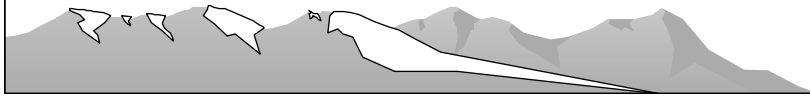


High Altitude Populations

Joe Alcock MD
Adapted from a presentation by
Katie Swank, MD



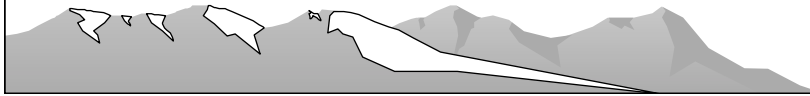
High Altitude Dwellers

- Humans have lived at altitude for thousands of years
- Sea level natives travel to high places - suffer from altitude sickness
- High altitude dwellers - better equipped to deal with thin air
- How?



Where did they go?

- The 3 major cultures that live at high altitude and have been well studied
 - Tibetan plateau
 - Andean Altiplano
 - Ethiopian highlands



When they arrived

- People moved to Andean Altiplano 11,000 years ago
- Hunter-gatherers in Tibetan plateau 25,000 years
- Ethiopian Highlanders have lived at high altitude for > 50,000 years
- Prediction- based on duration of experience



TABLE 1. HIGH ALTITUDE STUDIES, 1990-2001

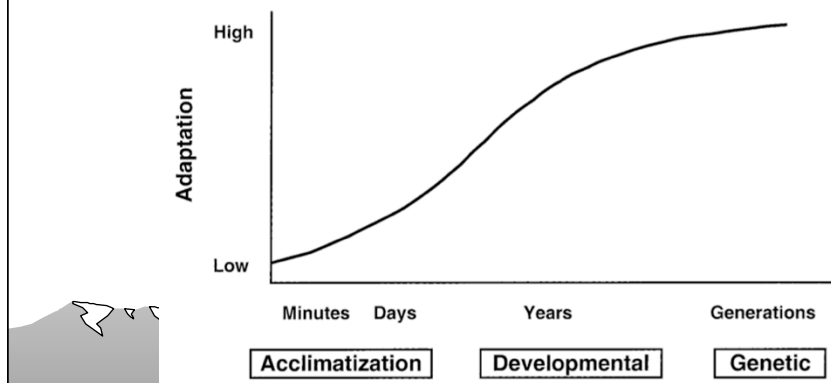
<i>Rocky Mountains, North America</i>	<i>Andes, Central and South America</i>	<i>Himalayas, Asia</i>	<i>More than 1 region</i>
(Asmus et al., 1999)	(Bailliar et al., 1990)	(Beall et al., 1994)	(Beall et al., 1997a)
(Jensen et al., 1997)	(Beall et al., 1992)	(Beall et al., 1998)	(Beall et al., 1997b)
(Niermeyer et al., 1993)	(Beall et al., 1999)	(Beall 2000b)	(Beall 2000a)
(Palmer et al., 1999)	(Bedu et al., 1991)	(Chen et al., 1997)	(Coudert 1992)
(Zamudio et al., 1993b)	(Bedu et al., 1994)	(Curran-Everett et al., 1992)	(Hochachka et al., 1998)
(Zamudio et al., 1994)	(Blonc et al., 1996)	(Curran et al., 1995)	(Hochachka 2000)
(Zamudio et al., 1995c)	(Brutsaert et al., 1999b)	(Curran et al., 1997)	(Moore 1990)
(Zamudio et al., 1995b)	(Brutsaert et al., 1999a)	(Curran et al., 1998)	(Moore et al., 1992)
(Zamudio et al., 1995a)	(Brutsaert et al., 2000)	(Droma et al., 1991)	(Moore et al., 1994)
(Zamudio et al., 1995d)	(Demarchi et al., 2000)	(Fiori et al., 2000)	(Moore et al., 1998a)
	(de Meer et al., 1995)	(Ge et al., 1994a)	(Moore et al., 1998b)
	(Desplanches et al., 1996)	(Ge et al., 1994b)	(Moore et al., 2000)
	(Favier et al., 1995b)	(Groves et al., 1993)	(Ramirez et al., 1999)
	(Favier et al., 1995a)	(Gupta et al., 1992)	(Winslow et al., 1990)
	(Frisancho et al., 1995)	(Halperin et al., 1998)	(Zamudio et al., 1993c)
	(Frisancho et al., 1997)	(Huang et al., 1992)	
	(Frisancho et al., 1999)	(Kayser et al., 1991)	
	(Grekss et al., 1994)	(Kayser et al., 1994)	
	(Grekss 1996)	(Kayser et al., 1996b)	
	(Grekss 1998)	(Malik et al., 1993)	
	(Hochachka et al., 1994)	(Moore et al., 1992)	
	(Hochachka et al., 1996a)	(Moore et al., 2001c)	
	(Hudson et al., 1999)	(Moore et al., 2001b)	
	(Kayser et al., 1996a)	(Niermeyer et al., 1995)	
	(Leon-Velarde et al., 1997)	(Niu et al., 1995)	
	(Leonard et al., 1995)	(Sun et al., 1990a)	
	(Luiselli et al., 2000)	(Sun et al., 1990b)	
	(Mayhew et al., 1990)	(Sun et al., 1996)	
	(Mayhew 1991)	(Torrioni et al., 1994)	
	(Mayhew 1998)	(Wiley 1994b)	
	(Monge-C et al., 1992)	(Wiley 1994a)	
	(Moraga et al., 2000)	(Wu et al., 1998a)	
	(Mortola et al., 1990)	(Wu et al., 1998b)	
	(Normand et al., 1992)	(Wu et al., 1998c)	
	(Rupert et al., 1999a)	(Zamudio et al., 1993a)	
	(Rupert et al., 1999b)	(Zamudio et al., 1993b)	
	(Tarazona-Santos et al., 2000)	(Zhuang et al., 1993a)	
	(Vargas et al., 1998)	(Zhuang et al., 1993b)	
	(Vitzthum et al., 2000)	(Zhuang et al., 1996)	

Cultural adaptation

- Population based - cultural transfer of information
- Chanting and deep breathing exercises of Buddhist monks, and high altitude Nepalese increase oxygenation and reduce hematocrits.
- Use of Coca

Acclimatization – phenotypic plasticity

- These occur within a life span – pulmonary, cerebral, hematologic and renal changes with altitude.



