



COMPARATIVE ASPECTS OF HIGH-ALTITUDE ADAPTATION IN HUMAN POPULATIONS

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1. POPULATION DIFFERENCES IN DURATION OF HIGH-ALTITUDE RESIDENCE

Nearly 140 million people live permanently above 2500 m (8,000 ft) throughout the world, with about 17% of these persons residing in Africa, 56% in Asia, 26% in Central and South, and <1% in North America (Moore *et al* 1998). Investigations at high altitude have helped to define the principal pathways through which organisms respond to hypoxic stress. As demonstrated by the presentations and publications of this conference, these studies have spanned the full range of levels of biological organization, from the molecular to cellular, organ, organ system, individual, population, species and beyond.

The central question here is whether the physiological responses to hypoxia vary in relation to the length of time (in generations) of high-altitude residence and, if so, the mechanisms responsible. The opportunity to answer this question has been provided by several, recent, in-depth studies conducted in the Himalayan, Andean and Rocky Mountain high-altitude areas. As a result, the requisite data are available with which to determine whether

adaptation in the evolutionary sense of permitting an organism to live and reproduce (Dobzhansky, 1968) increases with the number of generations of altitude exposure. A lack of comparable studies in Africa prevents inclusion of that region and there are no permanent human settlements above 2500 m in Europe. From considerations of evolutionary theory, we would predict that natural selection has operated to select the genetic traits conferring the greatest adaptive advantage in the populations which have lived the longest at high altitude and have had the least degree of interbreeding (genetic admixture) from lowland groups.

1.1 Archaeologic/paleontologic evidence

Hominids have been present in Asia for more than a million years, longer than the duration of hominid occupation of North and South America (Wanpo *et al.* 1995). Late Pliocene artifacts ~2 million yrs old in northern Pakistan (Denell *et al.* 1988) indicate the presence of hominids within 75 km of the Tibetan Plateau. Archaeologic materials have been found at 4500 to 5200 m in northern Tibet, consisting of more than 100 flakes and microliths that are similar in form and technology to Upper Paleolithic northern Asian tool cultures dated at 25,000 to 50,000 years of age (Sensui, 1981; Zhimin, 1982). Material dated *in situ* is more recent, consisting of 5000 yr old farming implements (Chang, 1992). Newcomer populations are also present on the Tibetan Plateau. Increasing numbers of Han (ethnic Chinese) began settling in Tibet in significant numbers following the 1951 Chinese takeover of Tibet, although small numbers of Han have lived longer in the northern portion of the Tibetan Plateau (Qinghai Province). Hence, the Han have resided at high altitude in significant numbers for less than 50 years.

Humans reached South America as early as 9,000 to 12,000 years ago, having migrated in several waves over the Beringian land bridge from northeastern Asian groups (Neel *et al.* 1994). The source population for these early migrants is not likely to be closely related to ancestral Tibetans (Lell *et al.* 1997). Early South American inhabitants lived at coastal sites, relying on fishing but spent some of their time foraging or trading in the highlands, as demonstrated by the presence of stone tools made of obsidian from highland quarries (Sandweiss *et al.* 1998). Persons of European origin have lived at high altitudes in Central and South America for the ~450 yrs following the Spanish Conquest in the early 1500s. Considerable genetic admixture has occurred with indigenous inhabitants, resulting in the introduction of 5-30% of European genes into the contemporary gene pool (sum total of all genes present in a population) of Ecuador, Peru and Bolivia (Moore *et al.* 1998).

Permanent habitation of the high-altitude region of North America, encompassing portions of Wyoming, Colorado, Utah and New Mexico, began only 150 years ago. Current residents are genetically heterogeneous groups which are descended from low-altitude Amerindian, European and Hispanic populations.

1.2 Linguistic and genetic evidence

Linguistic and genetic evidence supports a longer period of residence with less genetic admixture from lowland groups for the Tibetan population than the Andean population. Dental morphology, mitochondrial and nuclear genetic markers show Tibetans to be related to Korean, Siberian, Mongolian, Japanese and northern Han populations and to differ considerably from southern Han, Cambodian and other southern Asian groups which are likely to be more recent migrants to Asia (Matsumoto, 1987; Torroni *et al.* 1994; Turner, 1987; Lee *et al.* 1988; Zhao and Lee, 1989; Chu *et al.* 1998). The Tibetans' membership in the Tibeto-Burmese language group differentiates them from northern Asian (including Mongolian) populations and indicates that Tibetans have resided in their current location long enough for linguistic separation to have occurred. Surprisingly, Quechua and Aymara belong to separate linguistic groups, even though they reside next to each other on the altiplano and have much in common with each other culturally (Merriwether *et al.* 1995).

