Percent of Oxygen Saturation of Arterial Hemoglobin Among Bolivian Aymara at 3,900–4,000 m

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ABSTRACT   A range of variation in percent of oxygen saturation of arterial hemoglobin (SaO_2) among healthy individuals at a given high altitude indicates differences in physiological hypoxemia despite uniform ambient hypoxic stress. In populations native to the Tibetan plateau, a significant portion of the variance is attributable to additive genetic factors, and there is a major gene influencing SaO_2. To determine whether there is genetic variance in other high-altitude populations, we designed a study to test the hypothesis that additive genetic factors contribute to phenotypic variation in SaO_2 among Aymara natives of the Andean plateau, a population geographically distant from the Tibetan plateau and with a long, separate history of high-altitude residence. The average SaO_2 of 381 Aymara at 3,900–4,000 m was $92 \pm 0.15\%$ (SEM) with a range of 84–99%. The average was 2.6% higher than the average SaO_2 of a sample of Tibetans at 3,800–4,065 m measured with the same techniques. Quantitative genetic analyses of the Aymara sample detected no significant variance attributable to genetic factors. The presence of genetic variance in SaO_2 in the Tibetan sample and its absence in the Aymara sample indicate there is potential for natural selection on this trait in the Tibetan but not the Aymara population. Am J Phys Anthropol 108:41–51, 1999.   © 1999 Wiley-Liss, Inc.

With increasing altitude above sea level, hemoglobin carries less oxygen. This occurs because the partial pressure of oxygen in ambient air and in air inspired into the lung decreases and the amount of oxygen available for diffusion into the bloodstream decreases. The resulting hypoxemia stresses oxygen-dependent metabolic processes throughout the organism. A measure of hypoxemia is the percent of arterial hemoglobin that is saturated with oxygen (SaO_2). For example, Tibetan nomads residing at

4,850–5,450 m had an average SaO_2 of 84% compared with a median of 96% for US men measured at 208 m (Beall et al., 1994; Decker et al., 1989). However, there is a range of variation in SaO_2 among individuals at a given high altitude that indicated differences in hypoxemia despite uniform ambient hypoxia. A significant determinant of the variation among high-altitude Tibetans was intrapopulation genetic variation. A major gene with an autosomal dominant mode of inheritance was detected in the Tibetan sample from 4,850–5,450 m and in another from 3,800–4,065 m. The major gene accounted for 39% and 21% of the total phenotypic variance in SaO_2 in the former and latter, respectively (Beall et al., 1994, 1997a). The effect of the major gene was to increase SaO_2 5–6%, (i.e., to decrease hypoxemia). Those findings raised the question of whether similar genetic variation exists in other high-altitude populations. The question is of interest to evolutionary studies because genetic variation is required for the operation of natural selection.

This paper reports the results of a test of the hypothesis that additive genetic factors contribute to phenotypic variance in SaO_2 among Aymara natives of the Andean plateau, a high-altitude population geographically distant from the Tibetan plateau and with a long, separate history of high-altitude residence. In order to make the comparison with the Tibetan findings as close as possible, we conducted the study at 3,900–4,000 m (in the altitude range of one of the Tibetan studies) and used the same procedures for recruiting study participants, obtaining measurements, and performing analyses. Quantitative genetic analyses revealed that additive genetic factors did not account for significant phenotypic variance in the Aymara sample. Consequently, there is no potential for natural selection on SaO_2 in the Aymara.

MATERIALS AND METHODS
Population and sample

The study site was composed of four dispersed agropastoral communities in Provincia Murillo, Departamento La Paz, Bolivia, with a population of 1,175 ethnic Aymara living at 3,900–4,000 m. The average barometric pressure was 478 torr. Each household was contacted between May and August 1994 in order to invite household members and their biological relatives 14 years of age and older to participate in the study. Age was verified by birth certificates and identity cards and by reference to historical events for a few elderly people. Sixty-four percent provided a birth certificate or an identity card annotated as issued upon presentation of a birth certificate. Seventy-seven percent of all households participated. Fifty-seven percent of the residents eligible by age participated to yield a total sample of 608 people 13–94 years of age. Seventy percent of the sample resided in the four communities, and the rest were relatives residing elsewhere (one at low altitude). All were Aymara (except for one Quechua) natives of this or nearby high-altitude communities. Ethnicity was determined on the basis of birth and residence in one of the study communities where Aymara was the everyday language or on the basis of biological relationship to someone from the community.

