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# Letters to the Editor

## Acute Mountain Sickness, Vitamin C, Free Radicals, and HIF-1α

*To the Editor:*

We were interested to read Bailey's reply[1] to the recent publication examining the effects of oral medroxyprogesterone as chemoprophylaxis against acute mountain sickness.[2] In his letter entitled ''Ascorbate, Blood-Brain Barrier Function and Acute Mountain Sickness: A Radical Hypothesis,'' he suggests that a possible confounding factor in that study was the choice of vitamin C (ascorbate) as a placebo. He hypothesized that the free radical scavenging effects of vitamin C may have significant effects in protecting against acute mountain sickness. A small field study supports his theory.[3] We believe that Bailey's ''radical hypothesis'' may only partially explain the theoretical benefits of vitamin C at high altitude.

Recently, vitamin C has been implicated in the process of oxygen sensing. A universal system for oxygen sensing is now recognized within all mammalian species that involves the action of prolyl hydroxylase enzymes on hypoxia-inducible factor 1α (HIF-1α). HIF-1α is a transcriptional activator that regulates the expression of a number of hypoxia-responsive genes such as erythropoietin, heme oxygenase, and vascular endothelial growth factor.[4]

HIF-1α is constitutively expressed in all cells but is almost immediately broken down in the presence of oxygen. However, under conditions of hypoxia, it accumulates within cells and induces transcription of its target genes. Recently, vitamin C has been found to be an essential cofactor in the HIF-1α degradation pathway,[4] where it may act by maintaining the cofactor iron in the reduced state ($Fe^{2+}$), which is required for the action of prolyl hydroxylases.

Knockout mice with deficient HIF-1α expression (HIF-$1\alpha^{\pm}$) show a significantly decreased acute hypoxic ventilatory response after exposure to chronic hypoxia. Furthermore, they are protected against the development of hypoxia-induced pulmonary hypertension when compared with wild-type mice with normal HIF-1α expression.[5] Conversely, desferrioxamine, an iron chelator that induces HIF-1α activity, has been shown to induce a rise in pulmonary artery pressure in healthy humans similar in time course to that of hypoxia.[6] This suggests that by enhancing or inhibiting HIF-1α, it may be possible to affect human physiological responses to hypoxia. Vitamin C may be capable of such manipulation of the HIF-1α pathway in humans, as experiments in cell culture have shown that ascorbate supplementation potentiates HIF degradation.[7] This raises the possibility that vitamin C supplementation, by facilitating prolyl hydroxylase–mediated breakdown of HIF-1α, may affect physiological responses to hypoxia and therefore be beneficial at altitude.

Further evidence suggesting that vitamin C may play a critical role in oxygen sensing and augmenting the responses to hypoxia has been shown in a recent study of ascorbyl palmitate in hypoxic cats.[8] Ascorbyl palmitate is a lipid-soluble derivative of vitamin C; its lipid solubility increases its availability to chemoreceptors in the carotid body. The study showed modification of the ventilatory response to hypoxia and concluded that ascorbyl palmitate may have therapeutic effects in hypoxia. The authors suggest a number of hypotheses for its action, including a possible role in prolyl hydroxylase oxygen sensing and HIF-1α.

These studies suggest that the theoretical benefits of vitamin C on acute mountain sickness may be through a HIF-1α–related oxygen-sensing mechanism instead of or in addition to its radical scavenging effect on the blood-brain barrier as proposed by Bailey. Although the role of vitamin C in HIF-1α regulation and oxygen sensing is not yet fully understood, we cannot ignore its role in this system or attribute all its potential beneficial effects to Bailey's radical hypothesis.

