NOTE: All quoted texts are from Storz and Moriyama. (2008). Mechanisms of Hemoglobin Adaption to High Altitude Hypoxia. *High Altitude Medicine & Biology 9*: 148-157.

> "One of the most celebrated case studies of high altitude adaptation involves a pair of distantly related waterfowl species, the bar-headed goose (*Anser indicus*) and the Andean goose (*Chloephaga melanoptera*), that have independently evolved exceptionally high Hb–O_2 affinities. The bar-headed goose spends the breeding season on high alpine lakes at 4000 to 6000 m on the Tibetan Plateau and spends the winter months in wetland habitats in different parts of the Indian subcontinent. This requires an annual round-trip migratory flight over the crest of the Himalaya at altitudes of nearly 10,000 m where ambient PO_2 is less than one-third of that at sea level. As might be expected for an animal capable of sustaining powered flight at such altitudes, the bar-headed goose is characterized by an exceptionally high Hb–O_2 affinity relative to its lowland sibling species, the greylag goose (*Anser anser*; P_{50}, the PO_2 at 50% saturation of Hb 29.7 vs. 39.5 torr at 37°C, pH 7.4). The observed difference in P_{50} is attributable to a small difference in the intrinsic Hb–O_2 affinity…"

1. **Draw a single graph of theta vs. PO_2 (torr = mmHg), which contains expected oxygen binding curves to (*i*) bar-headed goose hemoglobin and (*ii*) graylag goose hemoglobin.**

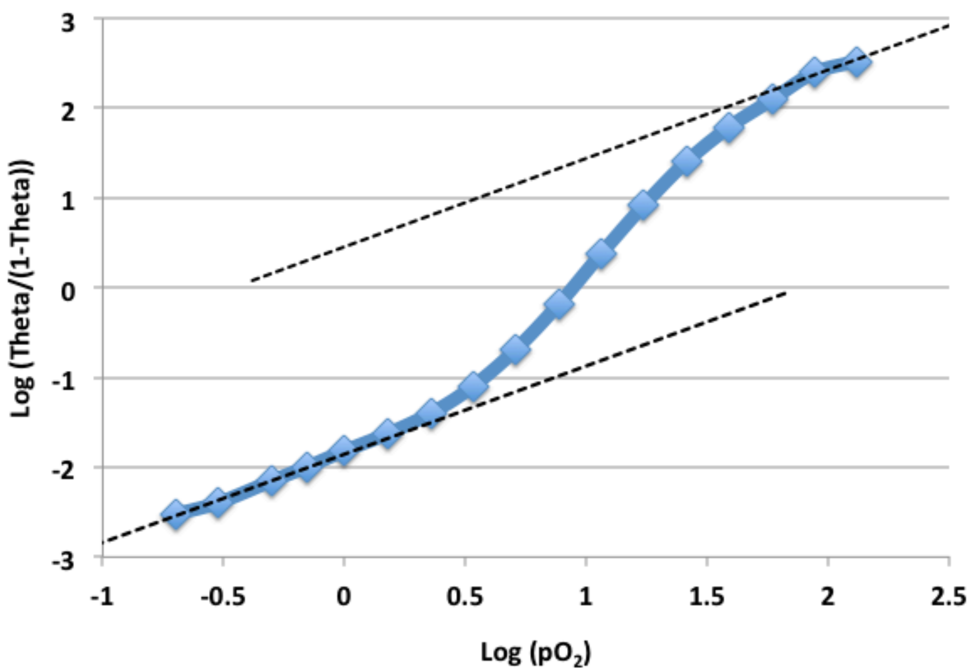
2. **The difference between the oxygen affinities of the hemoglobins of these geese "is attributable to a small difference in the intrinsic Hb-O_2 affinity". If only the intrinsic affinity of oxygen is different between the geese hemoglobins, fill in each blank with "<", ">", or "=" for the parameters of the MWC model. [NOTE: K_{site} parameters are association equilibrium constants.]**

$$K_{site}^{T}(bar-headed)\_\_\_\_K_{site}^{T}(graylag)$$

$$K_{site}^{R}(bar-headed)\_\_\_\_K_{site}^{R}(graylag)$$

$$K_{o}^{T\rightarrow R}(bar-headed)\_\_\_\_K_{o}^{T\rightarrow R}(graylag)$$

Imagine that the curve on the Hill plot below is for the bar-headed goose hemoglobin. Using the relative values of the parameters of the MWC that you indicated above, add a curve for the graylag goose hemoglobin.