Measurements

Participants were asked to abstain from coca chewing on the day of measurement. Individuals who reported coca chewing that day or whose mouths held masticated coca leaves were asked to return another day. After the participant sat quietly for 5–15 min, resting SaO_2 was measured with a finger pulse oximeter (Criticare model 501+; Criticare Systems Inc., Waukeshau, WI) during quiet wakefulness. No other measuring devices were attached to the individual at the time of SaO_2 measurement. A noninvasive sensor was placed on the index finger (occasionally on another finger if a reading were not obtained promptly or if the index finger were missing); the investigator waited 10–15 sec after the first reading appeared on the output screen and then recorded SaO_2 readings every 10 sec for a total of six measurements, as in our previous studies (Beall et al., 1994, 1997a,b; Beall and Goldstein, 1990). The reported values are the average of the six measurements. The pulse oximeter updates and displays a 1 sec moving average SaO_2 every 4–6 heartbeats. Anthropometric measurements were taken according to standard protocols (Cameron et

TABLE 1. *Characteristics of Aymara study sample at 3,900–4,000 m*[1]

| | Teenagers, 13–19 years of age | | | | Adults, ≥20 years of age | | | |
| | Males | | Females | | Males | | Females | |
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
N	39		38		169		135	
SaO$_2$	93.3	0.35	92.7	0.35	92.1	0.22	90.9	0.26
Age	16	0.2	16	0.30	39	1.2	38	1.1
Height (cm)	153.8	1.35	150.0	0.78	160.5	0.39 (n = 166)	149.2	0.39 (n = 134)
Weight (kg)	46.3	1.39	47.9	1.34 (n = 37)	59.3	0.66	52.0	0.69 (n = 126)
BMI (kg/m^2)	19.4	0.35	21.2	0.48 (n = 37)	23.0	0.22 (n = 166)	23.4	0.28 (n = 125)
Percent body fat	19.8	0.007	33.6	1.40 (n = 37)	21.5	0.004 (n = 166)	31.5	0.55 (n = 126)
Chest width (cm)	26.7	0.34	26.7	0.33	28.9	0.15	28.0	0.16 (n = 134)
Relative chest width	0.17	0.001	0.18	0.002	0.18	0.001 (n = 166)	0.19	0.001 (n = 133)
Chest depth (cm)	18.1	0.27	18.2	0.40	21.0	0.15	18.9	0.16 (n = 134)
Relative chest depth	0.12	0.001	0.12	0.002	0.13	0.001 (n = 166)	0.13	0.001 (n = 133)

[1] BMI, body mass index; SaO$_2$, percent of oxygen saturation of arterial hemoglobin. Relative chest depth, chest depth divided by height; relative chest width, chest width divided by height.

al., 1981). Adults provided genealogical information about their own households and their extended families. These reports were cross-checked when relatives provided the same information. Inconsistencies were reconciled during follow-up interviews. In addition, each participant was interviewed to elicit information on illness symptoms and lifestyle characteristics and, for females, current and past pregnancies. Measurements and interviews were conducted during a single visit to a field laboratory established in a central location in the community. A subsample of 22 people was remeasured in the same location on a different day in order to obtain measures of repeatability.

Analyses

An individual was excluded from SaO$_2$ analyses if she was pregnant or if he or she reported an illness or symptoms that might influence SaO$_2$, such as positive responses to questions about symptoms of tuberculosis, chronic cough, or exertional dyspnea, or if he or she had an SaO$_2$ more than 3 standard deviations from the mean. Table 1 describes characteristics of the resulting sample of 381 people, 13–94 years of age. Adults were defined as individuals 20 years of age and older because height growth was complete by then. Teenagers were defined as individuals from 13–19 years of age.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Relative chest width was calculated as transverse chest width in centimeters divided by height in centimeters. Relative chest depth was calculated as anteroposterior chest depth in centimeters divided by height in centimeters. Fat free mass in kilograms was calculated from weight, triceps skinfold, and subscapular skinfold with an equation developed for high-altitude Aymara that used the doubly labeled water dilution technique for validation (Kashiwazaki et al., 1996). Fat mass was calculated as weight minus fat free mass. Percent body fat was calculated as fat mass in kilograms divided by weight in kilograms and then multiplied by 100.

