Creation Research Society Quarterly 2014. 50:132–140.

Adaptation of Endotherms to High Altitudes

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Abstract

God created His creatures to reproduce and fill the earth. As they do so, numerous challenges are faced in different environments, requiring creatures to adapt. High altitudes present serious challenges for endotherms, including a reduced partial pressure of oxygen. Through a variety of mechanisms, many creatures adapt quite successfully to this hytpoxia. Adaptation includes immediate, short-term responses followed by longer-term, more sustainable responses. For mammals and birds that have lived for generations at high altitudes, genetic changes have been identified, reflecting a more permanent response. The neo-Darwinian model does not account for the observed phenotypic and genetic changes. Instead, this adaptation is clear evidence of the care God bestows upon His creatures, even in our current fallen world.

Introduction

The Bible provides an eyewitness account of the origin of life, given to us by the very Author of life Himself. From it we gain valuable information regarding the history of life and its purpose. Animals were created according to their kinds and directed to reproduce and fill the earth (Genesis 1:20–22, 24–25). Disease and death entered the world at the Curse (Genesis 3), and a severe population bottleneck occurred at the Flood (Genesis 6–8). Yet despite these judgments that serve to remind us of the horridness of sin, God still intended for His creatures to fill and inhabit the earth (Genesis 8:15–17; Isaiah 45:18). He provides for them even in this fallen world (Psalm 147:9).

As animals have reproduced and filled the earth, they have had to adapt to different environmental niches. For example, we can see hares in the desert, hares in the arctic, and hares in other environments, each of which poses a unique array of challenges. Similarly, foxes, ducks, and numerous other creatures have a cosmopolitan distribution. Adaptation can seem so commonplace that we fail to consider what is required for this to happen.

One well-studied type of adaption is the adaption to high altitudes. While we have only begun to understand all that is involved, what is already known highlights the incredible robustness of design in God's creatures. They are faced with multiple stresses that are potentially life threatening, yet many are able to adapt and even thrive under these incredibly challenging conditions.

The most obvious high altitude challenges for endothermic vertebrates are

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Accepted for publication January 27, 2014

the reduced partial pressure of oxygen (PO_2) and the generally cooler temperatures. This reduction of atmospheric oxygen (O_2) can result in serious depletion of O_2 in the tissues, impairing metabolism. This not only may jeopardize the maintenance of normal activity, but also may impair the capacity to maintain a constant internal temperature in the face of the cooler ambient temperatures (Storz et al., 2010; Cheviron and Brumfield, 2012).

Another challenge is maintaining adequate hydration. Several responses to high altitude hypoxia (low O_2) also lead to increased water loss. Increased ventilation results in an increased respiratory water loss. Down-regulation of the renin-angiotensin-aldosterone system results in increased urinary output (Yanagisawa et al., 2012). These responses necessitate an increase in water intake to avoid dehydration. This highlights the fact that the many body systems are intricately interconnected. Changes are not made in isolation; instead they often impact many other areas that also must be kept in balance. Maintaining homeostasis is critical to survival and often involves an astounding array of details. Five components of the O_2 pathway where physiologic and/or genetic adaptation may compensate for high altitude stress are described below.

Increasing Oxygen in the Lungs

One of the first physiologic responses to hypoxia is an increase in ventilation (breathing). The carotid bodies, chemoreceptors located in (or near) the neck, sense the drop in PO_2 and stimulate a rapid rise in ventilation within minutes. This increases the PO_2 in the lungs, helping to compensate for the drop in PO_2 in the atmosphere. While this helps significantly, it does not restore lung PO_2 to sea-level values. This means other physiologic changes need to take place for the creature to adapt well to the high altitude (Storz et al., 2010; Ainslie et al., 2013).