The continued separation of language groups may reflect their comparatively recent (~10,000 yrs) arrival, since languages would be expected to become more closely related with time, and/or the effectiveness of cultural isolating mechanisms. Unlike the Tibetan population, the Andean gene pool has undergone two major events, both of which are likely to have limited the range of genetic variation present. The first resulted from the lack of genetic variation throughout the Americas, suggesting a relatively small number of initial migrants or a source population with little genetic variation (Neel *et al.* 1994; Merriwether *et al.* 1995; Chen *et al.* 1995; Torroni *et al.* 1993). The second was the loss of 95% of the population within the hundred years following Spanish Conquest as the result of fighting, infectious disease, malnutrition and forced resettlement (Cook, 1981).

1.3 Geographic evidence

The over 800,000 sq mi Tibetan Plateau is twice as large as the 400,000 sq mi Andean altiplano. At least 1000 miles from the Bay of Bengal, it is more than ten times more distant from the nearest sea coast. Whereas the Andean altiplano is readily accessible from the Pacific Coast, the Tibetan Plateau is bounded by the world's tallest mountains to the south, multiple

PO₂ in acclimatized newcomers of European or Han descent (Figure 1A, before vs. after acclimatization line). The similarity in responses suggests that genetic factors influencing ventilatory acclimatization are broadly distributed among human groups.

Rocky Mountain (Dempsey *et al.* 1971; Weil *et al.* 1971) and Andean lifelong high-altitude residents (Severinghaus *et al.* 1966; Beall *et al.* 1997) show a diminution in ventilation relative that present in acclimatized newcomers (Figure 1B). Earlier reports suggested that Sherpa, a population residing in Nepal but of Tibetan origin, also hypoventilated relative to acclimatized newcomers but these studies were conducted in small numbers of subjects, some of whom had been exposed to a range of altitudes (Lahiri, 1968; Lahiri and Milledge, 1967). Most (Zhuang *et al.* 1993; Huang *et al.* 1981; Hackett *et al.* 1980) but not all (Santolaya *et al.* 1989) recent studies find levels of effective alveolar ventilation in Tibetans which are equivalent to those of acclimatized newcomers. Summarizing these data (Figure 1B), nearly all the Tibetan high-altitude points are closer to the "after-acclimatization" curve than the Andean ones, indicating a greater effective alveolar ventilation in the Tibetan than Andean highlanders (Zhuang *et al.* 1993). This conclusion is supported by direct comparisons by Beall and co-workers in large numbers of Aymara and Tibetans living at the same altitude (Beall *et al.* 1997).

An important factor influencing ventilation at high altitude is the hypoxic ventilatory response (HVR) (Huang *et al.* 1984; Lahiri *et al.* 1969; Weil *et al.* 1971; Milledge and Lahiri, 1967; Severinghaus *et al.* 1966). Consistent with the maintenance of higher ventilation, we have found HVRs in lifelong Tibetan high-altitude residents that are at least as great as those of acclimatized newcomers, greater than newcomers who migrated to high altitude as children, and greater than Andean residents of similar altitudes (Zhuang *et al.* 1993; Huang *et al.* 1981; Hackett *et al.* 1980; Beall *et al.* 1997). The higher HVRs in Tibetans than Andeans are likely due to genetic factors. Twin studies at low altitude demonstrate that a significant portion of the variation in HVR is due to genes (Collins *et al.* 1978; Kawakami *et al.* 1982). At high altitude, the studies of Beall and co-workers demonstrate significant, higher heritability in Tibetans (34%) than Andeans (22%), leading the authors to suggest that natural selection has acted to increase the frequency of genes for high ventilation and maintain HVR in the Tibetans (Beall *et al.* 1997).

