

“So Mortal and So Strange a Pang”: A Tribute to Paul T. Baker

Is the high life a matter of adaptability or adaptation?

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An important aspect of human biology is our ability to acclimatize to essentially every environment on earth: our adaptability. A second aspect is evolutionary, how we got the ability to do that: our adaptation. Both adaptability and adaptation have a genetic component, in the first case concerning the genetic mechanisms that enable people to respond to different environmental conditions and, in the latter, the evolution of those mechanisms. The two seem to be related, but are the genes the same, and how can we tell?

One model system for understanding both adaptability and adaptation in the present as well as the evolutionary past may be life in the hypoxic (low-oxygen) environment of high altitude, because if you live up high, you can't escape the stresses posed by the lower partial pressure of oxygen. Beginning in the early 1960s, one of the homes of high-altitude research was the Department of Anthropology at Penn State, where Paul Baker (Fig. 1), his colleagues, and their students traveled the high road of human-adaptability research for many years.^{1–3} In the 1980s, Paul's colleagues, students, and grandstudents made 10% or more of all presenta-



Figure 1. Paul T. Baker, founder of a breathless legacy.

tions at annual meetings of the American Association of Physical Anthropology. Other prominent research groups have also been working on this problem, of course, but now, after a considerable hiatus, there is renewed research in this area here at Penn State. Consequently, we thought it would not be too parochial to discuss recent scientific advances in the context of honoring the Baker legacy.

Paul's academic descendants continue to conjure understanding out of thin air, but since his time the research atmosphere has changed. Major advances in technology, espe-

cially in molecular biology and genetics, have shifted the focus from phenomenology to mechanism and made it possible to be much more genetically specific about both adaptability and adaptation. But the new approaches also force us to confront the challenge of understanding the difference between them.

“THE AYRE. . . SO SUBTILE AND DELICATE”

People may have first wandered to high altitude in the Andes, Hima-

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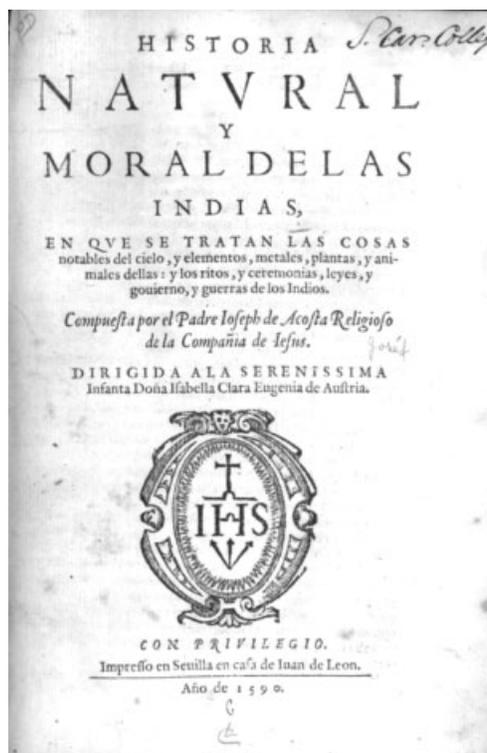


Figure 2. Adapting and adapted. Cover of Joseph de Acosta's book,⁵ courtesy of the University of South Carolina special collections library.

layas, and the Semien Moutains of Ethiopia, in search of game or plant food. How high they climbed, and how fast, before they settled there is unknown, but for the two high-altitude regions we will focus on, permanent habitation in the Andean altiplano dates back about 10,000 years, and in Tibet perhaps 25,000.⁴

One of the early Jesuit missionaries who traveled to the Peruvian Andes was Joseph de Acosta. He was the first European known to describe, in 1590, what has become known as Acosta's syndrome, *soroche*, or mountain sickness (Fig. 2).⁶ What he called "so mortal and so strange a pang" is the result of suddenly moving to the hypoxic environment at high altitude. He correctly intuited that people require "a more gross and temperate ayre." He noted that the populations native to the Andes don't suffer those symptoms and that in others the symptoms usually go away after a few days.