Further, increasing ventilation has other significant consequences in addition to increasing water loss as mentioned above. The rise in PO_2 is associated with a drop in the partial pressure of carbon dioxide (PCO_2). This causes a rise in pH and respiratory alkalosis. Ironically, CO_2 and hydrogen ion concentration ($[H^+]$, which declines as pH rises) normally stimulate breathing via central and peripheral chemoreceptors. It is possible that the decrease in CO_2 and $[H^+]$ play a role in reversing the initial spike in ventilation. This reversal occurs within the first 10 to 20 minutes. However, ventilation is still maintained at a significantly higher level than it would be at sea level (Ainslie et al., 2013).

Given that CO_2 and $[H^+]$ are important signals for breathing, and that the concentration is reduced as ventilation is increased, what is the signal to maintain this higher ventilation rate at high altitudes? At this point there is considerable conjecture as to how this occurs. It seems that changes within the central nervous system as well as interactions between central and peripheral chemoreceptors must be involved. Further, interindividual differences have been noted in the specifics of the response. It has been suggested that in individuals with a more dramatic ventilatory response, the drive to breathe is more peripheral, while a blunted response allows for a more acidic pH and the drive to breathe depends more heavily on the central chemoreflex (Ainslie et al., 2013).

Increasing Pulmonary Diffusion

Once O_2 is in the lungs, it must diffuse from the alveoli to the blood. Hypoxia is known to induce pulmonary alveolar and vascular remodeling (Semenza, 2004; Weir and Olschewski, 2006; Ravikurma et al., 2009). In some instances this is adaptive. Animal studies have demonstrated an increase in gas exchange surface area and diffusion capacity in response to (usually simulated) high-altitude exposure. Many of these studies were done on growing animals; at least one study failed to show such changes in adult beagles. So it would seem that significant adaptive changes affecting diffusion are more commonly the result of augmenting normal development. Effective adaptation affecting diffusion is not well documented in adults (Ravikurma et al., 2009).

Increasing Oxygen Delivery by the Blood

There are several strategies that can increase the amount of O_2 carried by the blood. The first is simply to pump more blood per minute. An increase in total cardiac output is observed with exposure to acute hypoxia. This is the result of an increased heart rate. The degree of tachycardia can vary with factors such as rate of ascent. Cardiac output declines to sea-level values within a few days, though generally the heart rate remains high with an accompanying decreased stroke volume (Naeije, 2010).

The increased cardiac output is transient as the body employs other strategies to maintain O_2 delivery to the tissues. Hypoxia results in an increase of hypoxia-inducible factors (HIFs). HIFs are protein heterodimers consisting of one of three α-subunits and a β-subunit also known as aryl hydrocarbon receptor nuclear translocator (ARNT). ARNT and the HIF α-subunits are constitutively expressed, with the 2α-subunit being more tissue specific than the 1α-subunit. These α-subunits are broken down rapidly in an O_2-dependant pathway. A drop in O_2 leads to a proportional increase in HIF levels, allowing for a rapid response to hypoxia. HIFs are transcription factors that regulate a number of genes involved in the response to hypoxia, including

the one encoding erythropoietin (EPO; Semenza 2004; Haase 2013).

Serum EPO levels peak within a day or two of arriving at a high altitude. Among its functions, EPO stimulates erythropoiesis, the production of red blood cells (RBCs). Within a few weeks of arriving at a high elevation, an increased number of RBCs are circulating. The increased hemoglobin (Hb) allows for increased binding of O_2 for transport to the cells. However, this response also needs to be carefully modulated. Excessive polycythemia can increase the viscosity of the blood, lower cardiac output, and result in other adverse outcomes (Gore et al., 2007; Storz et al., 2010; Naeije, 2010; Cheviron and Brumfield, 2012).

