

2. Curtis M, Zhu Y, Borroto-Esoda K. Hepatitis B virus containing the I233V mutation in the polymerase reverse-transcriptase domain remains sensitive to inhibition by adefovir. *J Infect Dis* 2007;196:1483-6.
3. Carrouée-Durantel S, Durantel D, Werle-Lapostolle B, et al. Suboptimal response to adefovir dipivoxil therapy for chronic hepatitis B in nucleoside-naïve patients is not due to pre-existing drug-resistant mutants. *Antivir Ther* 2008;13:381-8.

THE AUTHORS REPLY: Malgarini and Pimpinella inquire about the difference in baseline characteristics between the Latino and non-Latino white patients and the effect that these differences might have on the ability to conclude that the two groups have different responses to peginterferon alfa-2a and ribavirin. In designing our study, we took into consideration factors that could affect the response in the Latino versus non-Latino white patients with chronic HCV infection. These factors included black race and the presence or absence of cirrhosis, alcohol and drug abuse, human immunodeficiency virus infection, and other forms of liver disease, including hepatitis A and B. We limited the proportion of patients with cirrhosis in both ethnic groups. One of our goals was to identify factors that are predictive of a response in each group, in addition to investigating the overall difference between the two groups. As we noted in our article, we performed a multivariable logistic-regression analysis to evaluate the effects of baseline prognostic factors, such as the body-mass index, on the probability of a sustained virologic response. As

we show in Figure 2C of our article, the difference in sustained virologic response between Latino whites and non-Latino whites remained significant, and ethnic background was the strongest predictor of a response after adjustment for other significant factors. Therefore, we can confidently conclude that Latino whites have a lower rate of response to standard therapy for HCV than do non-Latino whites.

Schildgen shares his research findings regarding the altered host response to adefovir in HBV infection. We cannot make any relevant association between the findings in hepatitis B and those in hepatitis C, because they are very different diseases caused by biologically distinct viruses. In our article, we alluded to the fact that the difference in response rates between Latino whites and non-Latino whites could be due to dissimilar host factors, including genetic and immune characteristics; however, our objective — to explore whether there is a difference in the rate of response — has been achieved. Further research is needed to define the molecular mechanisms of this difference.

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Blood Oxygen on Mount Everest

TO THE EDITOR: Grocott et al. (Jan. 8 issue)¹ measured arterial blood gases in healthy climbers breathing ambient air on Mount Everest. The authors acknowledge the potential confounding influence of the subjects' use of supplemental oxygen before the sampling of blood gases, but further medication history is not provided. Apart from oxygen, a variety of medications, including acetazolamide, inhaled salmeterol, dexamethasone, sildenafil, and tadalafil, have been used by healthy climbers as prophylaxis against altitude-related illnesses.² Use of these medications may affect the physiological response and subsequent blood gas values in hypoxic, hypobaric conditions, particularly with respect to the pulmonary vasculature and the oxygen-hemoglobin dissociation curve.

In addition, the subjects' hemoglobin concentrations at 8400 m, and hence their arterial oxygen content, were estimated from the hemoglobin values measured at 5300 m. It is plausible that this calculation underestimates the hemoconcentration in the subjects at 8400 m that is likely to have occurred as a result of further dehydration and hypothalamic-renal effects,³ resulting in an underestimate of the subjects' true arterial oxygen content at the Balcony on Mount Everest.

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1. Grocott MPW, Martin DS, Levett DZH, McMorrow R, Windsor J, Montgomery HE. Arterial blood gases and oxygen content in climbers on Mount Everest. *N Engl J Med* 2009;360:140-9.

2. Luks AM, Swenson ER. Medication and dosage considerations in the prophylaxis and treatment of high-altitude illness. *Chest* 2008;133:744-55.
3. Blume FD, Boyer SJ, Braverman LE, Cohen A, Dirkse J, Mordes JP. Impaired osmoregulation at high altitude: studies on Mount Everest. *JAMA* 1984;252:524-6.

TO THE EDITOR: Grocott et al. calculated alveolar–arterial oxygen differences. But do the study’s calculations accurately reflect in vivo values? Oxygen solubility in whole blood is influenced by temperature,¹ but the actual body temperatures of the mountaineers were not taken into account in the authors’ calculations. A significant decrease in core temperature can be observed in climbers, owing to adaptive hyperventilation, which occurs when supplemental oxygen is suddenly diminished, withdrawn, or not used at all (Dujmovits R, AMICAL alpin: personal communication). Hypothermia leads to falsely elevated measurements of the partial pressure of oxygen (PO₂) and can thereby falsely decrease the calculated alveolar–arterial oxygen difference.² Exercise-induced hyperthermia would have an opposite effect.

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1. Sendroy J Jr, Dillon RT, Van Slyke DD. Studies of gas and electrolyte equilibria in blood. XIX. The solubility and physical state of uncombined oxygen in blood. *J Biol Chem* 1934;105:597-632.
2. Bacher A. Effects of body temperature on blood gases. *Intensive Care Med* 2005;31:24-7.

TO THE EDITOR: The calculation of arterial-blood oxygen content (CaO₂) by Grocott et al. uses a value of 1.39 ml of oxygen per gram of hemoglobin as the constant for oxygen-combining capacity. This constant is based on the molecular weight of hemoglobin.¹ Gregory reported a constant of approximately 1.31 ml of oxygen per gram of hemoglobin with the cyanmethemoglobin method for calculating hemoglobin concentration.² The difference between the constants can be attributed to iron hemochromogens. Since the Everest study used the azidemethemoglobin method for hemoglobin measurement, it is subject to the limitation described by Gregory.² Recalculation with the lower constant gives a new, lower estimate for CaO₂ at 8400 m, approximately 137 ml of oxygen per liter of blood, which is equivalent to the CaO₂ in persons at sea level who are anemic (hemoglobin level of approximately 10.5 g per deciliter).