Acosta's writing forms the symbolic cornerstone for European science's historical interest in this

problem. But it's probably false. Based on the altitude where Acosta resided at the time, as well as his symptoms, it is likely that he was suffering mainly from gastroenteritis.⁷ But perhaps because his whole entourage was suffering, de Acosta had a good insight. However, its less-than-critical repetition over several centuries shows the willingness of science to accept, too readily, ideas that we are predisposed to accept.

"ON PASSING THE GREAT HEADACHE MOUNTAIN"

The first comparable writing regarding the Himalayas comes from the Chinese classic *Ch'ien Han Shu*, which documents the history of the Han Chinese from 206 B.C.E. to 25 C.E. This encyclopedic work was started by Ban Biao (3–54 C.E.), then finished by his son Ban Gu (32–92 C.E.) and daughter Ban Zhao (35–100 C.E.). In Book 96 of the series, Ban Gu describes an envoy to China from Ke-pin (present-day Afghani-

stan) who wished to secure an escort for the return trip through Hindu Kush.

This escort was not granted because of the area's rough terrain. The author goes on to say that "on passing the Great Headache Mountain, the Little Headache Mountain, the Red Land and the Fever Slope, men's bodies become feverish, they lose colour, and are attacked with headache and vomiting."⁸ This description of mountain sickness is more accurate than Acosta's. It also indicates that the Chinese were circumspect about traveling through the Himalayas for fear of altitude sickness.

Interest by European scientists in high-altitude physiology began in the latter half of the nineteenth century. The early work conducted in highland Mexico and Andean Peru posited the rather racist idea that people at high altitude were inferior to their counterparts at lower elevations. After his expedition to the Andes, the prominent Cambridge physiologist John Barcroft opined that, "all dwellers at high altitude are persons of impaired physical and mental powers." Considering the huffing and puffing the advanced Europeans had to do to keep up with the barbarians, this seems at least a bit presumptuous.

A Peruvian school of high-altitude biology was partly a response to early European observations of indigenous high-altitude groups and focused on adaptability. The father of Peruvian high-altitude biology, Carlos Monge Medrano, was a physician and physiologist, author of a classic book on the subject, *La Enfermedad de los Andes*,⁹ and best known for his work on *chronic* mountain sickness, which can affect native and immigrant alike. His scientific interest was largely clinical, but he laid the foundation for later adaptability studies by other Peruvian researchers, including his son, Carlos Monge Casinelli, and Alberto Hurtado. Over the years, Peruvian scientists examined many aspects of disease, as well as normal growth and development in peoples at high altitude, though by no means could all of these diseases be attributed to high altitude *per se*.

