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Comments on Point:Counterpoint: High altitude is/is not for the birds!

FROM THE MOUNTAINS TO THE SEA—HYPOXIA TOLERANCE ACROSS SPECIES

TO THE EDITOR: The debate between Scott et al. (6) and Llanos et al. (4) highlights the remarkable ability of birds and mammals to adapt and survive at high altitudes and cope with reduced oxygen (O_2) availability. Scott and colleagues (6) make a compelling argument that birds are far superior to mammals at adapting and thriving in hypoxic environments, both at rest and during exercise. While their argument is supported by comparisons between birds and terrestrial mammals, it ignores marine mammals. Marine mammals such as seals are routinely exposed to and tolerate long bouts of hypoxia during breath-hold diving. For example, elephant seals may dive to depths of nearly 1,600 m and occasionally remain submerged for 2 h (3). Moreover, marine mammals can be exposed to partial pressures of arterial oxygen (Pa_{O_2}) as low as 12 mmHg during free dives (5), which is less than the $\sim$20 mmHg observed in the bar-headed goose (6). Interestingly, a Pa_{O_2} of 12 mmHg observed in elephant seals corresponds to arterial saturations and O_2 content of only 8% and 2.7 ml O_2/dl (5). Thus marine mammals such as the elephant seal demonstrate a remarkable hypoxia tolerance. The integration of several key physiological adaptations including *1*) substantially greater myoglobin concentrations compared to other mammals, *2*) reductions in metabolism, *3*) a greater reliance on aerobic metabolism (i.e., less lactate production), *4*) a host of dramatic acute cardiovascular adjustments; and *5*) an increased intrinsic cerebral hypoxia tolerance allow marine mammals to thrive in hypoxic environments and enable long deep dives (1–3).

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HIGH ALTITUDE IS/IS NOT FOR THE BIRDS: THE DIFFERENCE IS IN OUR HEADS

TO THE EDITOR: Every March, two Himalayan migrations occur. The bar-headed goose sets off from the lowland plains of India in the early mornings of the pre-monsoon season (median departure 24th March), climbs at 1,100 m/h, reaches altitudes as high as 9,000 m and so crosses the Himalayas all within a day (median 8 h) (3). At the same time of year, Everest climbers set off from Kathmandu to attempt to climb Everest. Most expeditions take 60–80 days and summit attempts are launched from about 8,000 m, also in the early hours of the morning. Ascent rates using supplementary oxygen are typically 150–250 m/h.

Although avian heart, lung, muscle, and blood have evolved to allow rapid ascent to altitude, in our opinion, it is the avian cerebral circulation's insensitivity to hypocapnia that is most important (5). Humans have lowland adaptations (such as Pa_{CO_2} being a surrogate marker for hypoxia), meaning that they need to acclimatize to high altitude. A human exposed to 8,848 m would become unconscious within 5 min. However after 60 days acclimatization, some mountaineers are able to summit, despite being profoundly hypoxic. Breathing ambient air at 8,400 m mean Pa_{O_2} was 3.28 kPa (2) At 7,950 m, mean $EtCO_2$ was 1.73 kPa, yet cerebral oxygen delivery was maintained by a number of processes including cerebral arterial vasodilatation (6).

Both birds (bar-headed goose) and mammals (humans) can travel to 8,848 m; the former has evolved to be able to do it in a day, while the latter needs 60 days to acclimatize and there is still an associated attrition rate (1).

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EVOLUTIONARY ADAPTATION TO HYPOXIC ENVIRONMENTS

TO THE EDITOR: That living organisms have an immense capability of adapting to a hypoxic environment was eloquently expressed by both Scott and Llanos and colleagues (3, 5). Based on the presented evidence as well as data that we recently discussed (1), it is our opinion that high altitude is not only for the birds. The biological needs of an animal appear to

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dictate the type of adaptation to an environment such as hypoxia. For example, differences in oxygen demand between species may provoke functional differences in physiological adaption trajectories. Furthermore, the level of adaptation may depend on multi-generational high-altitude ancestry, as genetic adaptations typically require prolonged periods of time (1). This is important to consider because responses to hypoxia are highly variable within species. As we recently discussed in this Journal (2), prenatal exposure to high altitude generates important vascular adjustments (e.g., increased blood flow in the uterine artery) in humans of multi-generational high-altitude ancestry that are not found in shorter-term residents of highland destinations who often demonstrate reductions in birth weight with increasing altitude (6). Thus depending on ancestry certain organisms may be in the process of adapting to hypoxia while others may have already evolved. In terms of adapting to exercise at high altitude, Tibetans exhibit extraordinary running economy during submaximal exercise compared with acclimated lowlanders (4), while athletes from the Kenyan Kalenjin tribes dominate marathon performance (1). These important considerations support our contention that high altitude is not only for the birds.