Develomental

- Studies of Migrants
- Short stature
- Increased AP diameter
- Increased Lung capacity
- Increased maximal exercise capacity?



Genetic adaptation

- the slowest to occur
 - mutation
 - natural selection
 - evolution

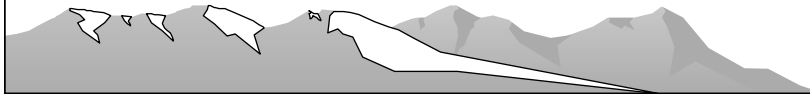


Andes



Andeans

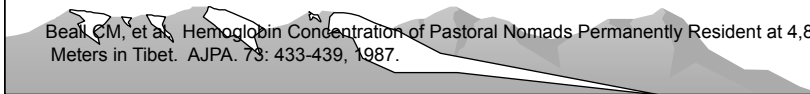
- Andean and Tibetan plateaus rise 13,000 feet above sea level
- Andeans adapted by developing an ability to carry more oxygen
- Breathe at the same rate as people living at sea level
- Ability to deliver oxygen throughout their bodies more effectively

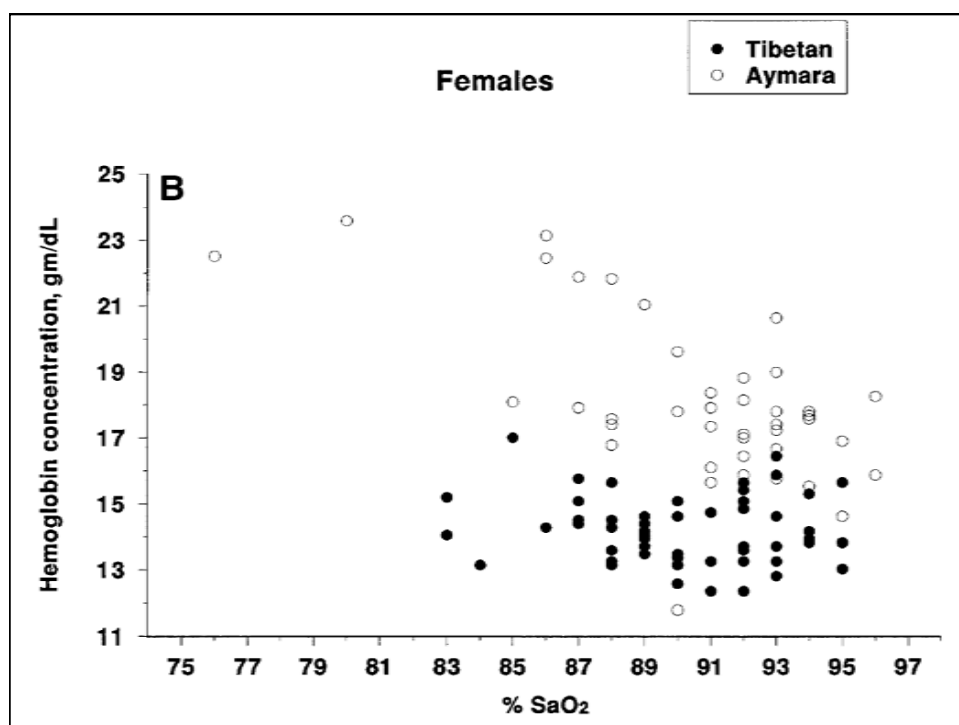
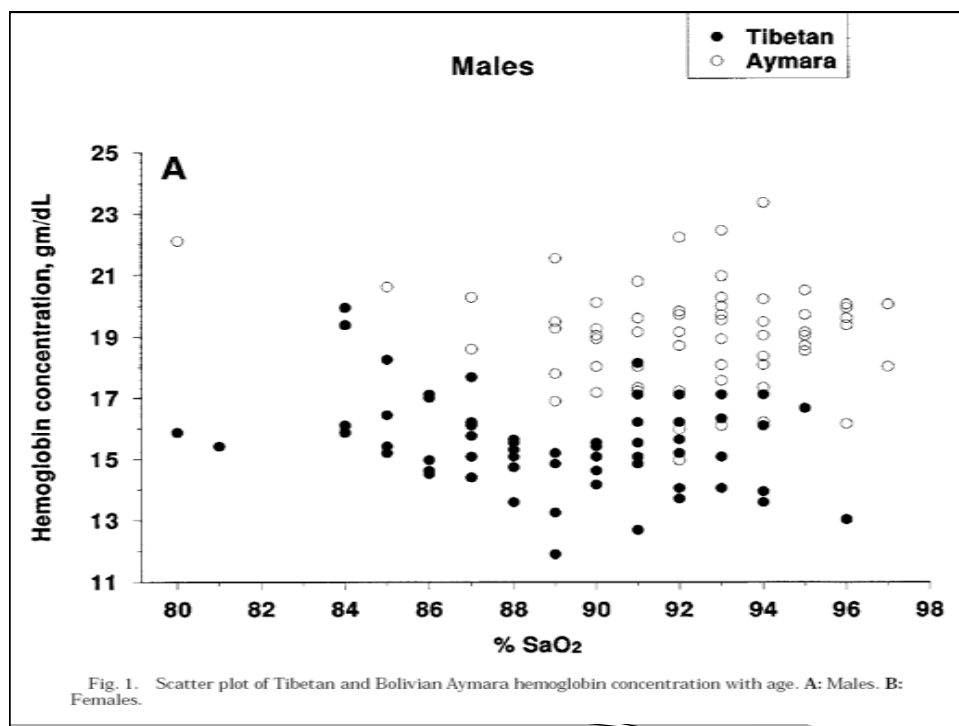