The normality of the distribution of the variables in the analyses was evaluated by inspection of probability plots displaying the observed cumulative proportions of each variable plotted on the y-axis against the expected cumulative proportions under the assumption of a normal distribution of that variable plotted on the x-axis. Those analyses were performed separately for teenage males, teenage females, adult males, and adult females. The data points clustered about the straight line y = x, and no values deviated markedly from that line. Therefore, it was concluded that they were nor-

mally distributed. The exception was adult BMI. For that reason, descriptive analyses involving adult male and female BMI were conducted using a transformed variable, the inverse of BMI (1 divided by BMI).

The repeatability of SaO_2, height, weight, chest width, and chest depth was determined by calculating the mean and standard deviation of the difference between measurements made of the same individual on different days (Bland and Altman, 1986). The repeatability of SaO_2 was $+0.3 \pm 2.9\%$ (n = 22), of height, $+9 \pm 22$ mm (n = 22), of weight, -1.3 ± 5 lbs (n = 22), of chest depth, -0.5 ± 10 mm (n = 22), and of chest width, -5 ± 12 mm (n = 22). The coefficient of repeatability, twice the standard deviation of the average difference, was 5.8%, 44 mm, 10 lbs, 20 mm, and 24 mm, respectively for SaO_2, height, weight, chest depth, and chest width.

Means and standard errors are reported. *T*-tests, correlations, and analyses of covariance addressed hypotheses about sources of SaO_2 variation. A significance level of .05 is used.

Quantitative genetic analyses tested a series of hypotheses regarding sources of variation in SaO_2 using maximum likelihood variance decomposition methods (Hopper and Mathews, 1982; Lange and Boehnke, 1983) available in the computer program FISHER (Lange et al., 1988). These analyses provided information regarding the relative importance of genetic, shared household, and random environmental effects on phenotypic variance of SaO_2.

Quantitative SaO_2 variation was modeled based on the linear function for the vector of phenotypes in a pedigree of size n (bold lower case letters denote vectors and bold upper case letters denote matrices):

$$\mathbf{y} = \mu \mathbf{l}_n + (\mathbf{X} - \mathbf{l}_n \mathbf{s}')\beta + \mathbf{g} + \mathbf{h} + \mathbf{e}, \quad (1)$$

where $\mathbf{y}$ is the $n \times 1$ vector of phenotypes, μ is the grand mean of the trait, $\mathbf{X}$ is an $n \times k$ matrix containing k covariates, $\mathbf{1}_n$ is a vector of n ones, $\mathbf{s}$ represents a vector of baseline covariates (e.g., 0 for qualitative covariates and x for continuous covariates), β is a $k \times 1$ vector of regression coefficients, $\mathbf{g}$ is the vector of additive genetic values, $\mathbf{h}$ is a vector of shared household effects, and $\mathbf{e}$ is a vector of random environmental devia-

tions. Given this model, the expected variance/covariance matrix for $\mathbf{y}$ is written:

$$\text{Var}(\mathbf{y}) = \Omega = 2\Phi\sigma_g^2 + \mathbf{Z}\sigma_h^2 + \mathbf{I}_n\sigma_e^2, \quad (2)$$

where Φ is the $n \times n$ matrix of kinship coefficients, $\mathbf{Z}$ is an indicator matrix whose ij-th element is 1 if the i-th and j-th individuals live in the same household and is 0 otherwise, and $\mathbf{I}_n$ is an identity matrix of order n. The variance terms in equation 2 include the additive genetic variance (σ_g^2), the variance due to shared household effects (σ_h^2), and the random environmental variance (σ_e^2). If we assume multivariate normality of $\mathbf{y}$, the likelihood of the pedigree is easily calculated, and optimization methods can be used for parameter estimation. Subsequent hypothesis testing is performed using likelihood ratio tests. As implied in equation 1, the effects of potential covariates (such as age, sex, BMI) were simultaneously estimated in all analyses. The effects of covariates were tested using likelihood ratio tests. Heritability (h^2) is the proportion of phenotypic variance resulting from additive genetic effects. Residual heritability (h^2) was calculated as the genetic variance divided by (1 - covariate variance). Household variance is the proportion of variance resulting from sharing the same environment as defined by living in the same residence. Residual household variance (c^2) was calculated as the shared household effects variance divided by (1 - covariate variance). The variance component analyses used 369 individuals in 41 pedigrees. Individuals were defined as belong to a pedigree if they were biologically related to anyone else in the pedigree. A large number of pairwise relationships were available (n = 1,185 pairs with complete data). There were 176 parent-offspring pairs, 199 sibling pairs, 20 grandparental pairs, 160 avuncular pairs, and seven half-sibling pairs. The remainder of the relative pairs was comprised of relatives of more than third-degree relationship (i.e., relatives who share less than 1/16 of genes from some common ancestor).