In addition to this physiologic response, various genes in the HIF pathway exhibit polymorphisms, presumably from mutations (i.e., changes in the DNA sequence), which are associated with an adaptive phenotype at high altitudes. The egl nine homolog 1 (EGLN1) protein, also known as prolyl-4-hydroxylase domain 2 (PHD2), is a key enzyme in hydroxylation of HIF-α. Endothelial PAS domain protein 1 (EPAS1) is another name for HIF-2α. The peroxisome proliferator-activated receptor-α (PPARA) also affects erythropoiesis. Genetic variants in these three genes are found in Tibetans and are associated with lower Hb levels (compatible with those of lowlanders at sea level) and protection against chronic mountain sickness compared to other humans living at high altitudes (Cheviron and Brumfield, 2012; Haase, 2013).

Another strategy for dealing with the decline in PO_2 is to adjust the affinity of Hb for O_2. Ideally, it is best if Hb binds strongly to O_2 when it picks it up (loading) at the lungs but releases it readily when delivering (unloading) it to the tissues. The binding affinity of Hb to O_2 changes with PO_2, but this change is not linear. The relationship is described by the oxyhemoglobin dissociation curve (ODC; Figure 1, p. 136).

The drop in PO_2 presents several challenges. The first is to maintain adequate delivery of O_2. O_2 delivery is represented on the ODC by the difference in the y-axis values between the points representing arterial and venous blood saturation (A1-V1 and A2-V2 in Figure 1). The decrease in PO_2 under hypoxic conditions (A2-V2) is partially compensated for because O_2 loading and unloading is occurring over a steeper portion of the ODC. Thus, despite a significantly smaller difference in PO_2 between arterial and venous blood, the amount of O_2 delivered is nearly the same as the normoxic example given (A1-V1).

The second challenge is to maintain adequate PO_2 to drive diffusion at the tissue capillaries. Adequately addressing these dual challenges of maintaining adequate O_2 delivery and PO_2 at the tissue capillaries may require a change in the affinity of Hb for O_2, which will result in a change in the shape and position of the ODC. Figure 2 (p. 136) illustrates a decrease in O_2 binding affinity resulting in a right shift in the ODC (red), and an increase in O_2 binding affinity resulting in a left shift in the ODC (green).

A number of factors can shift the ODC, including changes in pH (Bohr effect) and temperature. The body can also change the concentration of allosteric cofactors within the RBC to modulate Hb-O_2 affinity. The most potent example in mammals is 2, 3-diphosphogylcerate (DPG), which decreases Hb-O_2 affinity by binding and stabilizing the deoxygenated conformation. This will shift the ODC to the right and facilitate unloading of O_2 at the tissues. An increase in DPG has been documented to occur in humans within 24 hours of ascent to a very high altitude (Storz et al., 2010; Cheviron and Brumfield, 2012).

A right shift in the ODC is thought to be most adaptive under moderate hypoxia and is readily accomplished through phenotypic plasticity. In severe hypoxia, a left shift can be more beneficial because it allows for oxygen loading and unloading over a steeper portion of the ODC. A chronically left-shifted ODC is seen in various mammals and birds that have genetically adapted to alpine living. The left shift has been correlated with genetic polymorphisms affecting the α- and/or β-globin portions of the Hb molecule, which either directly increase the O_2 affinity of Hb or decrease its sensitivity to allosteric cofactors (Weber 2007; Storz et al., 2010; McCracken et al., 2009).

The α- and β-globin subunits of adult Hb are surprisingly variable, but only a few sites have been demonstrated to make significant contributions to O_2 binding affinity (Weber, 2007). One example of molecular adaptation is found in Andean camelids: llamas and vicuñas. The high O_2 affinity of their Hb is correlated with an amino acid substitution in the second residue of the β-globin polypeptide which decreases binding of DPG. The vicuña, which inhabits the highest elevations (4,000–5,000 meters) and has the highest oxygen affinity, possesses an additional amino acid substitution in the α-globin polypeptide (Storz, 2007).