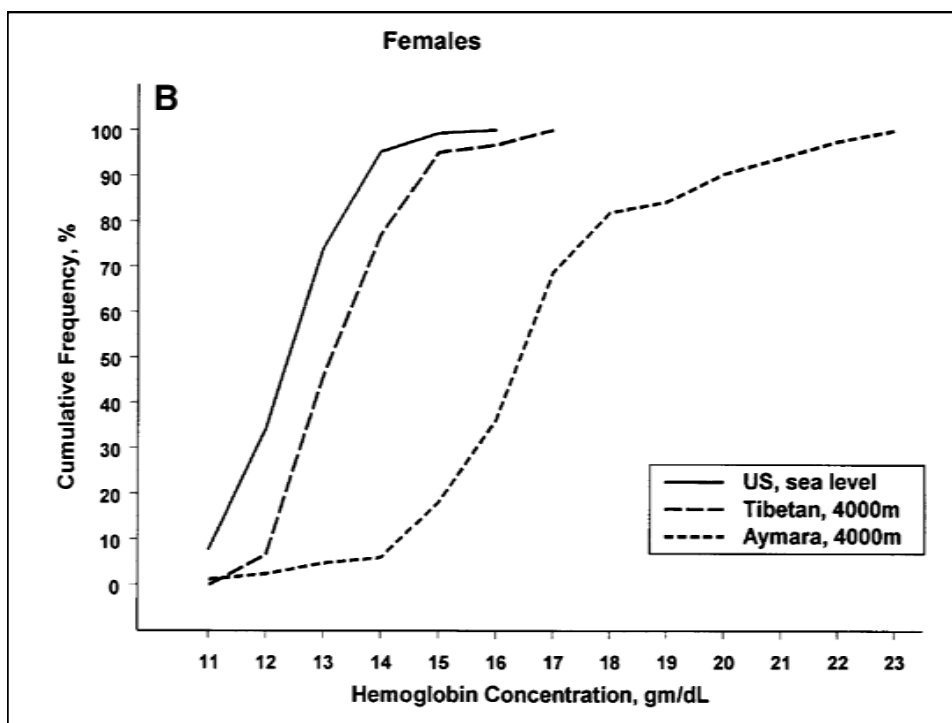
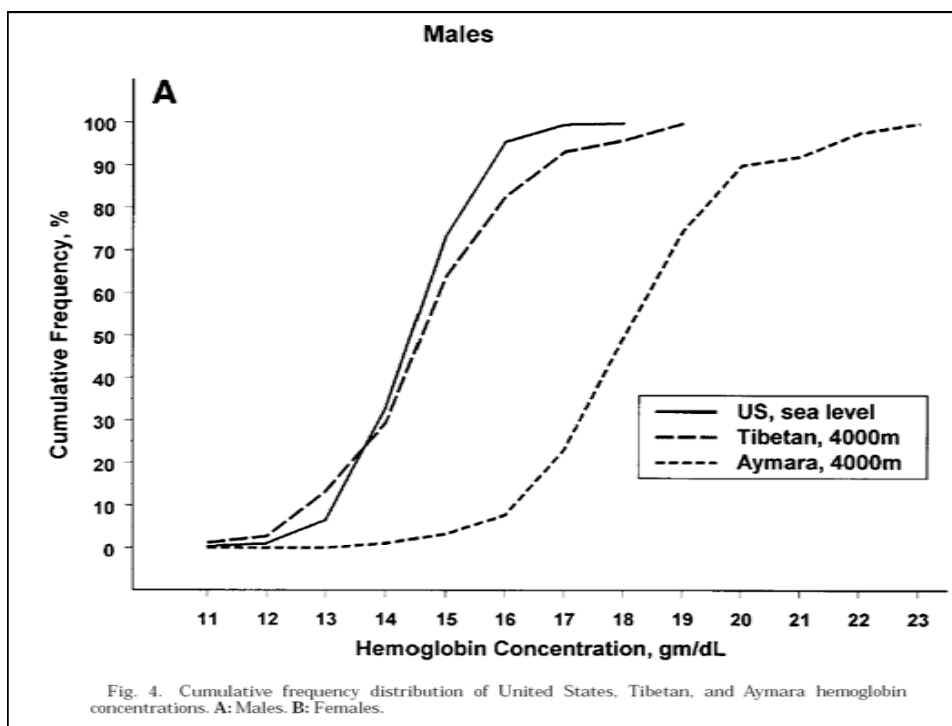
Hemoglobin levels

- Altitude 4850 to 5450 meters
- 136 male and female Tibetans
- 174 male and female Aymara from Bolivia
- Mean hemoglobin concentrations that were 3.5–3.6 gm/dl higher in Bolivians than in Tibetans

Beall CM, et al. Hemoglobin Concentration of Pastoral Nomads Permanently Resident at 4,850-5,450 Meters in Tibet. AJPA. 73: 433-439, 1987.