Early work in the United States on high altitude focused on identifying

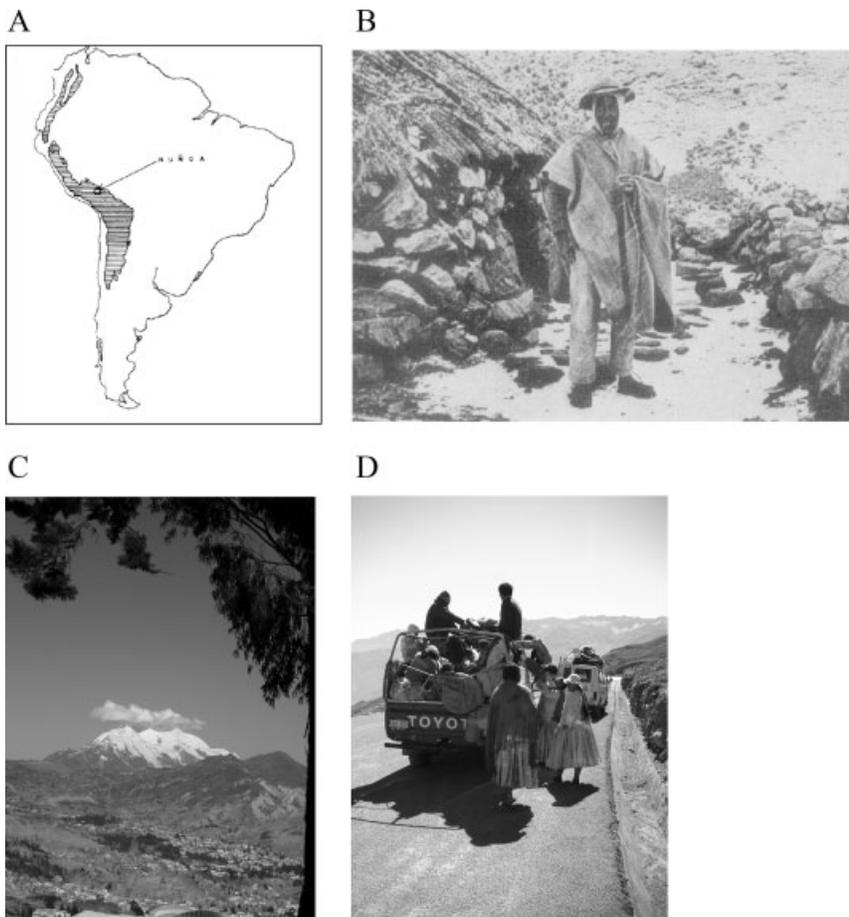


Figure 3. Up there, then and now. A: The Baker site in Nuñoa, at 2,500 M. B: A Nuñoan Quechuan weathers the storm. C: The peak of Illamini over the valley of La Paz D: Bolivian Aymara on the road to Sorata. Sources: A,B: Baker archives; C, D: photos by Abby Bigham.

the adaptive significance of the morphological and physiological differences observed in long-term residents of the altiplano, such as the Quechua of Peru and the Aymara of Bolivia, as compared to lowland populations. Much of this work was sponsored as part of the International Biological Programme (IBP; 1964–1974), a research consortium that addressed a variety of biological problems and was analogous to the International Geophysical Year in 1957–1958. Paul Baker was a leader of the Human Adaptability component of the IBP, which he and his students undertook by a large-scale, long-term study of the Nuñoan Quechuans in Peru (Fig. 3A,B).^{1,2,3}

As Baker pointed out in the introduction to *Man in the Andes*,² the Nuñoa project was directed at overcoming the shortfalls of the early Pe-

ruvian research conducted by Monge and Hurtado. One of Baker's main concerns was that Peruvian research had been based on the assumption that the physiological differences observed among high-altitude populations were the result of acclimatization, not adaptation. Baker and his contemporaries therefore started out with the “modern synthesis” as the foundation; that is, the idea that adaptation, not just adaptability, was involved.

Over many years they collected data on a large number of physical and metabolic processes involving many different biological pathways (Fig. 4). These included anthropometric measures, assessments of growth and development, gestational outcomes, and measures of oxygen use and ventilation capacity, blood oxygen and hemoglobin levels, physi-

cal performance ability, and efficiency. Baker's students and others have done extensive work among Tibetans as well.¹⁰ Comparative results show that although both populations have higher lung capacities than do corresponding lowlanders, they live at high altitude in physiologically different ways. No one of these traits, by itself, seems to predominate in the high-altitude response in either population.

Although understanding adaptation was the desired goal, this work has performed mainly been phenomenological. It shows adaptability to low oxygen levels, but reports vary among investigators and traits as to whether there has been adaptation. In some reports, lowland migrants to high altitude never reach the same physiological states as those of the natives no matter how long they live at high altitude.¹⁰ In the Andes, people with Andean ancestry have larger birth-weight babies and less intrauterine growth restriction than do Europeans, which could lead to greater infant survival.¹¹ But in other reports, Europeans and lowland Native Americans seem to acclimatize fully to high Andean altitude after long periods of exposure.^{2,3} Some reports say the same about Han Chinese relative to their Tibetan highlanders.^{12–14}

Baker, as well as others working with the Chilean Aymara,¹⁵ was interested in genetics, but the available tools provided no way to distinguish between variation associated with adaptability and selective adaptation. Genetic data at the time were basically confined to a small number of protein variants, like blood groups, mostly with no plausible relevance to high-altitude physiology, usually with only two alleles (genetic variant states) that could be detected. Such data could show general levels of genetic variability and patterns of population similarity, such as that the highlanders were not genetically identical to South American lowlanders. However, isolation and genetic drift (chance change in variant frequency from one generation to the next in small populations) could readily account for that.