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DOWN JACKETS AND WOOLLY SWEATERS: HIGH ALTITUDE ISN'T JUST ABOUT HYPOXIA

TO THE EDITOR: "Most people are heartless about turtles because a turtle's heart will beat for hours after he has been cut up and butchered."- Ernest Hemingway (1).

Scott et al. and Llanos et al. (3, 4) have elegantly outlined the abilities of bar-headed Geese and llamas to prosper in hypoxic environments. However, if the debate pertains only to the survival of birds compared with the rest of kingdom animalia in hypoxic environments, then the champion would be the freshwater turtle of the Trachemys and Chrysemys genera. Turtles can live in an anoxic environment for several months, a feat unmatched by birds or llamas (5). Also, there are other very hypoxia-tolerant animals to consider: the naked mole rat *Heterocephalus glaber*, who dwells in hypoxic environments or the bat *Pteropus poliocephalus*, with very high metabolic scope and excellent hypoxia tolerance (2, 6).

Our colleagues have not considered an important environmental factor aside from hypoxia: the cold. Anyone who has worn a down jacket or alpaca sweater knows the effect of insulating coats that protect both birds and llamas. Neither the naked mole rat nor the bat would survive at the altitude where birds and llamas thrive (3, 6). This is probably not because of lack of hypoxia tolerance, but because the mole rat lacks fur, and bat wings (equally furless) are heat exchangers. Thus the bird and llama's survivability at altitude likely relies on tolerance to cold as much as tolerance to hypoxia. To have a complete discussion of success at altitude, all environmental factors should be considered.

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HIGH ALTITUDE IS MOSTLY ABOUT AEROBIC CAPACITY

TO THE EDITOR: Whether high altitude is or is not for the birds (vs. mammals) has been placed in an evolutionary context by the authors (2, 3). It is notable that high altitude is generally regarded as about 2,500 m and above so the discussion is actually about extreme high altitude. I will comment on what I feel are two major issues relevant to the evolutionary discussion. First, the term "avian respiratory system" is phylogenetically incorrect. This type of respiratory system evolved in the archosaurs, millions of years before birds, and as such does not represent an avian adaptation (1). The second issue is that most, if not all of the adaptations commented on probably do not qualify as traits selected for by a high-altitude environment. The context of supporting an energetically expensive form of locomotion has been ignored. When bats and birds are compared, a number of the differences mentioned are eliminated or markedly reduced [e.g., times to unconsciousness, morphological and physiological parameters related to oxygen delivery (4, 6)]. Furthermore, exercise results in significant modifications in vascular regulation (vascular endothelial nitric oxide system). Exercise-related changes could be at least part of the solution to the issues raised about the mammalian pulmonary and cerebral circulations, and this is supported by the lack of problems in native extreme HA species (2, 5). Considering the above, high altitude in the context of this discussion was likely first for the Pterosaurs and was only claimed by birds and mammals millions of years later.

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TO THE EDITOR: This Point:Counterpoint about high altitude is/is not for the birds (3, 4) mainly focused on oxygen transport factor of the energy metabolism must also consider the carburant limitation. Bird flight requires high levels of mechanical and metabolic power (1). Migratory birds must adapt the physiology of their flight muscle to cope with a number of requirements, such as use of stored triglycerides as the major fuel, due to its high energy density; provision of additional power to meet higher flight costs, due to increases in body mass; and development of sufficient endurance to fly continuously for 3,000 km (1). At the end, we have to consider that llama are rather selected for their ability to have remarkable wool and are known for developing a number of disturbances related to energy metabolism (2). Some are similar to disorders seen in other species, but most relate to camelids' unusual characteristics of poor glucose tolerance, partial insulin resistance, and low concentrations of circulating insulin (2). So I do agree with Scott et al. (4) who pointed out the ability of several highland species for flying between altitudes of 4,000 and 6,500 m well above the llama's home in the Andean altiplano. However, humans are maybe one of the most efficient mammals in altitude considering their ability for climbing Everest (8,848 m) with $\dot{V}O_{2max}$ declining from an average of 49.0 to 15.3 $ml \cdot kg^{-1} \cdot min^{-1}$ at the summit (5) thanks to their anaerobic metabolism, which must also be discussed when speaking about exercise in altitude.