The most extensive research on genetic adaptation in Hb has been carried out on deer mice, which inhabit elevations from below sea level in Death Valley to 4,300 meters in some mountain ranges within North America. Lowland populations differ from those at high-altitude by 8 amino acid substitutions in the α-chain and 4 in the β-chain subunit. The high Hb-O_2 affinity in alpine populations appears to be from reduced binding affinity with allosteric cofactors (DPG and Cl^- ions) and is associated with a greater maximal rate of O_2 consumption at high altitudes. This allows for greater aerobic activity and thermogenic capacity in these active, non-hibernating rodents. Interestingly, the lowland genotype is correlated with a higher maximal rate of O_2 consumption at low altitudes (Storz, 2007; Cheviron

and Brumfield, 2012; Natarajan et al., 2013).

Genetic adaptation is usually believed to require extensive periods of time. However, Andean chickens, which were introduced to that region about 500 years ago, have a higher Hb-O_2 affinity than their lowland counterparts. This putatively genetic characteristic was retained after moving some to a low altitude for a year, and it was passed on to their offspring (Velarde et al., 1991). There was a gradual trend toward a lower Hb-O_2 affinity over the lifetime in both generations. This has not been characteristic of other high-altitude species transferred to long-term residence at low altitude (León-Velarde et al., 1997). Thus, it could be that this is a heritable epigenetic trait. Apparently no investigation to identify Hb polymorhpisms has been published.

Increasing Diffusion to the Tissue Mitochondria

As mentioned, sufficient PO_2 in the blood is necessary to drive the diffusion of O_2 from the blood to the tissue mitochondria, where it is used. Theoretically, O_2 diffusion capacity could be increased to offset some of the decline in PO_2 relative to sea-level values. This could be accomplished by increasing the density and distribution of capillaries in the tissues and/or changing the cellular arrangement of the mitochondria (Storz et al., 2010). While the transcription factor HIF is also known to affect angiogenesis (Gore et al., 2007; Semenza, 2004), it is unclear how much vascular remodeling occurs when adult lowland species become acclimatized to high altitude. Some of the debate over this may be related to differences in interindividual responses, which produce ambiguous results within and between studies. Storz and colleagues (2010) conclude that there appears to be negligible plasticity in the morphological capacity for O_2 diffusion during high-altitude acclimatization.

In contrast, studies have shown that some high-altitude species have adaptations improving diffusion. The bar-headed goose has an increased number of capillaries in the flight muscle and heart in addition to mitochondria that are redistributed closer to these capillaries. These morphologic features appear to be genetic, as previous exposure to high altitude is not required for their appearance. However, not all high-altitude species have this phenotype (Storz et al., 2010). This indicates that there is variation in the genetic responses of different high-altitude populations.

Adjusting Oxygen Utilization to Accommodate the Supply

There is also variability in the response of the tissue as lowland species become acclimatized to high altitudes. Metabolic capacity may decrease in muscle tissue through reductions in cell size and number of mitochondria. A shift in fuel preference may also help decrease O_2 demand (Storz et al., 2010). In athletes training under simulated high-altitude conditions, adaptations were observed that allowed better coupling between energy use and production sites resulting in improved mitochondrial efficiency (Gore et al., 2007). However, in other instances mitochondrial efficiency is merely sustained or even impaired (Storz et al., 2010).

One study in deer mice, which have high thermoregulatory demands, demonstrates that changes in expression levels for genes in the oxidative phosphorylation and fatty acid oxidation pathways contribute to an adaptive enhancement of thermogenic capacity in high-altitude populations. This is intriguing, as fatty acid utilization produces more energy per gram than carbohydrates but requires more O_2. Therefore, the alterations in the oxidative phosphorylation pathway appear necessary to allow for the increased use of lipids as a fuel source. The wild-caught mice from different altitudes were tested after acclimating to a common low-altitude environment (i.e., common garden conditions). It remains to be elucidated as to whether the underlying basis of differential gene expression is from genetic- or epigenetic-based differences (Cheviron et al., 2012).