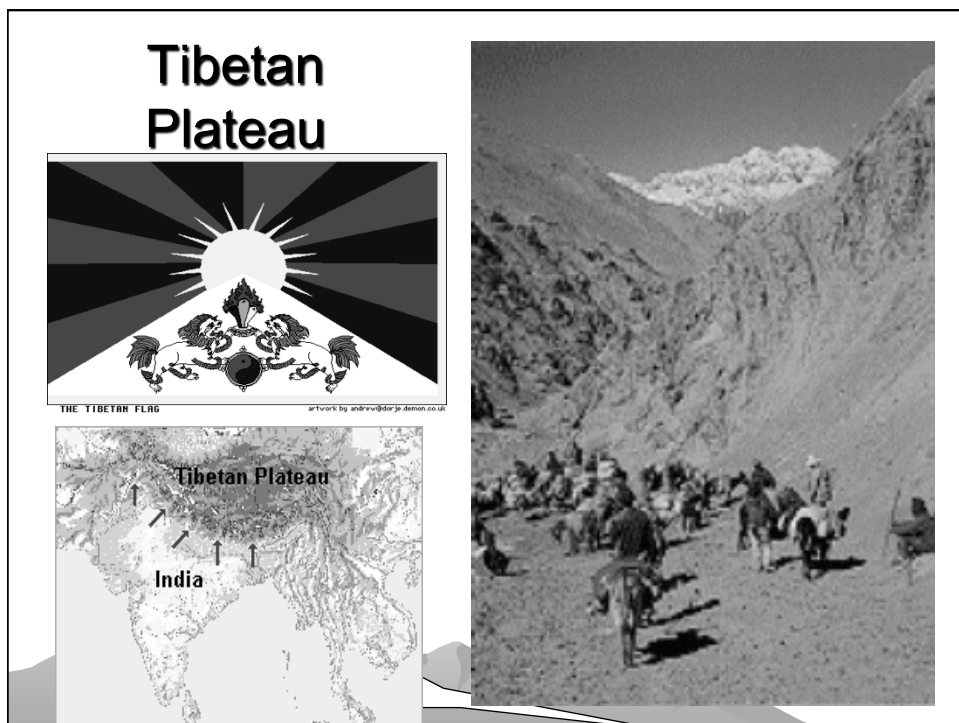
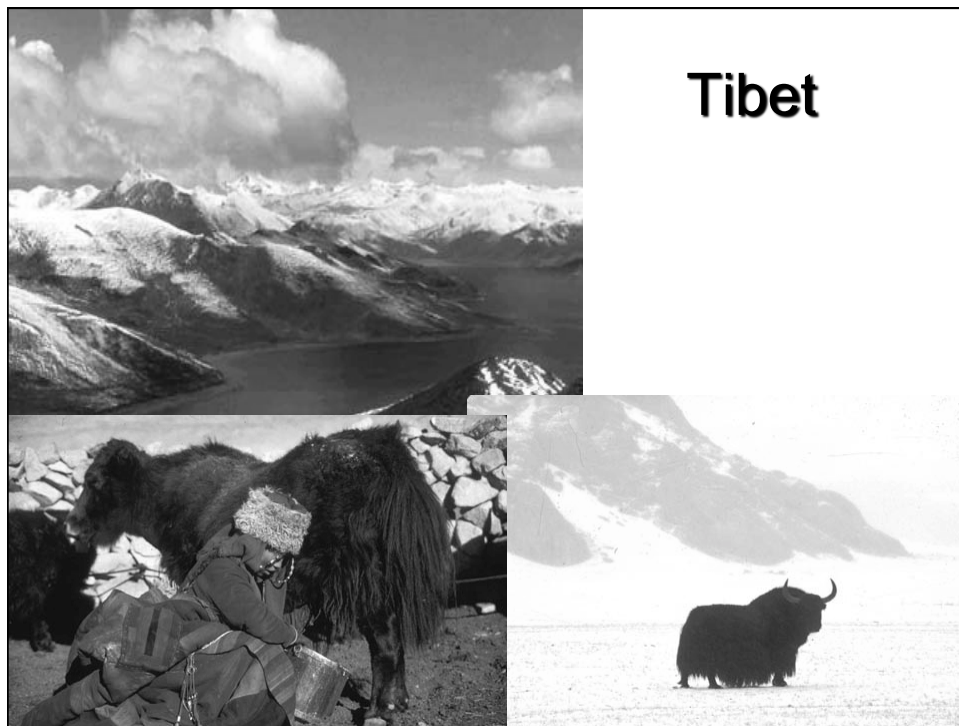
Andean genetics

- evidence for genetic adaptation in Andean highlanders (increased Hemoglobin)
- characteristics are expressed together with environment-dependent factors

Rupert JL, et al. The evidence for hereditary factors contributing to high altitude adaptation in Andean natives: a review. High Alt Med Biol. 2001 Summer;2(2):235-56.

Nothing is free

- Monge's Disease:
- Symptoms are seen as an overly exuberant protective mechanism.
- The red blood cell count: astronomically high.
- Arterial blood pressure is twice normal value
- Hemorrhages under the fingernails
- both ventricles dilate.
- Cyanosis.
- Does extreme adaptation have a price?



Tibetans

- Over 90% of the population are farmers and herders
- The upper altitude limit of crops is around 4500 m
- Nomads reside above 4800 m
- Recently, mines employ people living permanently at altitudes between 3700 and 6000 m

Wu, K. The Qinghai-Tibetan plateau: how high do Tibetans live? High Alt Med Biol. 2001 Winter;2(4):489-99.