RESULTS

The average SaO_2 of the total sample of 381 Aymara was $92.0 \pm 0.15\%$, with a range of 84–99%. Figure 1 illustrates a wide range of SaO_2 variation at all ages. The average of
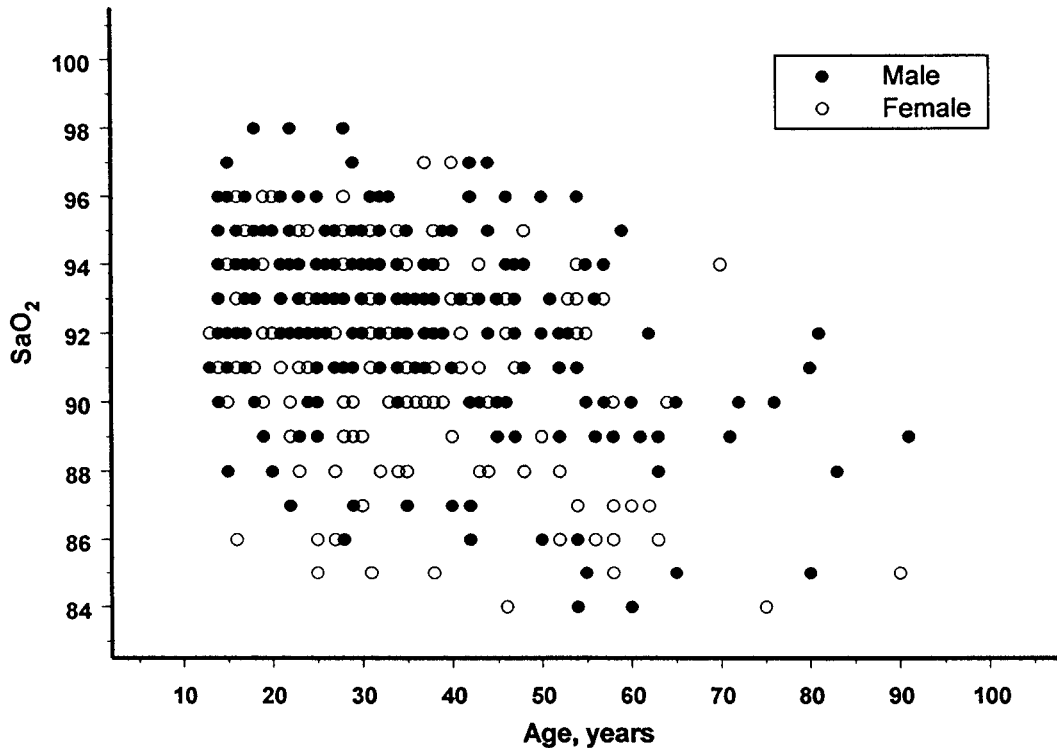
Fig. 1. Scatterplot of Aymara male and female SaO_2 with age.

the total male sample was 92.4 ± 0.20%, with a range of 84–99% (n = 208). That was higher than the average of the total female sample, which was 91.4% ± 0.30%, with a range of 84–97% (n = 173, t = 3.4, $P < .05$). Adults accounted for the sex difference. Adult males averaged 92.1 ± 0.22%, with a range of 84–99%, compared with adult females, who averaged 90.9 ± 0.26%, with a range of 84–97% (t = 3.5, $P < .05$). There was no significant sex difference among teenagers. Teenage males averaged 93.3 ± 0.35%, with a range of 88–98%, and teenage females averaged 92.7 ± 0.35%, with a range of 86–96% (t = 1.1, $P > .05$). Because these findings suggested a difference between processes occurring during growth and development and those occurring during adulthood, some analyses were conducted separately for the teenage and adult samples.