Failure in the Adjustment Process

The previous sections highlight some of the most elementary components of adaptation to high altitudes. God's creatures were not only designed to be able to make the necessary adjustments, but there is also interindividual variation allowing for a response that meets specific individual needs. This certainly testifies to a wise and caring Creator. However, given the reality of the Curse, failure in the process is expected to occur.

Acute mountain sickness (AMS) can occur when ascending rapidly to a high altitude. Symptoms appear within a day or two and may include headache, gastrointestinal upset (nausea, vomiting, and/or anorexia), fatigue, dizziness, and insomnia. Symptoms tend to be more severe with a more rapid rate of ascent, higher altitude, and more physical exertion. However, for most people they resolve within three days to a week (Beidleman, et al., 2013).

Sometimes AMS will progress to a more severe and potentially fatal syndrome: high-altitude pulmonary edema (HAPE) or high-altitude cerebral edema. In the case of the former, there is an exaggerated pulmonary vasoconstriction response to hypoxia with resulting hypertension and increased leakage of fluid from the vessels as a result of this stress. It is a condition that has claimed the lives of strong, young mountain climbers over the centuries. Though these conditions are serious and potentially fatal, they can be readily reversed if recognized early and treated promptly. Prevention and treatment is based on giving one's

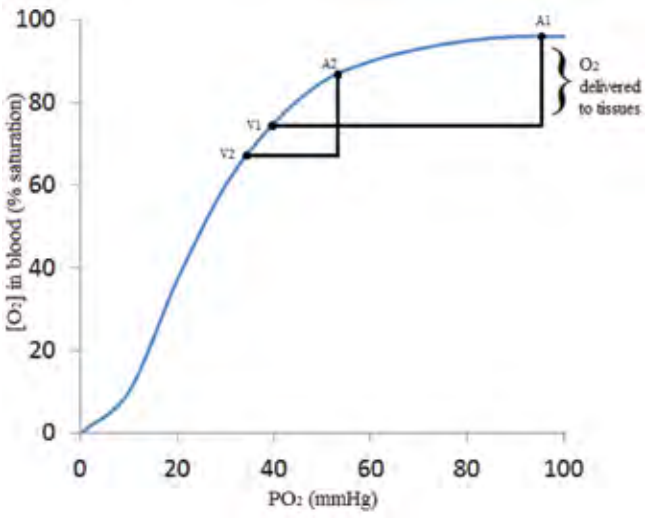

Figure 1. An oxyhemoglobin dissociation curve (ODC) has a sigmoidal shape. A1 and A2 represent theoretical examples of arterial blood under normoxic and hypoxic conditions, respectively. V1 and V2 are the corresponding values for venous blood after oxygen (O_2) unloading at the tissues. The difference between arterial and venous (A1-V1 and A2-V2) values on the x-axis shows the difference in PO_2 between the normoxic and hypoxic conditions. Note that the amount of O_2 delivered to the tissues (the change in value on the y-axis) is almost the same in both cases because O_2 was loaded and unloaded over a steeper portion of the curve in the second case. The shape and position of the ODC will often change under varying conditions, as illustrated in Figure 2.

