *Am. Rev. Respir. Dis.* 118:659–667.

Larrick, J.W., and S. Topgyal. 1985. Hemoglobin levels in high-altitude Tibetan natives of northwest Nepal. *Int. J. Biometeorol.* 29(1):7–10.

Lawler, J., S.K. Powers, and D. Thompson. 1988. Linear relationship between $V_{O_{2max}}$ and $V_{O_{2max}}$ decrement during exposure to acute hyoxia. *J. Appl. Physiol.* 64(4):1486–1492.

Leon-Verlarde, F., A.M. Arregui, M.M. Vargas et al. 1994. Chronic mountain sickness and chronic lower respiratory tract disorders. *Chest* 106(1):151–155.

Leon-Velarde, F., C.C. Monge, A. Vidal et al. 1991. Serum immunoreactive erythropoietin in high-altitude natives with and without excessive erythrocytosis. *Exp. Hematol.* 19:257–260.

Littner, M., E. Young, D. McGinty et al. 1984. Awake abnormalities of control of breathing and of the upper airway: Occurrence in healthy older men with nocturnal disordered breathing. *Chest* 86(4):573–579.

Marcus, C.L., W.B. Glomb, D.J. Basinski et al. 1994. Developmental pattern of hypercapnic and hypoxic ventilatory responses from childhood to adulthood. *J. Appl. Physiol.* 76(1):314–320.

Mazess, R.B. 1969. Exercise performance of Indian and white high-altitude residents. *Hum. Biol.* 41(4):494–518.

Monge, C.C. 1978 [1948]. *Acclimatization in the Andes.* Baltimore, MD: Johns Hopkins University Press.

Moore, G.C., C.W. Zwillich, J.D. Battaglia et al. 1976. Respiratory failure associated with familial depression of ventilatory response to hypoxia and hypercapnia. *New Engl. J. Med.* 295(16):861–865.

Moore, L.G. 1990. Maternal O_2 transport and fetal growth in Colorado, Peru, and Tibet high-altitude residents. *Am. J. Hum. Biol.* 2(6):627–637.

Moore, L.G., L. Curran-Everett, T.S. Droma et al. 1992. Are Tibetans better adapted? *Int. J. Sports. Med.* 13(suppl. 1):S86–S88.

Moore, L.G., R.E. McCullough, and J.V. Weil. 1987. Increased HVR in pregnancy: Relationship to hormonal and metabolic changes. *J. Appl. Physiol.* 62(1):158–163.

Moore, L.G., G.L. Harrison, R.E. McCullough et al. 1986. Low acute hypoxic ventilatory response and hypoxic depression in acute altitude sickness. *J. Appl. Physiol.* 60(4):1407–1412.

Moore, L.G., S.Y. Huang, R.E. McCullough et al. 1984. Variable inhibition by falling CO_2 of hypoxic ventilatory response in humans. *J. Appl. Physiol.* 56(1):207–210.

Moore, L.G., D. Jahnigen, S.S. Rounds et al. 1982. Maternal hyperventilation helps preserve arterial oxygenation during high-altitude pregnancy. *J. Appl. Physiol.* 52(3):690–694.

Moret, P., E. Covarrubias, J. Coudert et al. 1972. Cardiocirculatory adaptation to chronic hypoxia: Comparative study of coronary flow, myocardial oxygen consumption, and efficiency between sea-level and high-altitude residents. *Extrait Acta Cardiol.* 27:283–305.

Nesse, R.M., and G.C. Williams. 1994. *Why We Get Sick: The New Science of Darwinian Medicine.* New York: Vintage Books.

Niermeyer, S., P. Yang, Shanmina et al. 1995. Arterial oxygen saturation in Tibetan and Han infants born in Lhasa, Tibet. *New Engl. J. Med.* 333(19):1248–1252.

Okin, J.T., A. Treger, H.R. Overy et al. 1966. Hematologic response to medium altitude. *Rocky Mt. Med. J.* 63(1):44–47.

Penaloza, D., F. Sime, N. Banchero et al. 1963. Pulmonary hypertension in healthy men born and living at high altitudes. *Am. J. Cardiol.* 11(2):150–157.

Perusse, L., C. Leblanc, A. Tremblay et al. 1987. Familial aggregation in physical fitness, coronary heart disease risk factors, and pulmonary function measurements. *Prev. Med.* 16:607–615.

Peterson, D.D., A.I. Pack, D.A. Silage et al. 1981. Effects of aging on ventilatory and occlusion pressure responses to hypoxia and hypercapnia. *Am. Rev. Resp. Dis.* 124:387–391.

Poulin, M.J., D.A. Cunningham, D.H. Patterson et al. 1993. Ventilatory sensitivity to CO_2 in hyperoxia and hypoxia in older aged humans. *J. Appl. Physiol.* 75(5):2209–2216.

Reeves, J.T., R.E. McCullough, L.G. Moore et al. 1993. Sea-level P_{CO_2} relates to ventilatory acclimatization at 4,300 m. *J. Appl. Physiol.* 75:1117–1122.

Regensteiner, J.G., R.G. McCullough, R.E. McCullough et al. 1990. Combined effects of female hormones and exercise on hypoxic ventilatory response. *Resp. Physiol.* 82:107–114.

Regensteiner, J.G., C.K. Pickett, R.E. McCullough et al. 1988. Possible gender differences in the effect of exercise on hypoxic ventilatory response. *Respiration* 53:158–165.

Ruiz, L. 1973. Epidemiologia de la hipertension arterial y de la cardiopatia isquemica en las grandes alturas. Doctoral thesis, Universidad Peruana Cayetano Heredia, Lima, Peru.