There was no credible way to relate the observed patterns of variation to

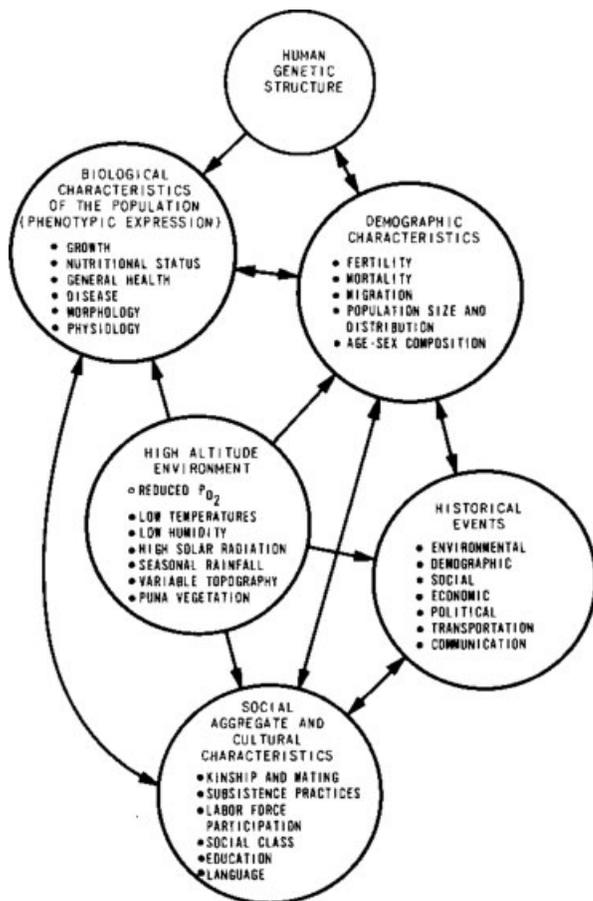


Figure 4. Life up there. Diagram from Baker's study of the Nuñoan Quechua illustrating the complex influences on high-altitude life, including genetic, biological, and cultural factors to be sorted out.²

natural selection. Moreover, matters were made more problematic by the need to take into account the potential effects of Westernization, coca use, and differences in way of life, physical condition, and nutrition, all of which can affect health and physiology and, in turn, impact selection. In addition, possible sources of selective pressure other than hypoxia exist; environmental pressures imposed by life on the altiplano include cold, increased solar radiation, and poor soil, which could lead to malnutrition. Knowing that these stresses exist is, however, the easy part. Understanding how so many variables might affect selection or, indeed, our ability to detect the evidence of selection, is a sobering challenge.

A direct approach to understanding whether genes are involved is to estimate the heritability of variation in altitude-related traits; that is, to parse

out the relative environmental or developmental contribution to a particular altitude phenotype from the genetic contribution. In a series of studies of Aymara from Camacani, Peru, genetic variation was shown to have a significant but moderate effect on several anthropomorphic traits.¹⁶ A family-based study in Tibet found statistical evidence that an unidentified gene controls about 21% of variation in blood oxygen saturation, which affects Darwinian fitness through fertility and infant survival.¹⁰ However, there was no evidence of a genetic component to this in Andeans.¹⁷ Measures of ventilation varied considerably between these populations,¹⁸ but hemoglobin concentration had significant genetic variation in both.¹⁹ As we'll see, such variability within and between groups has a ready evolutionary explanation. But studies that characterize the her-

itable component of variation are unsatisfyingly indirect. They don't identify any particular genes, which leaves room for doubt as to their meaning. And after many thousands of years in Tibet, why is there enough remaining variation at the putative gene for selection to be detectable in a simple family study? While it's nice to confirm that genes play a role, these results only inch a small way toward understanding. The question remains: What *are* the genes?