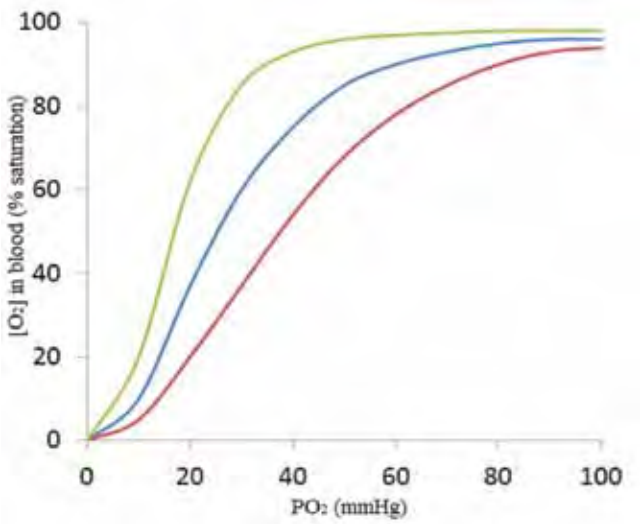

Figure 2. Examples of changes in shape and position that can occur in the oxyhemoglobin dissociation curve (ODC). A right shift (red) can result from a drop in pH or an increase in temperature or allosteric cofactors that decrease O_2-hemoglobin affinity. Under cases of mild hypoxia, a right shift can often be beneficial as it facilitates O_2 unloading at the tissues. A left shift (green) can result from an increase in pH or a decrease in temperature or allosteric cofactors affecting O_2-hemoglobin affinity. The latter is viewed as the most advantageous under extreme hypoxia since it maximizes O_2 loading in the arteries and both loading and unloading occur over a very steep portion of the curve. Adaptive mutations that affect hemoglobin affinity resulting in a left-shifted ODC are found in various endotherms that have lived for generations at high altitude.

body the time to adapt: ascending more slowly, avoiding extremely high altitudes, decreasing physical activity, and adding supplemental oxygen to alleviate symptoms if it becomes necessary. There are also some medications that can be helpful for individuals who are more susceptible (Paralikar, 2012).

Studies suggest that genetic polymorphisms in mitochondrial DNA, genes of the renin-angiotensin-aldosterone system, and genes of several other pathways may affect the risk of HAPE (Luo et al., 2012a; Luo et al., 2012b; Luo et al., 2012c; Srivastava et al., 2012). However, despite the intensity of research on this serious disease, is has been difficult to elucidate the pathogenesis of this condition. This is partially because the disease is rare, making it difficult to obtain a large enough sample size for statistical comparisons. Further, there are numerous biological pathways interacting to maintain homeostasis under hypoxic stress. This explains why a number of different polymorphisms have been implicated as having some effect (Luo et al., 2012a). Finally, the overall health and behavioral choices of the individual greatly impact the development of the disease (Paralikar, 2012).

People living long-term at altitudes over 2500 meters may develop a syndrome known as chronic mountain sickness (CMS). Symptoms vary somewhat, but commonly include breathlessness and/or palpitations, cyanosis, decreased exercise tolerance, headache, impaired mental function, tinnitus, and paraesthesia (tingling or other skin sensations with no obvious physical cause). Underlying

features include excessive pulmonary hypertension (which is correlated with maladaptive pulmonary vascular remodeling that increases the diffusion barrier) and/or excessively high hematocrit. These symptoms will normally disappear within a few weeks if the person moves to a low altitude (Hainsworth and Drinkhill, 2007; Naeije and Vanderpool, 2013; Gonzales et al., 2013).

CMS has not been documented among the Ethiopians of the East African high-altitude plateau. It is rare among Tibetans. Andeans are more susceptible to this disease. A recent genome-wide association study identified 11 regions associated with CMS susceptibility in Andeans. Two genes (SENP1, a regulator of erythropoiesis, and ANP32D, an oncogene) from these regions were transcribed at a higher level in response to hypoxia in individuals with CMS compared to those without. Further studies of the orthologs in flies indicate that down-regulation of these genes enhanced survival in flies exposed to hypoxia (Zhou et al., 2013). This again highlights the point that the more we study adaptation to high altitude, the more it is evident that an astounding array of genes needs to be properly controlled for maintenance of homeostasis.

An Obvious Trend

Endotherms exhibit a profoundly complex, well-integrated response to high-altitude hypoxic stress. As a lowland species adapts to a high altitude, there are immediate effects (spike in ventilation and increased cardiac output) that subside as more long-term adjustments are made. Young mammals developing at high altitudes have been shown to adapt even more than adults (e.g., in remodeling alveoli and vasculature to improve diffusion between lungs and the blood). Populations that have lived for generations at high altitudes often carry adaptive genetic changes. Given how effectively adaptation occurs in most endotherms, it would seem that these genetic changes are merely a further coordinated response to the high-altitude environment.