Tibetans

- Tibetans compensate for low oxygen content much differently
- They increase their oxygen intake by taking more breaths per minute than people who live at sea level



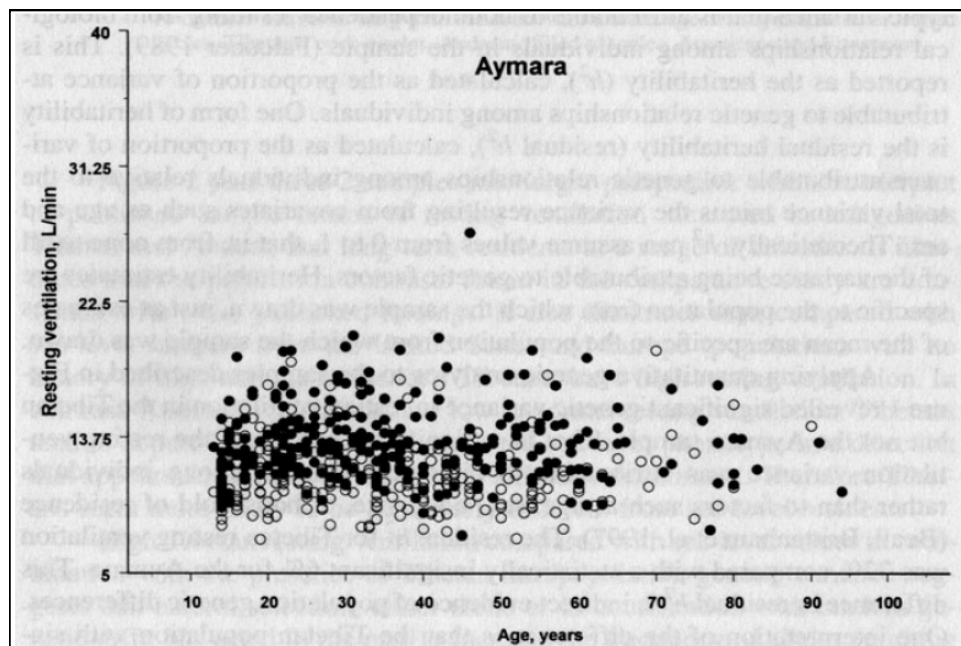
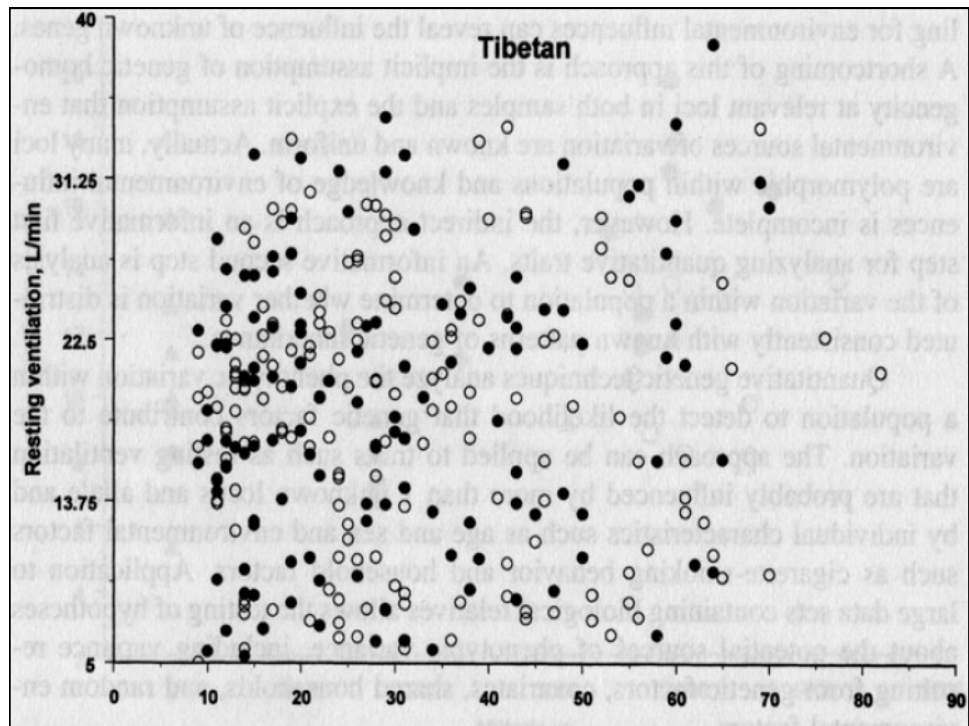


Figure 1. Scatterplot of resting ventilation with age comparing Tibetan and Aymara high-altitude natives at a median altitude of 4,000 m. Filled circles, males; open circles, females.

Ventilatory Response

- Comparison of resting ventilation and hypoxic ventilatory response (HVR)
- 320 Tibetans 9–82 years of age
- 542 Bolivian Aymara 13–94 years of age
- Native residents at 3,800–4,065 m
- Tibetan resting ventilation was roughly 1.5 times higher & HVR was roughly double that of Andeans.

Beall CM, et al. Ventilation and Hypoxic Ventilatory Response of Tibetan and Aymara High Altitude Natives. *Am J Phys Anthropol* 104:427–447, 1997.