MODERN GENETICS: ARE THE QUESTIONS OR THEIR ANSWERS SEPARABLE?

Thanks to recent improvements in molecular genetics, research is poised to begin identifying specific genes that are involved in high-altitude adaptability as well as adaptation. Today's genetic studies are also greatly strengthened by advances made by physiologists with respect to oxygen-sensing systems. Genetic pathways involved in oxygen biology, such as the hypoxia inducible factor (HIF) system, have been extensively characterized in recent decades (Fig. 5). This is an ancient system by which cells respond to low oxygen pressure. It clearly was not evolved for high-altitude life *per se*, but is important, for example, during embryogenesis. Cells in growing tissue respond by HIF activation if they are too far from the nearest capillary to receive enough oxygen; this activation stimulates vascular growth. HIF is also active in gametes and gestation, and certainly is a plausible target for fertility and embryogenesis-related selection. However, this system was already in place, so it is not clear what further selective pressure was needed. One possibility is that there is selection for regulatory aspects of the system. We are now able to revisit earlier questions posed by researchers seeking to detect genetic evidence of both adaptability and adaptation in the various physiological systems that have been studied. For example, each gene in a pathway like HIF is a potential candidate for variation that is involved

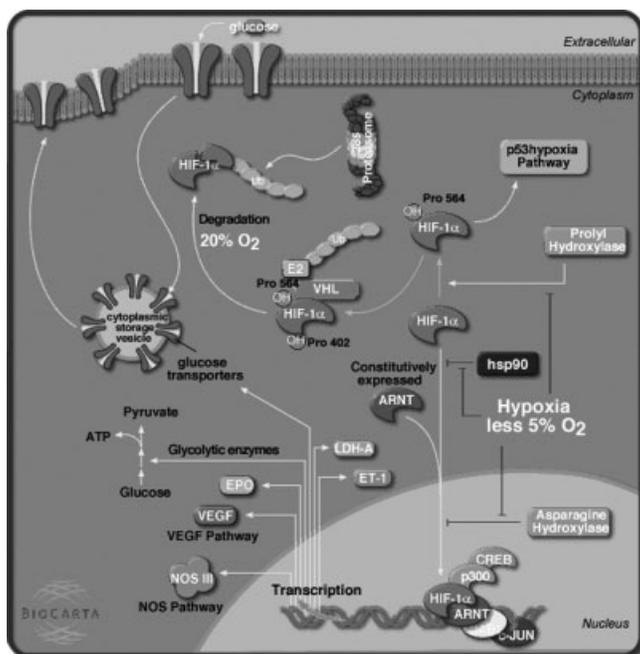


Figure 5. The HIF pathway regulates many of a cell's physiological responses to high-altitude habitation. The different components, from the pores in the cell membrane to gene regulation in the nucleus, are shown. Each factor is coded by a separate gene for which protein or regulatory sequence might vary. Diagram courtesy of <http://www.biocarta.com/>.

in selective adaptation as well as adaptability to hypoxia.

Genes involved in adaptability can be identified in a direct way known as gene mapping. Basically, with polymorphic markers spaced at close intervals across the entire genome, specific markers having variation that is associated with variation in a measured response variable such as oxygen metabolism can be found. The genes in the implicated chromosomal regions are then identified by looking at the human genome sequence and can be tested for their functional basis and for variation that affects the measured trait. Similarly, genes known from physiological studies to be involved in oxygen exchange or metabolism can be sequenced in individuals with different hypoxia responses to see if their coding or regulatory variation is associated with those responses. A recent mapping paper on a small sample of Sherpas found very preliminary evidence of candidate chromosomal regions, though it did not identify specific genes in those regions or genes that could be attributed to adaptation to hypoxia. Sherpas, like any other pop-

ulation, are presumably adapted in all sorts of ways.²⁰

Mapping identifies genes specifically involved in oxygen physiology, showing that variation in these genes affects variation in response. But this contemporary variation of genetics of adaptability does not imply that the same genes have been affected by selection in the past. To identify those genes, a different approach is possible. It involves use of the same kinds of genome-wide genetic markers.