Kyle T. S. Pattinson, BM, FRCA
*Nuffield Department of Anaesthesia*
*University of Oxford*
*Oxford, UK*

Andrew I. Sutherland, MB, BCh, BSc(Hons), MRCS
*Nuffield Department of Surgery*
*University of Oxford*
*Oxford, UK*

Thomas G. Smith, MB, BS;
Keith L. Dorrington, DPhil, DM, FRCA
*University Laboratory of Physiology*
*University of Oxford*
*Oxford, UK*

Alex D. Wright, FRCP
*Birmingham Medical Research Expeditionary Society*
*University of Birmingham*
*Birmingham, UK*

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## Alternative Footwear to Avoid Jungle Rot

*To the Editor:*

I read with interest the letter to the editor regarding jungle boots and jungle rot.[1] I have been trekking in the Amazon Basin with jungle-dwelling tribesmen since 1966. On the basis of my personal experience and the experience of North American and European expeditioners, who have on occasion accompanied me and my Amerindian guides on 75 or so treks lasting days to months, military-style ''jungle boots'' are unsuitable for serious, long-distance trekking in the tropical rainforest. One or 2 hours of hard walking through streams and muddy trails with such footwear can lead to blister formation with the skin peeling off in sheets, thereby bringing a jungle trip to a premature end. Furthermore, safely crossing log bridges and mossy, slime-covered river rocks is almost impossible in these boots. For jungle trekking, you need 2 pairs of shoes: a pair suitable for the wet, slippery conditions imposed by the trail and another pair that meets the need for dryness and comfort in camp.[2]

The following features are desirable in trail shoes:

- Uppers that hit just above or just below the ankles. Some people who choose the above-ankle design reason that the extra height gives some added protection from snakes.
- Extra protection over the big toe. Protective rubber or leather toecaps help keep the big toe from being severely battered and bruised.
- Moderately deep-tread outsoles. Traction on rugged and muddy terrain is important. Running shoes with hard, ''high-impact'' soles should not be worn because they become slippery on wet logs or river rocks.
- Quick drying time. Uppers of Cordura nylon and split leather, in addition to resisting abrasion and being somewhat breathable, dry out surprisingly quickly when placed in the sun. Even though hiking shoes usually become soaked within minutes on the trail, it is a psychological boost to start off each day with dry (or less-than-soggy) shoes. Because jungle travelers can be in waist-high water many times each day while on the trail, waterproof shoes with Gore-Tex liners are not essential.
- Snag-proof design. Shoes or boots with ''quick-lace'' steel hooks should be avoided, for vines and weeds become tangled around the metal hooks and may cause the wearer to stumble and pull the laces untied. Shoelaces should always be double knotted.
- Lightweight.
- Well broken in.

Any good brand with the above-mentioned characteristics will suffice.

Footwear needs are very different in camp. Being wet on the trail is one thing, but the trekker wants dry feet in camp. Lightweight, lug-soled rubber boots meet the criteria for jungle camp boots.

I have not known anyone to develop jungle rot who has followed the above recommendations.

A military jungle boot might be a consideration in a setting where the trekker or expeditioner does not have the assistance of porters and is carrying extreme loads on his or her own back and would benefit from the greater support of an actual boot rather than the trail shoes I have recommended. It is, by the way, always a mistake to traverse jungle long distances without the assistance of a native resident who is thoroughly acclimatized to the hot and humid conditions of the tropical rainforest.[3]

John Walden, MD, DTM&H
*Department of Family and Community Health*

*Marshall University School of Medicine*
*Huntington, West Virginia, USA*

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## Wolf-Rancher Health Maintenance Organization: A Conservation And Community Health Model

*To the Editor:*

We wish to share information about our collaborative effort of ranchers and environmentalists to resolve the conflict between wolves and ranchers in rural western communities by using health as a framework. Wolf restoration in the Northern Rockies has been an ecological and biological success, but wolves remain a source of controversy in western rural communities. In addition to being associated with livestock losses, the wolf is a surrogate for cultural and sociopolitical conflict affecting rural western communities beyond the wolf.[1] Although wolf-related livestock losses are few compared with other causes, predation further jeopardizes the marginal financial viability of ranchers and thus threatens loss of ranchlands that support biodiversity and wildlife habitat to exurban development, in effect escalating a destructive disconnection between economy and ecology.[2,3] Reactive killing of wolves by ranchers endangers the species recovery and its beneficial ecosystem effects. Ironically, a solution to this dual tragedy of conflict—and a novel economic resource—may be the wolf.