2.2 Pulmonary arterial pressure

Pulmonary arterial pressure rises after ascent to high altitude as a result of hypoxic pulmonary vasoconstriction. Elevated pulmonary arterial pressure and resistance are probably maladaptive responses to high altitude, because

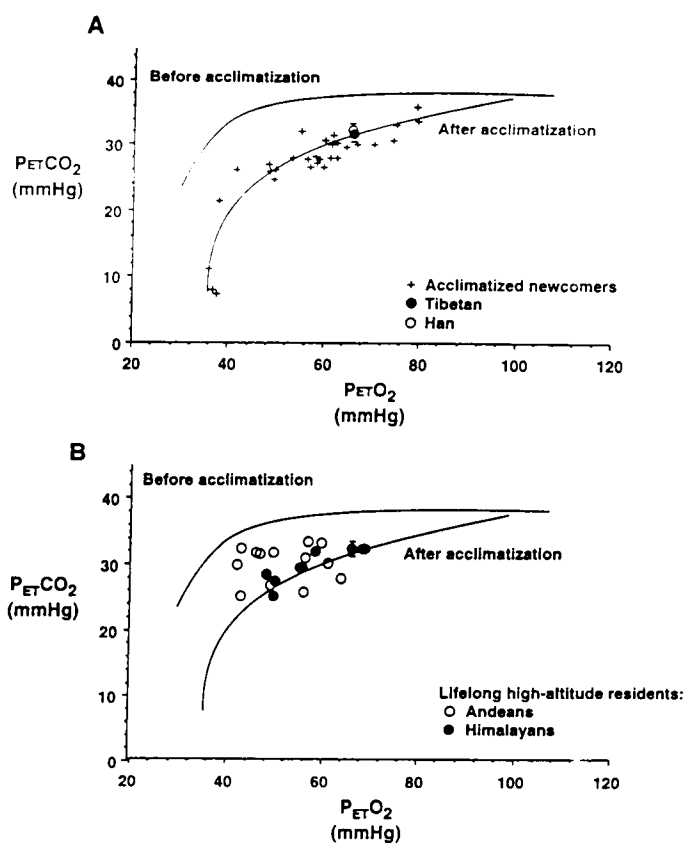


FIGURE 1. Circles represent average values for groups of persons residing at a given altitude. A. Compared with unacclimatized persons (<1 hr of hypoxic exposure), persons of low-altitude ancestry who have resided at high altitude for 4 da - 2 yr have an increased alveolar ventilation. B. Alveolar ventilation is greater (lower $P_{ET}CO_2$) in lifelong Himalayan high-altitude residents but Andean highlanders in many studies ventilate less than acclimatized newcomers (Reprinted from (Zhuang *et al.*1993)).

they result in minimal improvement in ventilation-perfusion matching, increased work load for the right ventricle, limited cardiac output reserve, and can lead to right ventricular decompensation and death. We found pulmonary arterial pressure and resistance to be remarkably low and unresponsive to added hypoxia in healthy Tibetan residents of high altitude in comparison with lifelong Rocky Mountain or Andean high-altitude natives (Figure 2). Neither exercise to near-maximal levels nor breathing hypoxic gas mixtures sufficient to lower arterial PO_2 to 36 mmHg raised the Tibetans' pulmonary arterial pressure (Figure 2) or resistance (Groves *et al.* 1993). Consistent with the absence of hypoxic pulmonary vasoconstriction were observations in Tibetan men at 3600 m in Ladakh which showed a lack of smooth muscle in the small pulmonary arteries (Gupta *et al.* 1992). Resistance to hypoxic pulmonary hypertension, a trait for which a genetic contribution has been well established, has also been observed in yak and other long-resident, high-altitude species (Durmowicz *et al.* 1993; Sun *et al.* 1989; Banchero *et al.* 1971). Thus, it appears that Tibetans, unlike Andeans or Rocky Mountain high-altitude residents, are protected from hypoxic pulmonary hypertension.

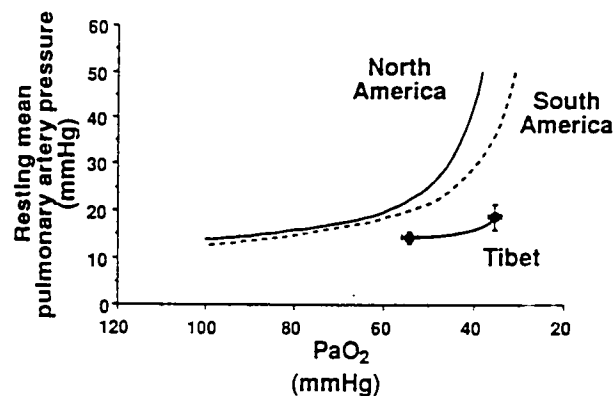


FIGURE 2. Mean pulmonary artery pressure rises with increasing hypoxia, expressed as a fall in arterial PaO_2 in North and South American high-altitude residents but not in Tibetans (Reprinted from (Groves *et al.* 1993)).