Teenage males and females exhibited no correlation between SaO_2 and age or between SaO_2 and BMI (Table 2). SaO_2 decreased with age and with BMI among adult males and females (the positive sign of the

TABLE 2. Bivariate correlations with SaO_2[1]

	Teenagers, 13–19 years of age		Adults, 20+ years of age	
	Male r	Female r	Male r	Female r
Age	0.07	0.05	−0.33*	−0.34*
BMI (kg/m²)	−0.10	−0.14	0.17*	0.31*
Percent body fat	0.15	0.06	−0.04	−0.18*
Chest width (cm)	−0.01	−0.12	−0.03	−0.03
Relative chest width	−0.15	−0.17	−0.15	−0.06
Chest depth (cm)	−0.04	−0.26	−0.20*	−0.15
Relative chest depth	−0.14	−0.29	−0.27*	−0.18*

[1] Adult male and female correlations with BMI (body mass index) are with the inverse of BMI. Relative chest depth, anteroposterior chest diameter divided by height; relative chest width, transverse chest diameter divided by height.
* $P < .05$, two-tailed test of significance.

correlation with BMI in Table 2 is with the inverse of BMI). Adult females exhibited a negative association between SaO_2 and percent body fat. Chest size and chest size relative to height, morphological traits thought to be associated with high-altitude adaptation, did not correlate with SaO_2 in the teenage subsample (Table 2). The negative associations with chest depth and rela-

TABLE 3. *Analyses of covariance examining the influence of having recently given birth on SaO$_2$ of Aymara women*

	Observed			
	SaO$_2$ (%)	Age (years)	Body fat (%)	Adjusted SaO$_2$
Group				
Gave birth in the past year	90.8	27	30.2	90.1
Did not give birth in the past year	91.5	35	32.4	91.9
	SS	df	MS	F
Source of variation				
Within cells	1,112.75	159	7.00	
Regression	317.92	2	158.96	22.71*
Gave birth in the past year	81.25	1	81.25	11.61*
Model	341.11	3	113.70	16.25*
Total	1,453.87	162	8.97	
Adjusted R^2 = .22				

* $P < .05$.

TABLE 4. *Relative variance components of percent of SaO$_2$ in a high-altitude Aymara sample*

Percent of total phenotypic variance in SaO$_2$ due to	
Covariates[1]	0.267*
Genetic differences	0.115
Shared household environment	0.023
Random environmental differences	0.559
Total phenotypic standard deviation	3.190
Residual h^2 [2]	0.157
Residual c^2 [3]	0.031

[1] Covariates were sex, age and age^2 of females, age and age^2 of males, and BMI.
[2] Residual heritability h^2 = genetic variance divided by (1 − variance due to covariates).
[3] Residual household variance c^2 = shared household variance divided by (1 − variance due to covariates).
* $P < .05$.

tive chest depth among adults were simply explained by the increase in chest depth with age (male r = 0.40; female r = .24; both $P < .05$). The partial correlation of SaO$_2$ and chest depth controlling for age was -0.08 for adult males and adult females (both $P > .05$).

The mean SaO$_2$ of 20 pregnant women was 94.4 ± 0.31%, with a range of 92–97%. Two women were remeasured after delivery. One woman whose SaO$_2$ was 96% when measured during the seventh month of her pregnancy declined to an SaO$_2$ of 92% when remeasured about 1 month after delivery. Another women whose SaO$_2$ was 95% when measured during the eighth month of pregnancy declined to an SaO$_2$ of 90% when remeasured about 1 month after delivery. Women who had given birth in the year prior to measurement (n = 34) had 1.8% lower SaO$_2$ than women who had not, after adjustment for age and body composition (Table 3).

The hypothesis that genetic factors influenced variation in SaO$_2$ was rejected because the variance components analyses detected no significant variance due to additive genetic differences (Table 4), and thus the residual heritability (h^2) of .157, or 15.7%, was not significant. Similarly, there was no evidence that membership in the same household influenced variation in SaO$_2$. The estimate of residual variance due to shared household environment was not significant, and thus the residual variance due to shared household environment (c^2) of .031, or 3.1%, was not significant.