Natural selection leaves distinct signatures in the genome.^{21,22} In positive adaptive selection, if a specific genetic variant is helpful for life at high altitude and if it leads to greater Darwinian fitness (net reproductive success), then that variant will increase in frequency. Over time, the gene will have less variation in the population than it once did or less variation than that in regions of the genome in which variation is not related to adaptation. If the selection were recent or intense enough, we would expect, when evaluating the amount of variation along the genome, to find regions of reduced var-

iation that would lead to "candidate" genes. Similarly, if the phenotypic differences observed between low- and high-altitude populations are only the result of adaptability, we would expect the variation present in our candidate genes to be similar in closely related low-altitude control populations to the variation observed in high-altitude populations.

The approach that Mark Shriver and one of us (AB), along with collaborators elsewhere, are taking to identifying the effects of selection is to compare existing genomic variation in Andeans and Tibetans to that in closely related low-altitude populations. What makes this even possible is microarray technology, panels of known polymorphic sites at hundreds of thousands of markers that can easily and affordably be genotyped in every individual in a study sample. The markers themselves are unlikely to be involved in adaptation; they are just previously identified variable sites of known genomic location. However, the pattern of different levels of variation between highlanders and lowlanders may indicate which markers' genome regions have been affected by selection for adaptive variants, thus reducing genetic variation in those regions. For example, one of several different available tests searches the genome for reduced variation in short regions, evaluated by a statistical measure called *lnRH*. This statistic measures the relative variability in that region between Andeans and their lowland counterparts, an example of which is shown in Figure 6. The genome regions with significantly lower variability potentially reflect the effects of a history of selection.

Lowlanders are only one sort of control or contrast sample that we can use. We can also let the highlanders' own genomes stand as controls. This is because areas near genes that have been under adaptive selection in their ancestors can be less variable than other areas in their same genomes. We can thus use the same panels of genetic markers to look *along* the genome of highlanders for areas that vary significantly less than others do.

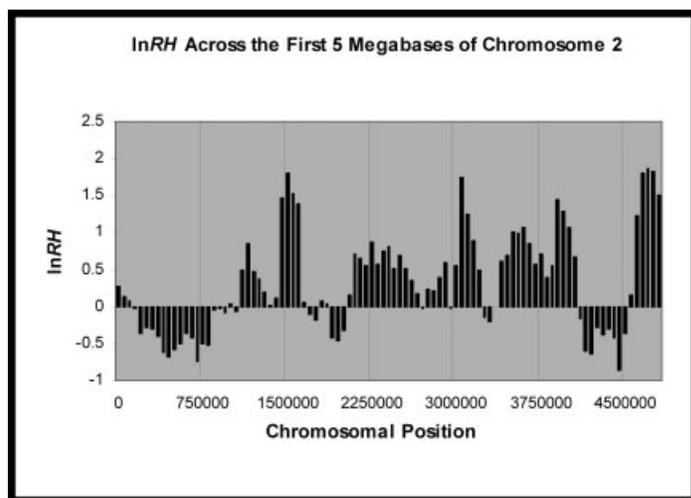


Figure 6. Taking it to the genome. A “sliding window” approach in which a window the size of 200,000 nucleotides moves along each chromosome, 50,000 nucleotides at a time, in each window assessing levels of variability in Andeans compared to a sample of lowland Mesoamericans based on the $\ln RH$ measure.²³ The figure shows the first 5 million nucleotides from the end of chromosome 2. The highly negative $\ln RH$ values (below the 0-line) indicate decreased variability in the Andeans compared to the Mesoamericans.

Based on the results of this initial search for genomic signatures of selection, the identified candidate genes will be subjected to sequencing-based tests of selection. In this approach, we look for variation that is reduced specifically in functionally important parts within the candidate genes. This relative reduction in variation provides indirect statistical evidence of selection. More direct genotype-phenotype studies can then be performed to show whether different variant states are associated with differences in a measure of physiological response.