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AVIAN LUNGS ARE BETTER

TO THE EDITOR: Scott et al. (3) make a compelling case for the superior pulmonary gas exchange in birds compared with mammals (2). Here are some additional points.

Birds have separated the gas exchange and ventilatory functions of the lung. What a crazy idea to use delicate alveoli for the process of ventilation when robust air sacs would do. No wonder that breakdown of the alveolar walls as in emphysema is so common in humans. Next the bird uses a flow-through rather than reciprocating form of ventilation that allows the gas exchanging tissue to be exposed to the full P_{O_2} of the inspired air. By contrast in the human, the pulmonary capillaries are exposed to alveolar gas that has already lost about 1/3 of the available P_{O_2}. Another disadvantage of the mammalian lung is that the capillaries are strung out along the alveolar wall and are therefore unsupported at right angles to the wall. Contrast this with the situation in the bird parabronchi where the capillaries are supported by surrounding air capillaries (4). The result is that bird capillaries have much thinner walls than in mammals. Furthermore the walls are uniformly thin, unlike the situation in mammals where a type I collagen cable snakes along the alveolar wall and thickens one side of the capillaries. The result is that in humans only half of the area of the blood-gas barrier is available for efficient gas exchange (1). No question about it. Birds have superior lungs and therefore tolerate hypoxia better.

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PHYSIOLOGICAL ADAPTATIONS AND OPTIMAL CONTROL IN BIRDS WHICH FLY AT HIGH ALTITUDES

TO THE EDITOR: In a sense, one could propose that birds are the living solutions of the famous Goddard problem dealing with high altitudes. Many birds on their long distance migration fly at high altitudes, at which some environmental features like oxygen availability, humidity, wind speeds, air temperature, and density have a significant consequence on avian flight performances (1). Authors (3, 4) elegantly elaborated on the adaptations in birds and llamas, respectively, during hypoxia.

Compared with other vertebrates, birds are endowed with high endurance to hypoxia induced at higher altitudes thanks to unidirectional air flow, higher heart beat per breath, reduced brain vasoconstriction, greater compliance of airways, heart stroke volume, optimal capillary perfusion, efficient transient and steady-state vascular response, and so on (5). The respiratory system of birds occupies one-fifth of the body volume, a value four times greater than that in mammals (2). The wide wing span and synchronized flapping rate prequalify the high-flyers. Not only is the body morphology of birds well-suited for aerodynamic advantage, even physiological adaptations observed in birds like bar-headed geese exemplify their compatibility for higher altitudes. Instances of variation in the kinetics of enzymes like cytochrome-c oxidase, an enzyme that catalyzes oxygen reduction, corroborate the view that birds are for high altitude (6).

If soaring, flying, and migrating, all combined, could be posed as an optimal control problem, birds emerge as ideal candidates offering the most feasible solution. Do birds adopt dead-reckoning or do they sense the Earth's magnetic field for navigation? If so, surely altitude is for them.

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HIGH ALTITUDE IS FOR KITTENS?

TO THE EDITOR: In 1670 Robert Boyle and Robert Hooke and colleagues challenged the anoxic tolerance of many species using Hooke's fantastic exhausted receiver (a vacuum chamber). They were astonished to observe that day old kittens could tolerate hypoxia three times longer than adults of a "similar bigness"; adults like birds (1).

Now, admittedly, your average kitten is not very aerodynamic, but as pointed out by Llanos and colleagues (4) in this debate, they, like other young mammals (pre- and postnatally), are very tolerant of hypoxia and arguably better than your average bird contrary to the assertion of Scott and colleagues (5). Anaerobic tolerance of young animals is at least in part due to phenomenal glycogen stores and the capacity to reduce metabolic demand (2).

Tolerance is not, however, simply the domain of the young and perky. Marine species are very hypoxia tolerant while active. Furthermore, many species, like turtles and frogs, have the capacity to overwinter under icy water thanks to energy stores and metabolic adaptations (3). Indeed many cold-hardy creatures do well in oxygen-limited environments, including insects. Take the beautiful alpine Weta of New Zealand (*Hemideina maori*), who can suffer having up to 82% of its body frozen and live to tell the tale (6).

Many of these species are not particularly aerodynamic, but that is not the point of this debate. Both papers conclude the same thing: it is all about adaptation to the demands of the environment. Birds do it, bees do it, and frankly just about everybody else including fleas do it!