DISCUSSION

The findings of the present study are consistent with the available data on Aymara SaO$_2$. The adult male mean of 92.1% in the present study is the same as that reported for 22–35-year-old Aymara men measured with the same instrument at 3,600 m (Beall et al., 1992). A lower SaO$_2$ at older ages was reported in both studies. Some of the findings of the present study were consistent with those from studies of Tibetan samples: women had higher SaO$_2$ during pregnancy than afterward, there was a negative association with adult age, and shared household environment did not account for a significant portion of the variance (Beall et al., 1997a). However, there were substantial contrasts between the findings of the present study and those reported for a Tibetan sample at the same altitude. The mean SaO$_2$ of this Aymara sample at 3,900–4,000 m was 2.6% higher than reported for a Tibetan sample at 3,800–4,065 m that had a grand mean of 89.4% and no sex differences (Beall et al., 1997a). That is, the Aymara were less hypoxemic than their Tibetan counterparts at the same altitude. Additive genetic factors did not account for a significant portion of the variance in SaO$_2$ in this Bolivian Aymara community, whereas they did account for a significant proportion (0.397, or 39.7%) in the Tibetan sample (Beall et al., 1997a).

It is very unlikely that measurement noise, measurement bias, or sample selection bias accounts for the Aymara-Tibetan contrast in mean and genetic variance. Measurement noise might arise from SaO_2 fluctuation due to physiological factors and from measurement error that could cause the SaO_2 reading to deviate from a true value. Because SaO_2 varies over a 24 h period, an individual actually has many SaO_2s (Slutsky and Strohl, 1980), just as he or she has many blood pressures during that time (Pickering et al., 1991). The measurement reported here represents an individual's SaO_2 measured under standardized circumstances in order to control for this known variation. Measurements of the Aymara and Tibetans were obtained with the same instruments following the same protocol. Repeatability was equally good in both sites, as indicated by the repeatability coefficient of 5.6% in the Aymara sample and 5.4% in the Tibetan sample. The variance of the repeated measures was about the same proportion of the total sample variance in both sites (30% and 28% in the Aymara and Tibetan samples, respectively). To our knowledge, there are no other published reliability data for comparison. SaO_2 measurement was sufficiently reliable in two Tibetan samples to allow detection of a major gene for the trait (Beall et al., 1994, 1997a). Because the indicators of reliability in the present Aymara sample are so similar to those in the Tibetan sample, it is unlikely that measurement noise or bias in the Aymara sample accounts for the lack of significant additive genetic variance. There was a high rate of participation in both sites, the procedures for identifying a subsample based on self-reported good health, and the quantitative genetic analyses were the same in both. This evidence leads to the conclusion that the population contrasts in mean SaO_2 and in genetic variance are substantive rather than methodological.

The higher mean Aymara SaO_2 is unexpected. The Aymara sample and the Tibetan sample to which it is compared live in the same altitude range and are exposed to virtually the same reduced barometric pressure and partial pressure of inspired oxygen relative to sea level; that leads to the expectation of similar SaO_2. The Aymara have lower resting ventilation and hypoxic ventilatory response (HVR) and perhaps lower alveolar ventilation than their Tibetan counterparts (Beall et al., 1997b; Zhuang et al., 1993); that leads to the expectation of lower Aymara SaO_2 (Lenfant and Sullivan, 1971) rather than the higher SaO_2 found in the present study. The higher Aymara SaO_2 must be achieved at another link or links in the chain of oxygen transport. Possibilities include the oxygen affinity of hemoglobin, the pulmonary artery pressure, and the pulmonary diffusing capacity. Those traits were not measured in the present study, although there are some relevant published data. A higher Aymara oxygen affinity of hemoglobin could result in a higher SaO_2 at a given arterial partial pressure of oxygen (p_aO_2). However, the available evidence indicates that Aymara and Tibetans both have normal (compared to sea level) oxygen affinity as measured by the p_aO_2 corresponding to a 50% SaO_2 (p_{50}) (Moore et al., 1992; Winslow et al., 1985). A higher Aymara pulmonary arterial pressure could increase lung perfusion and SaO_2, although the effect is thought to be trivial (Ward et al., 1989). Andean high-altitude natives have significantly elevated pulmonary arterial pressure compared with sea level (Penaloza et al., 1963). There are inconsistent findings about the pulmonary artery pressure of Tibetan high-altitude natives. One study of Tibetan men and women reported an elevated pulmonary artery pressure similar to that reported for Andean samples (Yang et al., 1985), while another study of Tibetan men reported a pulmonary artery pressure within the range of normal sea-level values (Groves et al., 1993). A higher Aymara pulmonary diffusing capacity could also increase SaO_2. While Andean high-altitude natives have elevated pulmonary diffusing capacity relative to sea level (Pasquis et al., 1981), to our knowledge there are no published data on this trait among Tibetans. Thus, the currently published literature is not sufficiently complete to permit a convincing explanation for the higher Aymara SaO_2 (other than to indicate that it is probably not due to differences in oxygen affinity of hemoglobin).