Tibetans

- Second biological adaptation
- Tibetans' lungs synthesize larger amounts of nitric oxide from the air they breathe
- One effect of nitric oxide is to increase the diameter of blood vessels
- Tibetans may offset low oxygen content in their blood with increased blood flow

Nitric Oxide

- Nitric oxide is synthesized in the lungs to help regulate blood flow
- Its levels have been found to drop in species native to low altitudes
- Exhalation of nitric oxide by Tibetans living at 4,200 m and of Bolivian Aymara at 3,900 m is increased compared with a low-altitude reference sample from the US

Beall CM, et al. Nitric Oxide in Mountain Dwellers. *Nature*. 414: 411-412, 2001.

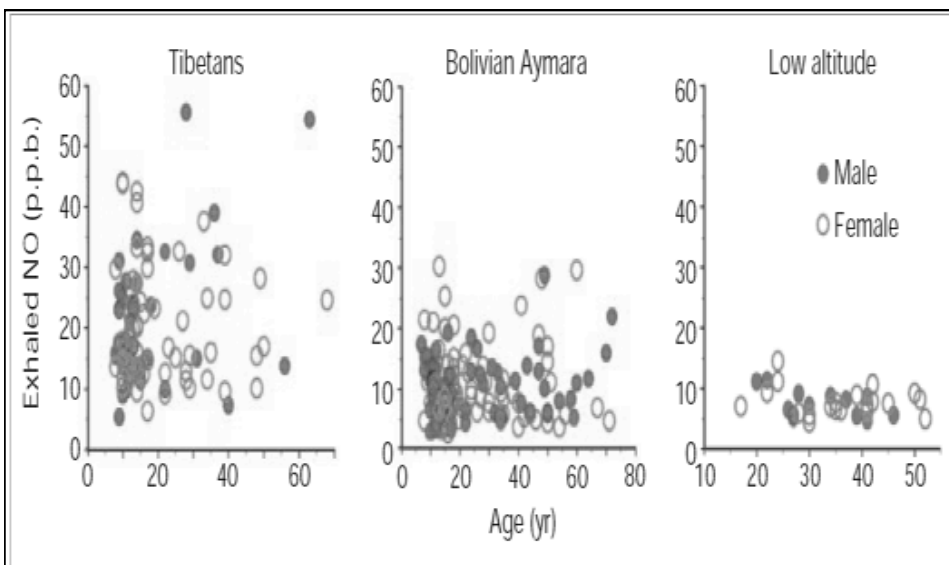
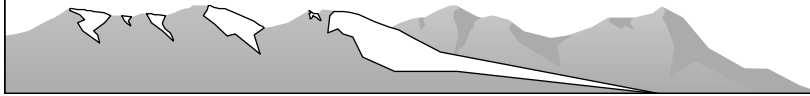


Figure 2 A Tibetan population living at 4,200 m, a Bolivian Aymara population at 3,900 m and a low-altitude population in the United States differ significantly in their mean concentrations of exhaled nitric oxide (NO; ANOVA, $F=77.9$, d.f. = 2, $P<0.05$); no sex or age differences are evident in the results. Details of methods are available from the authors.

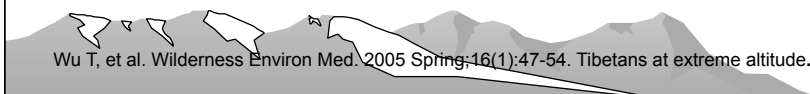
Nitric Oxide

- Increased exhalation of NO is thought to be due to increased synthesis in the lungs
- Similar response in two distant high-altitude locations suggests adaptive function.
- Increasing the concentration of nitric oxide in the lungs may represent a means of offsetting hypoxia



Tibetans

- Between 1960 and 2003, 13 Chinese expeditions reached the summit of Everest
- 45 of the 80 summiteers were Tibetan highlanders
- Medical and physiological investigations were carried out on the Tibetan mountaineers compared to Han (ethnic Chinese from lowland)
- Determined that at altitude, Tibetans have a greater physical capacity than Han



Wu T, et al. Wilderness Environ Med. 2005 Spring;16(1):47-54. Tibetans at extreme altitude.

Tibetan genetics

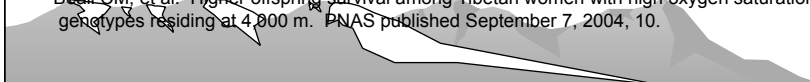
- higher maximal oxygen uptake
- greater ventilation
- more brisk hypoxic ventilatory responses
- larger lung volumes
- greater diffusing capacities
- better quality of sleep
- lower incidence of acute mountain sickness
- less body weight loss



Beall, et al

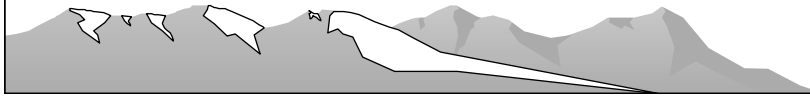
- Tibetans at a given high altitude vary widely in percent oxygen saturation of hemoglobin
- A major gene with an autosomal dominant mode of inheritance is associated with 6% higher oxygen saturation has been detected in two areas of Tibet

Beall CM, et al. Higher offspring survival among Tibetan women with high oxygen saturation genotypes residing at 4,000 m. PNAS published September 7, 2004, 10.



Beall, et al

- Tibetan women with one to two alleles for high oxygen saturation had more surviving children
- These findings suggest that high-altitude hypoxia is acting as an agent of natural selection
- Higher infant survival of Tibetan women with high oxygen saturation genotypes



Beall cont.