A ''think tank'' of professionals in wolf biology, wildlife conservation, ranching, natural resource economics, environmental ethics, public policy, and health care have proposed a concept for resolving wolf-rancher conflict. By using a risk-sharing health maintenance organization model, viable wolf numbers are maintained in a suitable habitat adjacent to participating communities by matching the presence of wolves to ''premium'' dollars funded by a national development campaign. Funds flowing through this organization will provide financial incentives for improving the health of rural western communities and for protecting wolves and wildlife habitat by transforming the wolf from a perceived liability into an asset, thus elevating debate beyond economics versus the environment. Our model is linked to community foundations to provide social, health, economic, and educational value to rural western communities as a means to help achieve our goals:

- Demonstrate that economic development and wildlife conservation are compatible
- Provide economic assistance for sustainable ranching and best ranching practices
- Provide compensation for livestock predation by using a reasonable formula that accounts for tangible and intangible costs
- Support proactive programs to prevent wolf predation on livestock
- Promote healthier food products to sustain rural western economies
- Prevent loss of rural western ranches and farms to exurban development
- Preserve private lands that support wildlife and biodiversity
- Develop opportunities for eco-tourism and eco-labeling to bolster local economies
- Provide support to colleges and universities to engage with their rural communities in research and applied programs in health, economy, and the environment
- Provide scholarships for community youth to attend local colleges and universities
- Transform cultural and political attributes toward the wolf and ranching
- Preserve wolves, wildlife, and the ranching way of life

In an effort to build local tolerance for the wolf, Defenders of Wildlife initiated the first privately funded livestock compensation program of its kind in 1987 to provide reimbursement for wolf-related losses. The Bailey Wildlife Foundation Wolf Compensation Fund, named in honor of its largest contributor, has reimbursed ranchers more than $328 000 in the Northern Rockies since its inception. This program was designed to compensate for livestock losses while wolves were listed as a federally protected endangered species. However, the US Fish and Wildlife Service is proposing delisting wolves from federal protection under the Endangered Species Act and allowing states in the Northern Rockies to manage them under state authority. State officials have identified compensation from predation as important to their future management of wolves. Defenders of Wildlife and our ranching partners agree that an innovative, comprehensive approach inclusive of but beyond compensation is necessary if both ranching and wolves are to survive.

The collaborative process of developing this project has created a unique partnership of the ranching and environmental community. Members of our steering com-

mittee have attended meetings in rural western communities to present our model and to receive feedback. As a result of grassroots efforts, we have developed partnerships within the ranching communities of Madison Valley, MT; Eagle Creek, AZ; and Salmon, ID. Ranchers from these areas serve on our steering and advisory committees along with representatives from Defenders of Wildlife and from the state and federal government.

Our program is designed to change attitudes, culture, behavior, and philosophy toward ranching, wolves, and other wildlife by demonstrating the positive economic and social outcomes that result when the economy is partnered with its environment. We hope that changing conflicts into cooperative and mutually beneficial outcomes will influence public policy by encouraging more solution-based regulations and management. Our program endeavors to achieve a ''win-win'' outcome for economy and ecology in the rural west by using health as a framework.

John B. Sullivan Jr, MD, MBA
*Tucson, AZ, USA*
Suzanne Stone
*Boise, ID, USA*
Lane Adamson
*Ennis, MT, USA*
Frank Casey, PhD
*Washington, DC, USA*
Lowell Cerise
*Salmon, ID, USA*
Jan Holder
*Safford, AZ, USA*
John B. Sullivan III
*Missoula, MT, USA*

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