A priori, it would seem that restoring SaO_2 closer to sea-level values would be a

more successful adaptation because it represents a greater reduction in hypoxic stress. This logic would lead to the conclusion that the Aymara, with the higher SaO_2, are better adapted than the Tibetans to altitudes around 4,000 m. In contrast, some authors have suggested that Tibetans might be better adapted than Andean highlanders when compared on the basis of other cardiorespiratory traits (Moore et al., 1992). However, there may be no particular reason to translate biological differences into a hierarchy of degrees of adaptation. There is evidence that both Andean and Tibetan high-altitude populations are well adapted.

Both Andean and Tibetan high altitude populations are well adapted as assessed by the fundamental Darwinian demographic measures of long-term population persistence and increase. With respect to the Andean plateau, multiple chronometric (radiocarbon) dates ranging from 13,460 to 10,240 years BP from several highland Peruvian sites provide evidence of the earliest habitation above 2,500 m. A review of the evidence for early human occupation of Peru concludes that the highlands were occupied sometime after 11,000 years ago (Aldenderfer, in press). A much earlier radiocarbon dated site from 20,000 to 14,000 years BP is controversial because of uncertainty about whether the purported artifacts really are artifacts (Lynch, 1990; Rick, 1988). With respect to the Tibetan plateau, there are very few chronometric dates (at least in the English language literature). The earliest is a single site with a radiocarbon date of 6,745 years BP (Chang, 1986). Two other sites with radiocarbon dates are thousands of years later and associated with farming and thus offer little information on the time of earliest occupation (Chang, 1986, 1992). Claims of 25,000 or more years of human habitation on the Tibetan plateau have been made (e.g., Moore et al., 1992; Niermeyer et al., 1995); however, they are unsubstantiated. Those claims reference two reports. One (Dennell et al., 1988) describes purported stone tools found at an altitude below 1,000 m at a site located south of the Himalayas in Pakistan. Therefore, that article offers no information on the timing of the habitation of the Tibetan plateau. The other

article (Zhimin et al., 1982) referenced by those claiming great antiquity of human habitation reports on surface finds of stone tools on the Tibetan plateau. However, Zhimin et al. (1982:498) state, "Lacking stratigraphic evidence, it is difficult to describe and date the cultures represented by these stone tools...." That article does not provide dates for its findings. Thus, neither cited source provides information about the antiquity of human habitation of the Tibetan plateau. Currently, the strongest statement supported by chronometrically dated evidence about the occupation of the Tibetan plateau is that it had occurred by about 7,000 years BP. More archaeological work is needed to provide an accurate estimate of the length of time natural selection could have been operating on human inhabitants.

From the standpoint of evaluating successful adaptation of the present indigenous populations of the Andean and Tibetan plateaus, the chronometric dates presently available indicate that both populations have maintained themselves for at least 7,000 years, and demographic data indicate that both have expanded to populate large geographic areas. Both continue to increase in numbers. The Tibetan population had a 15.2/1,000 rate of natural increase in 1990 (Xi Zang Tong Ji Nian Jian, 1993), and the Andean region had a 20.5/1,000 rate of natural increase in 1990–1995 (Pan American Health Organization, 1994). Demographic measures reflect public health and health care delivery systems in the two areas as well as successful adaptation to the environment.