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2. Gregory IC. The oxygen and carbon monoxide capacities of fetal and adult blood. *J Physiol* 1974;236:625-34.

TO THE EDITOR: It is unusual to see bicarbonate concentrations of less than 14 to 16 mmol per liter in response to chronic hypocapnia, as were found in the study by Grocott et al. Below this level, on the basis of studies in dogs at an arterial partial pressure of carbon dioxide (PaCO₂) of 22 to 25 mm Hg¹ with extrapolation to clinical practice, some handbooks on acid–base disorders suggest that metabolic acidosis is present in addition to chronic hypocapnia. Few studies have been performed in humans because of the difficulty of studying humans under extreme hypoxic conditions; the studies that have been performed have not shown bicarbonate concentrations below 17 to 20 mmol per liter in response to chronic hypocapnia (PaCO₂ of 28 to 30 mm Hg at an altitude of 3450 to 4880 m).^{2,3} Although the study by Grocott et al. involves more extreme altitudes, the bicarbonate concentrations of 10 to 11 mmol per liter at 8400 m strongly suggest a mixed acid–base disorder consisting of a chronic respiratory alkalosis and metabolic acidosis, which is also evidenced by the negative base excess. Since lactate levels were only minimally increased, the presence of a normal anion-gap acidosis is suggested. Did climbers use acetazolamide, a carbonic anhydrase inhibitor used for protection against mountain sickness?

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1. Gennari FJ, Goldstein MB, Schwartz WB. The nature of the renal adaptation to chronic hypocapnia. *J Clin Invest* 1972;51:1722-30.
2. Krapf R, Beeler I, Hertner D, Hulter HN. Chronic respiratory alkalosis: the effect of sustained hyperventilation on renal regulation of acid–base equilibrium. *N Engl J Med* 1991;324:1394-401.
3. Lahiri S, Milledge JS. Acid-base in Sherpa altitude residents and lowlanders at 4880 m. *Respir Physiol* 1967;2:323-34.

TO THE EDITOR: Grocott et al. speculate about the lower limit of arterial hypoxemia in humans and

the relevance of their findings to critically ill patients. However, I think that the relevance to the critically ill patients in the intensive care unit (ICU) is limited. Oxygen consumption and oxygen transport in the mountaineers were probably elevated (maybe these data can be provided). These values depend not only on arterial-oxygen content but also on blood flow, which is much more fluctuating. With respect to the latter, trained mountaineers differ considerably from patients in the ICU, who usually have multiple coexisting conditions.

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THE AUTHORS REPLY: Daley questions whether hemoconcentration due to dehydration might have resulted in an underestimation of the hemoglobin values used in the calculation of oxygen content at 8400 m. We cannot exclude this possibility, since hemoglobin was not directly measured at the time of sampling and the climbers had been active for 12 hours with limited rehydration (approximately 500 ml of fluids). However, immediately before the ascents to the summit, all subjects had free access to adequate fluids and were judged, on the basis of good volumes of clear urine, to be well hydrated. Daley also asks whether our subjects took any medications other than supplemental oxygen. Subjects took no medications, except for simple analgesics (acetaminophen and nonsteroidal antiinflammatory drugs), from the start of the expedition to the end of measurement.

Hilberath and FitzGerald ask whether hypothermia (or hyperthermia) may have altered the in vivo solubility of oxygen in whole blood and thereby falsely elevated (or lowered) the reported values. Although body temperature was not measured in the subjects at the time of sampling, all subjects were subjectively comfortable (neither cold nor hot), and this was confirmed by the clinical impression of attending investigators. Samples were taken with subjects at rest in a shelter (no wind chill), and they had recently shed layers of insulation in order to maintain comfortable normothermia.

Tasker suggests that the oxygen-combining capacity of hemoglobin should be 1.31 ml of oxygen per gram,¹ rather than the theoretical capacity of 1.39.² We chose 1.39 because the degree by which the oxygen-combining capacity of hemoglobin at high altitudes differs from the theoretical maximum is unknown. Furthermore, we highlighted the relative changes in oxygen content in comparison with sea-level values, and these relative values would not have been affected by the choice of constant.

De Vries and Berend are surprised by the metabolic acidosis observed in the measurements at 8400 m. This is a well-documented response to the respiratory alkalosis that occurs with acclimatization to high altitude, and similar values have been reported previously in both hypobaric-chamber³ and field⁴ studies. No subject took acetazolamide.

Hager expresses skepticism about the relevance of findings in mountaineers at high altitude to critically ill patients. Although we recognize that there are important differences between the two groups, we contend (and we have argued elsewhere⁵) that prolonged exposure to hypoxia (at high altitudes or in a hypobaric chamber or tent) in healthy, normal subjects provides a means of exploring the integrative physiology of adaptation to hypoxia in a controlled manner that is not currently achievable by other means.

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2. Gregory IC. The oxygen and carbon monoxide capacities of fetal and adult blood. *J Physiol* 1974;236:625-34.
3. Sutton JR, Reeves JT, Wagner PD, et al. Operation Everest II: oxygen transport during exercise at extreme simulated altitude. *J Appl Physiol* 1988;64:1309-21.
4. Winslow RM, Samaja M, West JB. Red cell function at extreme altitude on Mount Everest. *J Appl Physiol* 1984;56:109-16.
5. Grocott M, Montgomery H, Vercueil A. High-altitude physiology and pathophysiology: implications and relevance for intensive care medicine. *Crit Care* 2007;11:203.