This idea that physiologic adaptation is somehow linked to evolution (i.e., genetic change) actually was suggested by evolutionists over a hundred years ago (reviewed in Kirschner and Gerhart, 2005). It has never been a popular part of evolutionary explanations for several reasons. It fails to account for major anatomical innovations (e.g., eyes or wings). It also requires the preexistence of well-integrated, complex systems that allow for both physiologic and genetic change. These preexisting systems clearly exist, but neo-Darwinian mechanisms cannot account for their origin or the observed adaptive changes within them.

Failure of Neo-Darwinian Mechanisms to Account for Observations

The neo-Darwinian mechanisms of random mutation and natural selection are proffered as a naturalistic explanation for genetic adaptation. It is well known that mutations aren't truly random in that there are hotspots where they occur far more frequently. However, it is assumed that mutations are essentially errors, induced either by environmental insults (e.g., UV radiation) or replication errors that are not properly repaired (Akashi and Yoshikawa, 2013). If mutations are biased to produce beneficial changes, it would be evidence of design, which is rejected *a priori* by evolutionists. Of course, random mutation and natural selection are believed responsible for far more than just the type of adaptation accepted by biblical creationists; they are invoked to explain the origin of all the diverse life-forms today from a putative common ancestor—a natural history at odds with the biblical history of original created kinds.

The field of population genetics, which is highly mathematical, has produced some impressive literature that is largely ignored in popular-level evolutionary explanations. It is well recognized in this field that the frequency of a particular lineage will fluctuate over time; this is termed genetic drift. It is well established in this naturalistic model that *most beneficial mutations that arise would be lost due to genetic drift*! Of those that survive drift, they are unlikely to become prominent or fixed in a population unless they have a large selective advantage, something that would be absent where phenotypic plasticity allows for robust adaptation (Patwa and Wahl, 2008).

Population genetics models did not predict the patterns of change we observe. The idea that many mutations of miniscule effect should be the underlying basis of evolution was reinforced by the work of Ronald A. Fisher, who showed that as the size of the mutational effect increased, the probability that it would be beneficial became vanishingly small. This was largely due to the effects of pleiotropy, where a mutation can affect a number of characters, some in a positive way and others in a negative way. Yet the reality is that we have a number of clear examples where one or a few mutations of sizable effect underlie adaptation (Orr, 2005).

Evolution by natural selection should occur only if each mutation added provides some benefit. Further, only a few steps are predicted to occur in a typical adaptive walk (Orr, 2005). This creates a serious problem when attempting to account for the dozen amino acid substitutions in the two Hb subunits of high-altitude-adapted deer mice. Epistasis was demonstrated among these adaptive mutations (Natarajan, 2013). This epistasis would obstruct the pathway of an adaptive walk.

Although some newer models do allow for mutations of sizable effect, they do so by ignoring the reality of nonlethal harmful mutations (Orr, 2005). Most mutations are near neutral

and not significantly affected by natural selection. Realistic numerical simulation shows that deleterious mutations, which would be far more frequent than beneficial ones unless mutations are biased to be beneficial, would become fixed in a population via genetic drift at a rate that vastly exceeds the rate that beneficial ones are fixed. This means postulating more time for beneficial mutations to arise and become fixed will result in a staggering load of deleterious genetic mutations. Rupe and Sanford (2013) term this phenomenon "Haldane's ratchet." Thus, natural selection of randomly generated mutations is not a plausible mechanism for the genetic adaptation that is observed.