From the standpoint of function in high-altitude environments, measures of oxygen delivery to tissues under conditions of very low and very high oxygen demand provide useful integrative indicators of adaptation to hypoxic stress. Sea-level natives acutely exposed to high altitude exhibit an elevated basal metabolic rate and a diminished maximal oxygen consumption compared to sea level (Butterfield, 1990; Gill and Pugh, 1964; Buskirk, 1976). In contrast, Andean and Tibetan high-altitude natives have basal metabolic rates and levels of maximal oxygen consumption that are in the normal range of sea-level natives measured at sea

level (Baker, 1976; Beall et al., 1996; Lahiri et al., 1976; Mazess et al., 1969; Sun et al., 1990). Thus, both populations are well adapted from the functional standpoint of delivering sufficient oxygen to tissues across the complete range of levels of oxygen consumption. These geographic, demographic, and functional lines of evidence suggest that the Andean and Tibetan populations are equally well adapted.

The adaptations may have been attained and/or maintained differently in the two populations. The Aymara and Tibetan samples differ in the contribution of genetic sources of variance to total phenotypic variance in SaO_2. The Aymara did not exhibit significant variance due to additive genetic differences or significant heritability of SaO_2, while the Tibetans did (Beall et al., 1994, 1997a). There are several possible explanations for the absence of significant additive genetic variance in the Aymara sample. The straightforward explanation is that the lack of genetic variance simply reflects a lack of allelic variation. That is, the population is near fixation for one allele influencing SaO_2 as a result of past natural selection or because mutations have not occurred or have been lost. Other alleles, if present, have a very low frequency. This possibility cannot be evaluated presently because the genes themselves (e.g., chromosomal location, gene product) are unknown, although their existence has been detected in two Tibetan samples (Beall et al., 1994, 1997a). If this explanation is accurate, then it appears that the alleles influencing SaO_2 in the Aymara population result in higher genotypic means among the Aymara than the Tibetans.

Another possible explanation for the lack of significant additive genetic variance could be uniform exposure to an unknown, external environmental factor that prevents the expression of existing genetic variation. This alternative seems unlikely because altitude is the only environmental factor presently known to operate on all healthy residents. If this explanation were accurate, it would change the basic assumption of high-altitude studies that altitude is the overriding determinant of SaO_2 in healthy people.

While the relevant factors in the external environment are probably the same in the two populations, relevant factors in the internal environment could differ in ways influencing the expression of genetic variation in SaO_2. This could occur if epistatic or pleiotropic interaction with other loci or genetic correlation with other traits influenced the expression of genetic variation and/or the genotypic means. Genes for other physiological traits could create contrasting internal milieux that might influence SaO_2. The Aymara and Tibetan samples compared here differ biologically in many ways despite living at the same altitude with the same barometric pressure. The present Aymara sample had roughly 20% higher hemoglobin concentration as well as roughly 30% lower resting ventilation and 50% lower HVR than the Tibetan sample (Beall et al., 1997b, 1998). The latter traits all have significant genetic variance (with the exception of resting ventilation in the Aymara). Genes for these or other traits could hypothetically influence expression of genes for SaO_2.

Current knowledge of the genetics of these traits and environmental influences does not offer clues as to the more likely explanation for the lack of significant additive genetic variance and heritability in the Aymara sample. The importance of these findings for understanding evolution and adaptation to high-altitude environments lies with the implications for natural selection. Because the response to natural selection is proportional to the heritability of a trait (Falconer, 1989), a consequence of the absence of significant heritability among the Aymara is the absence of potential for natural selection on that trait.

In conclusion, there were Aymara-Tibetan population differences in mean SaO_2 and in the contribution of additive genetic factors to phenotypic variation. This Aymara sample had 2.6% higher mean SaO_2 and exhibited no significant genetic variance in contrast to a Tibetan sample residing at the same altitude evaluated with the same measurement and analytical techniques. These results indicate that forces of evolution have acted differently on a locus or loci influencing SaO_2 in the two geographic populations. They resulted in genetic variance in the

Tibetan but not in the Aymara population. The presence of significant genetic variance in the Tibetan samples and its absence in the present Aymara sample indicate there is potential for natural selection on SaO_2 in the contemporary Tibetan but not the Aymara population.

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