2.3 Hemoglobin concentration

Hemoglobin concentration is lower in Himalayan than Andean highlanders, averaging 1-4 gm/100 ml whole blood at a given altitude (Beall *et al.* 1990; Beall and Reichsman, 1984; Beall and Goldstein, 1987; Beall and Goldstein, 1990; Beall *et al.* 1998; Winslow *et al.* 1989). Lower hemoglobin may result from a lesser hypoxic stimulus, due perhaps to better-maintained ventilation during the day or night and/or a lesser erythropoietic response (Winslow *et al.* 1990). Other factors may be involved, including developmental

Summarizing all published data for Andean, Tibetan and North American high-altitude residents, birth weights decline an average of 100 gm per 1000 m altitude gain (Moore et al.1998)¹. When data are differentiated by population ancestry, the magnitude of fetal growth retardation varies in relation to the duration of high-altitude residence (Figure 3). The longest-resident population (Tibetans) experienced the least decline, followed by the Andeans, Europeans, and lastly the Han.

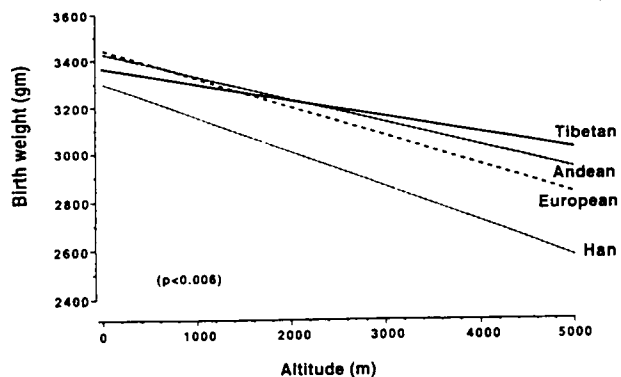


FIGURE 3. The magnitude of altitude-associated reduction in birth weight lessened with increasing number of generations of high-altitude residence ($p < 0.006$). Tibetans, living at 1200-4700 m, have the least birth weight decline, followed by Andeans living at 0-4600 m, persons of European ancestry living at 0-3600 m in South or North America. Han, residing at 0-3800 m, have the greatest birth weight decline. Best-fit regression lines are shown for data obtained from previously published studies.

These population differences are supported by three kinds of studies. The first is the comparison of studies conducted by the same investigator in women of the same genetic background who resided at sea level or 3100-3600 m. The greatest birth weight reduction was seen in the Rocky Mountain region (-352 gm, $p < 0.001$), an intermediate decline occurred in Andeans (-270 gm in Peru and -282 gm in Bolivia, $p < 0.001$), and the least change was found in Tibetans (-72 gm, $p = \text{NS}$) (reviewed in Zamudio et al.1993). Second, we collected birth weight, gestational age and related data from Tibetan and Han residents of 2800 to 4800 m altitudes in Tibet. The altitude-associated birth weight reduction in the Tibetans was much less than that observed in the Han (Moore et al.1999b). Third, we studied healthy Tibetan, Han, European, and Andean women residing at 3600 m (Table 2, Figure 4). No woman smoked cigarettes during her pregnancy, all received prenatal care, and all were well-nourished, representing a middle- to upper-class segment of the

¹ Data reported by Wiley for women residing in Ladakh, India are not included in the data set used for generating the Tibetan line since only 6% of the sample was Tibetan (Wiley, 1994).

population in their respective communities. Birth weights were heaviest in the babies born to the Tibetan women and progressively lower in the Andean, European and Han women (Figure 4). Gestational age was greater in the Tibetan than Andean or European women but if births were restricted to term births (37-40 wks gestational age), a similar pattern of variation in birth weight was seen. Gravidity was greater in the Andean women than in each of the

TABLE 2. Birth weights and other characteristics of samples of women residing at 3600 m.