If all these tests are passed, a final test can help affirm the findings. In this test, lowland-highland admixed individuals are studied to see whether those with high-altitude like phenotypes have inherited the putative adaptive genetic variants from their altiplano ancestors. Genotype-phenotype association testing is necessary to determine whether genes that appear to have been subject to genetic adaptation are functionally relevant. This testing also will substantiate the link relating the observed physiological differences between low and high-altitude groups with their respective genotypes. This battery of sequential testing, starting with purely genomic

considerations and moving to specific genotype-phenotype associations, has not yet been used to detect genetic signatures of adaptive selection to high altitude, but that work is in progress.

An additional challenge is presented by genetic drift, the changes in genetic variation that are due to the chance aspects of survival and reproduction. The same patterns used to distinguish adaptability from adaptation can be the result of geographic isolation followed by drift, a fairly reasonable demographic scenario given the remoteness of the Andean altiplano and Himalayan plateau. However, genetic drift is a genome-wide affect. If there is no adaptive selection, all regions of the genome in a population will be equally affected by it, while natural selection only affects specific adaptive genes. But these are statistical arguments, and there are complications.

When we search a large “space” like the entire human genome, we expect to find local regions that by chance resemble the signature of selection. Alternatively, selection may have occurred in other regions but be essentially undetectable: When selection is a weak effect, it changes variation only slightly more than drift alone does. An important fur-

ther complication is, of course, that the genome is adapting to all sorts of factors all the time, so that a signature of selection does not necessarily reflect high-altitude stress. Only follow-up studies such as those we’ve mentioned can sort out the chance chaff from the selective grain.

If the same gene shows direct evidence of adaptability and if its pattern of variation shows a signature of adaptive selection, then it will be time to get excited. So far, one of us (AB) has assessed the patterns of variation present in Andean populations compared to low-altitude control populations. The genomic statistical results are pointing to some interesting HIF pathway genes, but have not yet been substantiated by genotype-phenotype correlations.

But how do we interpret genes having variation that we can show affects the trait today, but don’t show signatures of natural selection, or vice versa? This is likely to happen for many reasons. For example, the relevant variation in phenotypes today may not be variation that was related to past selection. Another possibility is that, the distribution of selection over many systems may make the effects on individual components very weak. When many genes affect a trait, even under selection, chance may determine which ones respond most to the selection. This raises another important question.

Do the Tibetan and Andean populations exhibit similarities or differences in genes or functionally different changes in the same genes involved in high-altitude adaptation? We know that the characteristic “barrel-chested” thorax of the Andeans can provide additional lung capacity in a way not found in Tibet. Generally, we expect to find multipathway phenotypes like HIF or adaptive phenotypic similarities that are controlled by different genes or different suites of genes in these two highland groups. That would jibe with the variable results for different measures mentioned earlier. There clearly are several other physiological and even morphological systems, such as lung capacity, that relate to oxygen biology (not to mention cold adaptation). Each involves many genes.

We have clear precedents indicating what we should expect to find in high-altitude adaptation. Multiple genetic pathways affect two well-studied human adaptive traits. Many pathways are involved in skin pigmentation. Recent study has shown that Europeans and East Asians use separate genetic pathways to produce their light-skinned phenotypes.²⁴ Similar phenotypic convergence, but also genotypic divergence has been observed in adaptation to malaria.^{25–27} Because evolution works through phenotypes rather than directly on genotypes, independent or convergent evolution is expected and well-documented. This is what is found between Tibet and the Andes in terms of phenotypes, at least. It will be surprising if it is not the genetic result as well.