Explanatory Value of the Creation Model

If neo-Darwinism cannot account for genetic changes that allow creatures to adapt to new environments, it certainly cannot account for the origin of the complex, well-integrated pathways that allow for adaptation to begin with. In contrast, the biblical creation model accounts elegantly for all these observations. Creatures can adapt to new environments, which present challenges that may not have been encountered by their ancestors. This is attributable to the fact that there is a Creator who designed them with the capability to adapt to new environmental challenges. As a result of the Curse, not everything works perfectly today. There is enough disease and death to make it clear the world is broken; this should lead us to recognize that we need a Savior. Yet when examined in detail, it is clear that adaptation is an amazing process that we have barely begun to understand.

There are a number of genes where mutations have occurred since the Flood (Lightner 2008, 2009). We know this because, regardless of the standing variation at Creation, a maximum of 4 alleles would have been preserved through the Flood for any of the unclean kinds on the ark. The variety added by these mutations can be adaptive. So at the very least, some genes were designed to allow for adaptive mutations. Given the amazing responsiveness of endotherms to environmental challenges, it is reasonable to assume that many mutations may be biased to be at least potentially adaptive. This would account for why most mutations seem to be near neutral; their effect is often difficult to discern without extensive study, and they may be advantageous only in a limited set of circumstances.

It is clear that when adaptive mutations arise, natural selection is not an adequate mechanism to preserve them. The vast majority would be lost to genetic drift. Therefore, God must have designed some way for adaptive mutations to increase in frequency in populations. In some instances individuals with adaptive alleles might be the ones that migrate into a new area. In this case the adaptive alleles would become common in the resulting population due to the founder effect. Yet it appears that more than this is occurring. A coherent creation model predicts that many mutations are biased to be beneficial and that a created mechanism must exist to increase allele frequency of adaptive mutations.

The exciting part is that recent scientific research provides evidence that biased mutations could likely be the case (reviewed in Lightner, 2013). It is well known that homologous recombination, which occurs during meiosis, can change the DNA sequence. This process is initiated by enzyme-induced double-stranded DNA breaks. While crossing over is the best-known outcome, gene conversion may actually be more common. Other break-repair mechanisms incorporate other changes into the DNA sequence. Further, biased gene conversion has been documented to occur in mammals. Biased gene conversion would increase allele frequency. It also violates the assumptions of models using statistical tests to identify selection, meaning that where biased gene conversion is occurring to a significant degree, it is being mistaken for natural selection. So while considerably more research needs to be done to establish the significance of these meiotic mutations, it already appears that the Creation model provides the most robust scientific explanation for genetic adaptation.

Summary

God created His creatures to reproduce and fill the earth, and so they have. Even today He provides for His creatures in amazing ways so they can adapt to some incredible challenges. High-altitude adaptation is one example where numerous changes must be effectively made so that life can inhabit even some surprisingly high regions of the world. In some instances there can be failure in the process, highlighting the fact that we live in a world that has been cursed because of sin. Yet in most cases the process of adaptation proceeds remarkably well. Immediate, short-term responses are followed by longer-term, more sustainable responses. For mammals and birds that have lived for generations at high altitudes, genetic changes have been identified, reflecting a more permanent response. In all these details, it is clear that we have an awesome Creator who provides for the needs of His creatures.

Abbreviations

AMS — acute mountain sickness
Cl^- — chloride
CMS — chronic mountain sickness
CO_2 — carbon dioxide
DPG — 2, 3, diphosphoglycerate; also known as 2, 3 biphosphoglycerate (BPG)
EPO — erythropoietin, a hormone that stimulates erythropoiesis, the production of RBCs

$[H^+]$ — hydrogen ion concentration
Hb — hemoglobin
HAPE — high altitude pulmonary edema
HIF — hypoxia inducible factor
O_2 — oxygen
ODC — oxygen dissociation curve
PCO_2 — partial pressure of carbon dioxide
PO_2 — partial pressure of oxygen
RBC — red blood cell

Acknowledgments

This research was supported by funds from the Creation Research Society.

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