	Tibetan	Andean	European	Han
<u>All women</u>				
Sample size	21	53	16	13
Place of residence	Lhasa	La Paz	La Paz	Lhasa
Birth wt, gms	3333±78 ^â [□]	3208±66 ^â [□]	2972±64 [*] [□]	2645±96 [*] ^â
Gestational age, wks	40.6±0.3 ^â	39.5±0.3	38.4±0.3	39.4±0.6
Gravidity	1.5±0.1	2.9±0.2 ^â [□]	1.8±0.3	1.2±0.2
Pre-eclamptic, %	--	5.7 ^â	25	--
Intrauterine death, %	--	0 ^â	6.3	--
<u>Primigravida women</u>				
Sample size	11	13	8	11
Birth weight, gms	3300±118	3141±60	3050±83	2644±113

All statistical comparisons by one-way analysis of variance with Fisher's PSLD multiple comparisons. Place of residence is Lhasa, Tibet, PRC or La Paz, Bolivia.

- *comparison with Tibetans, p<0.05
- comparison with Andeans, p<0.05
- ^â comparison with Europeans, p<0.05
- [□] comparison with Hans, p<0.05

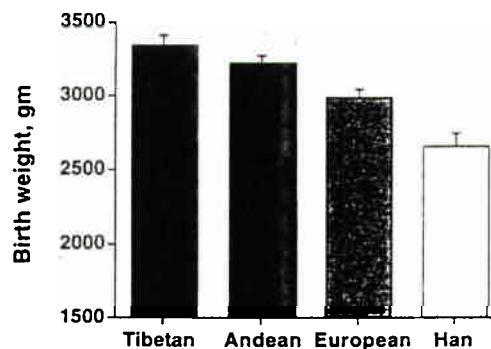


FIGURE 4. Mean ± SEM birth weights of babies born to all the women reported in Table 2 are shown. Women were participants in studies conducted by our group. Birth weights were heavier in Tibetans than European and Han women and heavier than Andean women when controlled for gravidity.

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other groups. When only first pregnancies were considered, a similar pattern of decline in birth weights was observed but the Andean babies weighed significantly less than the Tibetan newborns (Table 2).

3.2 Population differences in neonatal oxygenation at high altitude

At birth, the lungs change from fluid-to air-filled, and vascular shunts reverse directions and close. Current evidence indicates that this cardiopulmonary transition is altered under conditions of ambient hypoxia. Arterial O₂ saturation at high altitudes falls during the first week of postnatal life whereas it doesn't change at sea level (Thilo *et al.* 1991; Niermeyer *et al.* 1993; Niermeyer *et al.* 1995). Remarkably, Tibetan newborns had higher arterial O₂ saturations throughout the first four months of life than Han babies born at the same altitude (Niermeyer *et al.* 1995). Further, arterial O₂ saturation stabilized in the Tibetans at four months of age above the values seen by the same investigators in Colorado some 500 m lower, while arterial O₂ saturation declined progressively to an average of 76% in the Han (Niermeyer *et al.* 1995). Higher arterial O₂ saturations may be responsible for the protection reported for Tibetan compared with Han babies from a syndrome of pulmonary hypertension and right heart failure ("subacute infantile mountain sickness") (Khoury and Hawes, 1963; Sui *et al.* 1988).

4. SUMMARY AND CONCLUSIONS

The conditions and duration of high-altitude residence differ among high-altitude populations. The Tibetan Plateau is larger, more geographically remote, and appears to have been occupied for a longer period of time than the Andean Altiplano and, certainly, the Rocky Mountain region as judged by archaeological, linguistic, genetic and historical data. In addition, the Tibetan gene pool is less likely to have been constricted by small numbers of initial migrants and/or severe population decline, and to have been less subject to genetic admixture with lowland groups. Comparing Tibetans to other high-altitude residents demonstrates that Tibetans have

- less intrauterine growth retardation
- better neonatal oxygenation
- higher ventilation and hypoxic ventilatory response
- lower pulmonary arterial pressure and resistance
- lower hemoglobin concentrations and less susceptibility to CMS

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These findings are consistent with the conclusion that "adaptation" to high altitude increases with time, considering time in generations of high-altitude exposure.

Future research is needed to compare the extent of IUGR and neonatal oxygenation in South American high-altitude residents of Andean vs. European ancestry, controlling for gestational age and other characteristics. Another fruitful line of inquiry is likely to be determining whether persons with CMS or other forms of adult hypertension have experienced hypoxia during prenatal or neonatal life. Finally, the comparison of genetic polymorphisms with respect to the frequencies of genes involved in oxygen sensing and physiologic response to hypoxia will be useful, once candidate genes have been identified.

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