"In principle, substitutions at any one of these [DPG] binding sites can alter the sensitivity of Hb to the various allosteric effectors [i.e., DPG], thereby altering the equilibrium between the T- and R-state quaternary structures. Since the binding of allosteric effectors [i.e., DPG] typically stabilizes T-state deoxyHb, amino acid substitutions that inhibit effector binding will typically increase Hb–O_2 affinity by shifting the equilibrium in favor of R-state oxyHb."

"The relatively high Hb–O_2 affinity of Andean camelids (i.e., llama, vicuña, alpaca, and guanaco) is attributable to a His→Asn substitution that eliminates two of the seven DPG-binding sites per tetramer."

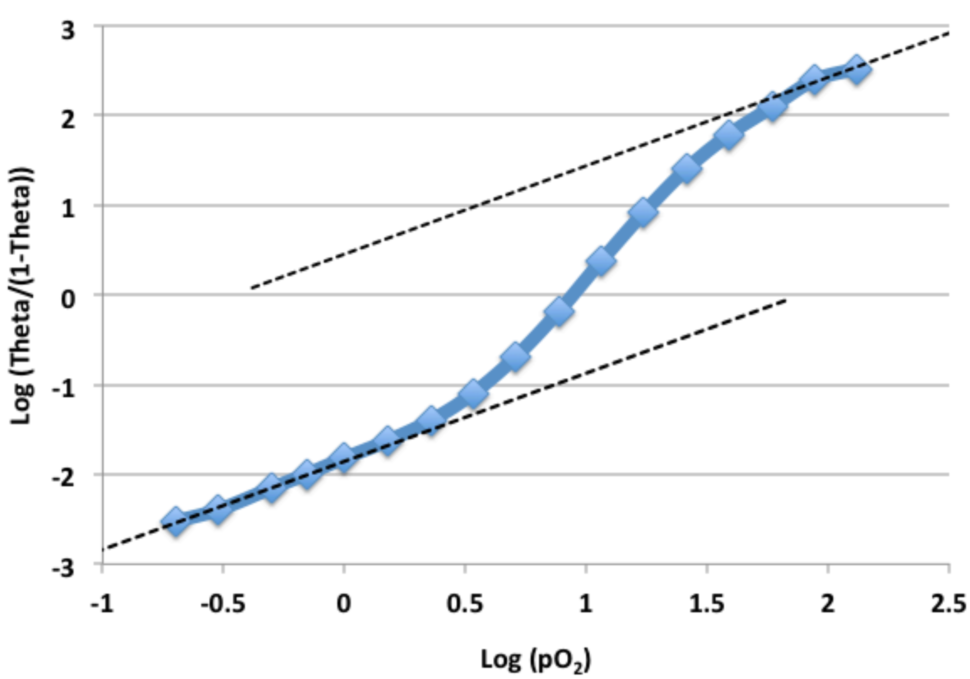
"The suppression of DPG binding that accounts for the high Hb–O_2 affinity of Andean camelids also accounts for the high O_2-binding affinity of human fetal Hb (HbF). The γ-chain subunits of HbF are encoded by the γ-globin gene, which is distinguished from the adult β-globin gene by the substitution His→Ser at key DPG-binding sites. The increased affinity of HbF relative to adult Hb is advantageous, because it facilitates placental O_2 transfer from the maternal circulation to the fetal circulation."

3. **Draw a single graph of theta vs. PO_2, which contains expected oxygen binding curves to (*i*) adult hemoglobin and (*ii*) fetal hemoglobin.**

4. **Fill in each blank with "<", ">", or "=" for the parameters of the MWC model. [NOTE: K_{site} parameters are association equilibrium constants.]**

$$K^{T}_{site}(adult)\_\_\_\_ K^{T}_{site}(fetal)$$
$$K^{R}_{site}(adult)\_\_\_\_ K^{R}_{site}(fetal)$$
$$K^{T\to R}_{o}(adult)\_\_\_\_ K^{T\to R}_{o}(fetal)$$

Imagine that the curve on the Hill plot below is for adult hemoglobin. Using the relative values of the parameters of the MWC that you indicated above, add a curve for fetal hemoglobin.



5. Fill in each blank with "<", ">", or "=" to compare the dissociation equilibrium binding constant (K_D) of the hemoglobin effector molecule DPG:

$$K_D^{DPG}(non-Andean\ camelid)\_\_\_\_K_D^{DPG}(Andean\ camelid)$$
$$K_D^{DPG}(adult)\_\_\_\_K_D^{DPG}(fetal)$$

The chemical structure of DPG is below. Explain the molecular basis for the observation that the His→Asn and His→Ser found in Andean camelids and fetal hemoglobins, respectively, suppresses DPG binding.