Letters to the Editor

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

To the Editor:

We were interested to read Bailey's reply¹ 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 1 α (HIF-1 α). HIF-1 α 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-1 α 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-1 α degradation pathway,⁴ where it may act by maintaining the cofactor iron in the reduced state (Fe²⁺), which is required for the action of prolyl hydroxylases.

Knockout mice with deficient HIF-1 α 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-1 α expression.⁵ Conversely, desferrioxamine, an iron chelator that induces HIF-1 α 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-1 α , it may be possible to affect human physiological responses to hypoxia. Vitamin C may be capable of such manipulation of the HIF-1 α 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-1 α , 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-1 α .

These studies suggest that the theoretical benefits of vitamin C on acute mountain sickness may be through a HIF-1 α -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-1 α 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.

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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

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