- Children of Tibetan women with blood-oxygen concentrations 10% higher than normal are significantly more likely to reach reproductive age themselves
- Selection for a "high-oxygen gene" resulting in a better adaptation to high altitude



Tibetan babies

- In Lhasa, Tibet, newborns had higher arterial oxygen saturation at birth and during the first four months of life than Han newborns
- Another genetic adaptation that permits adequate oxygenation

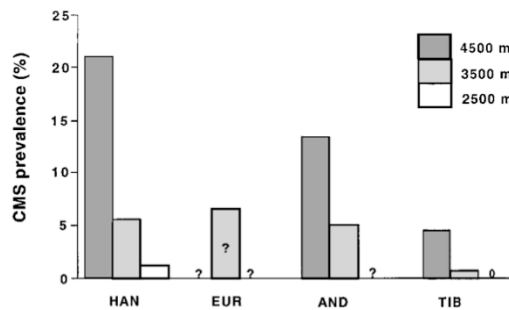
Niermeyer, et al. Arterial Oxygen Saturation in Tibetan and Han Infants born in Lhasa, Tibet. N Engl J Med 1995;333:1248-52.

Tibetans

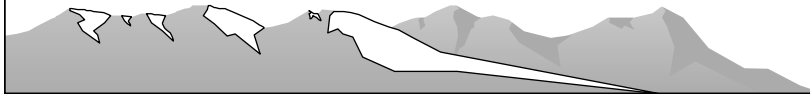
- Compared with acclimatized newcomers, lifelong residents of the Andes and/or Himalayas have
 - less intrauterine growth retardation
 - better neonatal oxygenation
 - more complete neonatal cardiopulmonary transition
 - enlarged lung volumes
 - decreased alveolar-arterial oxygen diffusion gradients
 - higher maximal exercise capacity

Moore, L.G., et al. Human adaptation to high altitude: regional and life-cycle perspectives. Am J Phys Anthropol. 1998;Suppl 27:25-64

chronic mountain sickness



- CMS = Excessive Polycythemia
- CMS never reported in Ethiopians!



Tradeoffs

- The increased Hgb levels of Andeans put them at highest risk for CMS
- What is the tradeoff for the Tibetans?
- Increased respiratory rate
- Less pulmonary reserve
- Less ability to compensate for acid-base changes (respiratory alkalosis).



Tibetan lowlanders

- Study by Marconi, et al found that second generation Tibetan lowlanders acclimatize to chronic hypoxia more quickly than Caucasians
- Looked at VO₂ maxes
- Another finding that shows Tibetans have genetically adapted to high altitude

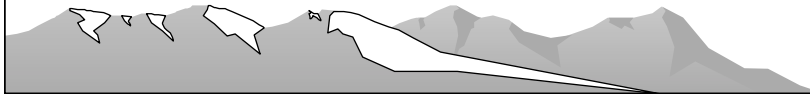


Ethiopia



Ethiopians

- Ethiopian highlanders living at 3,530 meters (11,580 feet)
- Unlike Tibetans- they don't breathe more rapidly and aren't able to more effectively synthesize nitric oxide
- Unlike the Andeans- they don't have higher hemoglobin counts



Beall, et al

- 236 Ethiopian native residents at 3,530 m (11,650 feet)
- Ages 14–86, without iron deficiency, hemoglobinopathy, or chronic inflammation
- Average hgb of 15.9 and 15.0 gdl for males and females, respectively
- Average O₂ sat of 95.3%

Beall CM, et al. An Ethiopian pattern of Human Adaptation to High-Altitude Hypoxia. www.pnas.org/cgi/doi/10.1073/pnas.252649199

Ethiopians

- Despite living at elevations with low oxygen content, the Ethiopian highlanders are not hypoxic
- Maintain Hgb concentrations and arterial oxygen saturation within the ranges of sea level populations
- Genetic adaptation is unclear



Ethiopians and Hypoxia

- Lowlanders exhibit vasodilatation to cerebral hypoxia
- This effect is obliterated by vasoconstriction from hypocapnia.
- Ethiopians lack cerebral response to low O₂.
- Ethiopians do not hyperventilate at altitude - preserves cerebral blood flow.



Table 1. Three patterns of adaptation to high-altitude hypoxia are identified by comparing the presence (+) or absence (–) of erythrocytosis and arterial hypoxemia

	Partial pressure of inspired oxygen, % of sea level	Erythrocytosis	Arterial hypoxemia
Sea level	100	–	–
Ethiopian	64	–	–
Tibetan	60	–	+
Andean	60	+	+

Data were obtained by using the mean values of hemoglobin concentration and oxygen saturation of hemoglobin of sea level populations as a point of reference, published values from Andean and Tibetan high-altitude populations at 4,000 m (12, 17, 18), and the present Ethiopian sample.