Samaja, M., A. Veicsteinas, and P. Cerretelli. 1979. Oxygen affinity of blood in altitude Sherpas. *J. Appl. Physiol.* 47(2):337–341.

Santolaya, R.B., C.J. Araya, C.A. Vecchiola et al. 1981. Hematocrito, hemoglobina y presion de oxigeno arterial en 270 hombres y 266 mujeres sanas residentes de altura (2,800 mts). *Rev. Hosp. R. H. Glover* 1(1):17–24.

Santolaya, R.B., S. Lahiri, R.T. Alfaro et al. 1989. Respiratory adaptation in the highest inhabitants and highest Sherpa mountaineers. *Resp. Physiol.* 77:253–262.

Saunders, N.A., S.R. Leeder, and A.S. Rebuck. 1976. Ventilatory response to carbon dioxide in young athletes: A family study. *Am. Rev. Resp. Dis.* 113:497–502.

Schoene, R.B. 1982. Control of ventilation in climbers to extreme altitude. *J. Appl. Physiol.* 53(4):886–890.

Sime, F., D. Penaloza, and L. Ruiz. 1971. Bradycardia, increased cardiac output, and reversal of pulmonary hypertension in altitude natives living at sea level. *Br. Heart J.* 33:647–657.

Sun, S., C. Oliver-Pickett, Y. Ping et al. 1996. Breathing and brain blood flow during sleep in patients with chronic mountain sickness. *J. Appl. Physiol.* 81(2):611–618.

Sun, S.F., T.S. Droma, J.G. Zhuang et al. 1990. Greater maximal O_2 uptakes and vital capacities in Tibetan than Han residents of Lhasa. *Resp. Physiol.* 79:151–162.

Torroni, A., J.A. Miller, L.G. Moore et al. 1994. Mitochondrial DNA analysis in Tibet: Implications for the origin of the Tibetan population and its adaptation to high altitude. *Am. J. Phys. Anthropol.* 93:189–199.

Tucker, A., J.M. Stager, and L. Cordain. 1984. Arterial O_2 saturation and maximum O_2 consumption in moderate-altitude runners exposed to sea level and 3,050 m. *J. Am. Med. Assoc.* 252(20):2867–2871.

Tufts, D.A., J.D. Haas, J.L. Beard et al. 1985. Distribution of hemoglobin and functional consequences of anemia in adult males at high altitude. *Am. J. Clin. Nutr.* 42:1–11.

Vargas, M., F. Leon-Velarde, C.C. Monge et al. 1998. Similar hypoxic ventilatory responses in sea-level natives and high-altitude Andean natives living at sea level. *J. Appl. Physiol.* 84(3):1024–1029.

Vincent, J., M.F. Hellot, E. Vargas et al. 1978. Pulmonary gas exchange, diffusing capacity in natives and newcomers at high altitude. *Resp. Physiol.* 34:219–231.

Wallace, D.C. 1995. Mitochondrial DNA variation in human evolution, degenerative disease, and aging. *Am. J. Hum. Genet.* 57:201–223.

Ward, M.P., J.S. Milledge, and J.B. West. 1989. *High-Altitude Medicine and Physiology.* Philadelphia, PA: University of Pennsylvania Press.

Weil, J.V., M.H. Kryger, and C.H. Scoggin. 1978. Sleep and breathing at high altitude. In *Sleep Apnea Syndromes,* C. Guilleminault and W.C. Dement, eds. New York: Alan R. Liss, 119–136.

Weiss, K.M. 1993. *Genetic Variation and Human Disease: Principles and Evolutionary Approaches.* Cambridge, England: Cambridge University Press.

West, J.B. 1985. *Respiratory Physiology: The Essentials,* 4th ed. Baltimore, MD: Williams & Wilkins.

White, D.P., N.J. Douglas, C.K. Pickett et al. 1983. Sexual influence on the control of breathing. *J. Appl. Physiol.* 54(4):874–879.

Whitfield, J.B., and N.G. Martin. 1985. Genetic and environmental influences on the size and number of cells in the blood. *Genet. Epidemiol.* 2:133–144.

Wiesenfeld, S.L. 1967. Sickle-cell trait in human biological and cultural evolution. *Science* 157:1134–1140.

Winslow, R.M., and C. Monge. 1987. *Hypoxia, Polycythemia, and Chronic Mountain Sickness.* The Johns Hopkins Series in Contemporary Medicine in Public Health. Baltimore, MD: Johns Hopkins University Press.

Winslow, R.M., K.W. Chapman, and C.M. Monge. 1990. Ventilation and the control of erythropoiesis in high-altitude natives of Chile and Nepal. *Am. J. Hum. Biol.* 2(6):653–662.

Winslow, R.M., K.W. Chapman, C.G. Gibson et al. 1988. Hematologic response to hypoxia in Sherpas and Quechua Indians. *FASEB J.* 2(5):A1721.

Winslow, R.M., C.C. Monge, N.J. Statham et al. 1981. Variability of oxygen affinity of blood: Human subjects native to high altitude. *J. Appl. Physiol.* 51(6):1411–1416.

Zhuang, J., T. Droma, S. Sun et al. 1993. Hypoxic ventilatory responsiveness in Tibetan compared with Han residents of 3,658 m. *J. Appl. Physiol.* 74(1):303–311.

Zhuang, J., T. Droma, J.R. Sutton et al. 1996. Smaller alveolar-arterial O_2 gradients in Tibetan than Han residents in Lhasa (3658 m). *Resp. Physiol.* 103:75–82.