WHEN “THE ORGANISM OVERCOMES THE ‘CLIMATIC AGRESSION’ OF THE ELEVATION”⁹

The usual notion of natural selection is that people are passively screened by the environment to determine the outcome of the reproductive sweepstakes. Cold and hypoxia could do that to humans trapped at high altitude, but that may not be what happened. In fact, hypoxia could illustrate an important alternative that could apply especially to a species like us. We adapt behaviorally and culturally in many active rather than passive ways. An obvious example is that if people decided whether or not to live at high altitude, those with genetically based abilities to deal more easily with hypoxia could have been more likely to go to or settle at high altitude. There, they would have met and mated with others of their kind. The relevant genotypes will be preferentially found at high altitude compared to lowland. This is organismal selection, an active rather than passive means of sorting genetic variation that can generate gene-specific patterns in the altiplano that resemble Darwinian selection. However, no differential reproduction would have been involved.

A founding leader of the IBP was C. H. Waddington, who was interested in the “epigenetic landscape” that relates organisms to their environments. Waddington believed that processes other than simple natural selection could account for biological diversity. One of them was “genetic assimilation,” an extension of ideas from the late nineteenth century.²⁸ This and related phenomena are called polyphenism,²⁹ or niche construction.³⁰ Genetically identical organisms can express different phenotypes in different environments. There is nothing in their genome that insists that they have a given phenotype. But if the phenotype they manifest in a given environment happens to be beneficial to their survival or reproduction, Darwinian selection can favor new mutations that arise in that environment and raise the probability of the favorable phenotype being expressed. Over time, what was initially an adaptability response becomes an adaptive characteristic.

Humans are the ultimate choosing organism, and may offer good examples of an active rather than passive response to environments. Given that hypoxia is always present at high altitude, but is escapable by paths up and down mountain, human adaptation to this stressor may provide an excellent example of organismal selection. However, it is a challenge to know how to differentiate among natural selection, organismal selection, and assimilation. All may continually be at work, and life on high today is probably a mix of these paths of ascent. But it will take creative thinking to show this genetically. One way might be that genes related to effects we can consciously perceive, like shortness of breath, might reflect organismal selection, while those related to effects we can’t see, perhaps such as immune compromise or gestational stress on birth weight, might reflect classical selection. Which kind of force should impose more stringent selection?

As things turned out, Waddington had been some what dragged into his IBP role, and had little to do with it in practice. As far as we know, his ideas of genetic assimilation were

not tested in the high-altitude part of the IBP. But he might be pleased to see the opportunities that now exist to probe some of the more subtle aspects of evolutionary ecology that the wandering of a few peasants into high altitude has presented. Investigators here and elsewhere are currently generating the genetic data that may enable us to reconstruct those wanderings.

Many questions remain to be answered about the way humans adapt to or have been adapted for life on high. Our history at high altitude may also illuminate the role of culture, as well as the roles of mechanisms other than classical Darwinian selection, in our ability to function in that environment. Work in this field today is a tribute to its pioneering anthropological ancestry, largely the inspiration (if you’ll forgive the pun) of Paul Baker at high altitude. He, his students, and many other contemporaries laid the basis from which we can aspire to use new approaches to understand what happens to people when they move up in the world.

The same logic and approaches can be taken in many other contexts in which we try to work out how we currently respond to the world we find ourselves in and how we got that way, and perhaps even where we may be going in the future. Not all of it is genetically predetermined, but it is genetically enabled. It is valuable and interesting to understand how.

However, we can always use new kinds of contrasts and comparisons. One of the more important strategies in science is to compare related species living in the same environment. The other organisms who live on high with humans have a variety of their own adaptations, too.^{31–34} Alpacas, llamas, and guinea pigs are good examples in the Andes. Of course the best comparison would be with other closely related primates. For that, we may have to turn to the Himalayas, and we’ll need the help of Cynthia Beall, a Baker student who has long worked in highland Tibet. If, like Slavomir Rawicz’s band of escapees from a Siberian labor camp,³⁵ she should cross a rise and happen upon a band of Yeti’s...

NOTES

We welcome comments on this column: kenweiss@psu.edu. There is a feedback and supplemental material page at http://www.anthro.psu.edu/weiss_lab/index.html. We thank Anne Buchanan, Ralph Garruto, Cynthia Beall, Brooke Thomas, and John Fleagle for assistance with this manuscript.

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