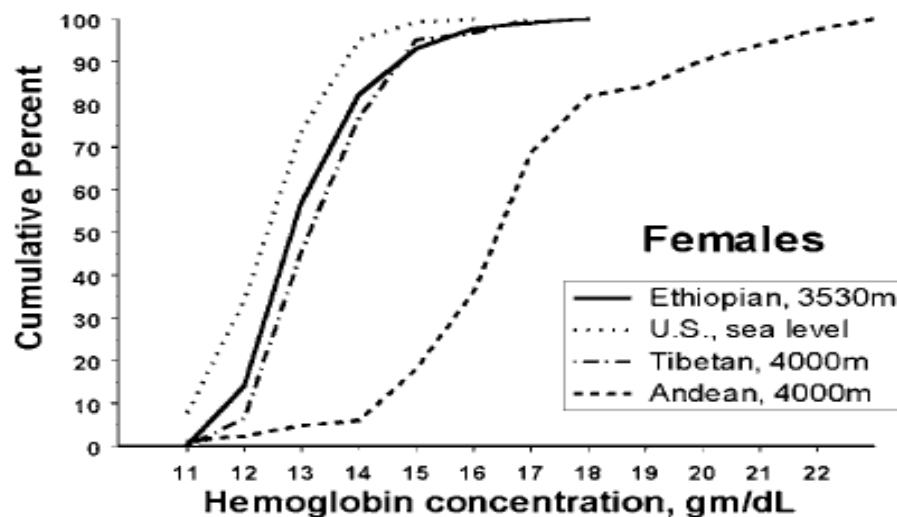
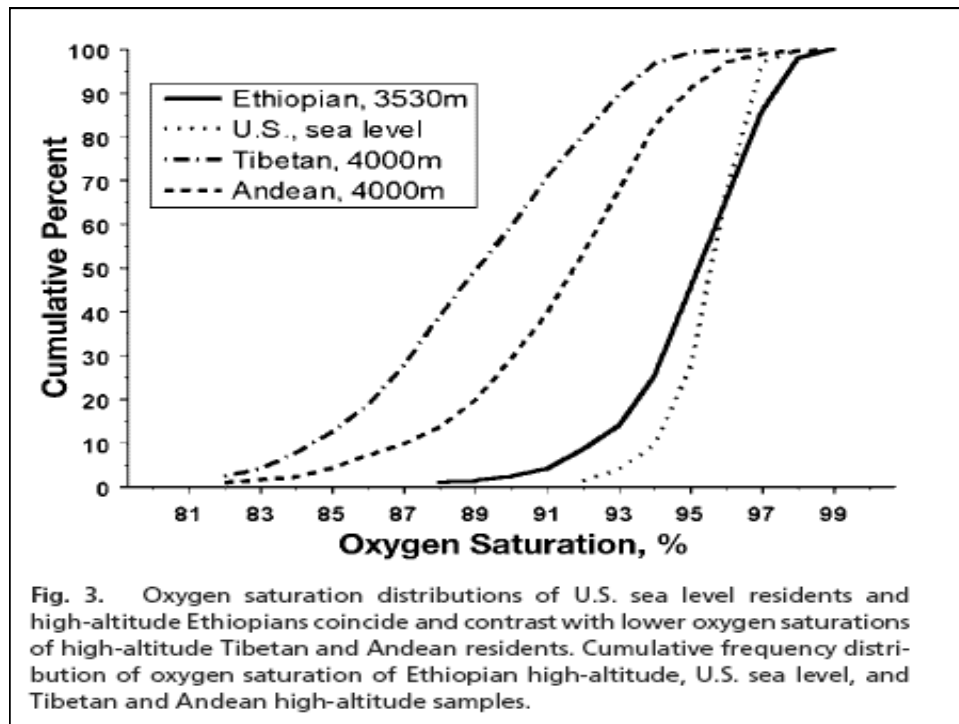


Fig. 2. Hemoglobin concentration distributions of U.S. sea level and Ethiopian and Tibetan high-altitude females coincide and contrast with the higher hemoglobin concentrations of Andean females. Shown is the cumulative frequency distribution of hemoglobin concentration of Ethiopian high-altitude, U.S. sea level, and Tibetan and Andean high-altitude females.



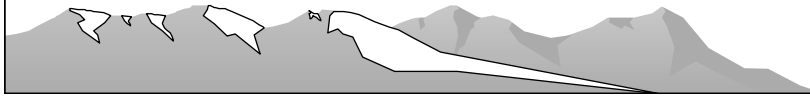
Live longer?

- Mixed reviews on if people at altitude live longer
- High altitude doesn't seem to increase or decrease life expectancy
- Reproduction is currency of natural selection. Effect in infancy or on reproduction



How they adapted

- Physiologically/Genetically
 - Andeans increased Hgb levels
 - Tibetans increased ventilatory rate and nitric oxide production
 - Ethiopians have adapted well, but exact mechanism is unknown.



References

- Mavell, H. Three High-Altitude Peoples, Three Adaptations to Thin Air. National Geographic News. Feb 25, 2004
- Beall CM, et al. Hemoglobin Concentration of Pastoral Nomads Permanently Resident at 4,850-5,450 Meters in Tibet. AJPA. 73: 433-439, 1987.
- Rupert JL, et al. The evidence for hereditary factors contributing to high altitude adaptation in Andean natives: a review. High Alt Med Biol. 2001 Summer;2(2):235-56.
- Wu T. The Qinghai-Tibetan plateau: how high do Tibetans live? High Alt Med Biol. 2001 Winter;2(4):489-99
- Beall CM, et al. Ventilation and Hypoxic Ventilatory Response of Tibetan and Aymara High Altitude Natives. Am J Phys Anthropol 104:427-447, 1997.
- Beall CM, et al. Nitric Oxide in Mountain Dwellers. Nature. 414: 411-412, 2001
- Wu T, et al. Wilderness Environ Med. 2005 Spring;16(1):47-54. Tibetans at extreme altitude.
- Beall CM, et al. Higher offspring survival among Tibetan women with high oxygen saturation genotypes residing at 4,000 m. PNAS published September 7, 2004, 10.
- Niermeyer, et al. Arterial Oxygen Saturation in Tibetan and Han Infants born in Lhasa, Tibet. N Engl J Med 1995;333:1248-52.
- Moore LG, et al. Human adaptation to high altitude: regional and life-cycle perspectives. Am J Phys Anthropol. 1998;Suppl 27:25-64
- Marconi C, et al. Second Generation Tibetan Lowlanders Acclimatize to High Altitude More Quickly than Caucasians. J Physiology 556.2 (2004) 661-671.
- Beall CM, et al. An Ethiopian pattern of Human Adaptation to High-Altitude Hypoxia. www.pnas.org/cgi/doi/10.1073/pnas.252649199