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HIGH ALTITUDE TOLERANCE IS NOT DETERMINED BY CLASS

TO THE EDITOR: Most birds do not live or fly at high altitude (HA), yet Scott et al. (5) suggest that birds are superior in this habitat. Their position appears to be, in part, attributed to birds' pulmonary anatomy and physiology: a flow-through system with small air capillaries that mechanically support blood capillaries via epithelial bridges, and a reduced thickness of the blood-gas barrier yielding an increased efficiency in gas exchange (6).

Although appearing to be advantageous, chicken broilers are known to display pulmonary hypertension that results in right heart failure and possibly death due to capillary rigidity and unaltered pulmonary vascular resistance, despite linear increases in pulmonary arterial pressure and pulmonary blood flow (6). In comparing broilers raised at HA (3,300 m) and sea level (SL), Cueva et al. (1) reported a 20% mortality rate in the HA birds that was attributed to right heart failure. Moreover, the Bar-headed goose (an HA dwelling bird) possesses a higher hemoglobin oxygen affinity compared with the SL Graylag goose and Canadian goose (4). Similarly observed in mammals, HA-adapted species (>4,000 m) such as the puma and fox display structural differences in hemoglobin and a higher oxygen affinity compared with similar SL species (3).

Thus, based on the available data and lack of direct comparisons between classes, an avian superiority at HA does not appear to exist. In agreement with Llanos et al. (2), successful adaptation to a habitat such as HA can be ascribed to the passage of evolutionary traits, regardless of animal class.

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

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TO THE EDITOR: Scott et al. (4) conclude from different experimental studies in birds and mammals that birds have a greater tolerance of hypoxia and a greater exercise capacity at high altitudes. For an organism to live and reproduce at high altitude complex adaptations are required dealing with acute, mid-, and long-term stresses at different physiological levels from molecule, to organ, to the whole body—and not surprisingly, it is therefore in every species also a very specific, long-lasting evolutionary process designed to be appropriate for the specific physiological needs in the life circle of that specific organism (2). Insofar, Llanos et al. (3) are right when they argue *1*) that a more appropriate exercise would be to compare directly high altitude-adapted birds with high altitude-adapted mammals. Along this line, it seems to be conclusive that they *2*) stress the point that the bird's superiority in pulmonary physiology is based largely on the hazards of pulmonary hypertension and edema formation in lowland species—and therefore any comparison by Scott et al. (4) might be inadequate and probably misleading. I feel what is actually missing in both articles is that any long-term evolutionary successful organism at high altitude has to deal besides hypoxia with other severe environmental strains such as low temperatures (hypothermia) and low humidity (dehydration), which might be in some cases helpful to overcome the hypoxic stresses (hypoxia/hypothermia cross-adaptations), in others deleterious (increased ventilation/increased respiratory fluid losses) as nicely shown by some easy calculations by Burton (1).

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TO THE EDITOR: The response to a physiological challenge such as hypoxia is clearly mutifactorial, and the debate highlights enhancements in cerebral/pulmonary capacity of birds (6) vs. placental/fetal tolerance in mammals (3). There are many points in a cascade where intervention may potentially increase flux, e.g., in juveniles, short diffusion distances afforded by small muscle fiber diameter allow an expansion of mitochondrial oxygen demand without exceeding microvascular capacity for oxygen delivery (1). An optimal solution to achieve the same outcome, however, depends on the relationship among elements with differential capacities. Due to plieotropic influences this is likely to be both species-specific and developmentally sensitive. Thus the unique unidirectional ventilation of avian lungs maximizes convective external O_2 delivery, while the thin maternal-fetal membrane maximizes diffusive internal oxygen exchange.

It is interesting to note that highly variable oxygen levels in the aquatic environment led to multiple sites for O_2 sensing in fish. Mammals required high stable environmental O_2 levels for development of placentation (allowing a single sensing site), while birds exploited variable O_2 levels without the need to recapitulate environmental O_2 sensing (4). There appears to be a parallel evolutionary trend for cerebral hypoxia tolerance. This is evident in some fishes and turtles (5), apparently maintained in the avian descendants of diapsid reptiles but lost in the mammals (synapsids) following divergence at 310 mya (2). We do need more data on the existence of cellular mechanisms underlying avian pulmonary vascular resistance to hypoxia and cerebral ionoregulation at high altitude. The jury may be out, but current betting is on the birds!

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