Humans have lived at altitude for thousands of years. Sea level natives suffer from altitude sickness when traveling to high places. High altitude dwellers are better equipped to deal with thin air. How is this possible?
• The 3 major cultures that live at high altitude and have been well studied
  – Tibetan plateau
  – Andean Altiplano
  – Ethiopian highlands

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

Acclimatization – phenotypic plasticity

- 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

Fig. 1. Scatter plot of Tibetan and Bolivian Aymara hemoglobin concentration with age. A: Males. B: Females.
Fig. 4. Cumulative frequency distribution of United States, Tibetan, and Aymara hemoglobin concentrations. A: Males. B: Females.
Andean genetics

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


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


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.
**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.


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**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


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

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, 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.


**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

• 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%

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

<table>
<thead>
<tr>
<th>Partial pressure of inspired oxygen, % of sea level</th>
<th>Erythrocytosis</th>
<th>Arterial hypoxemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sea level</td>
<td>100</td>
<td>−</td>
</tr>
<tr>
<td>Ethiopian</td>
<td>64</td>
<td>−</td>
</tr>
<tr>
<td>Tibetan</td>
<td>60</td>
<td>−</td>
</tr>
<tr>
<td>Andean</td>
<td>60</td>
<td>+</td>
</tr>
</tbody>
</table>

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 may result in decreased 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