Reply to Drs. Teppema and Berendsen

Erik R. Swenson
VA Puget Sound Health Care System, Seattle, Washington

TO THE EDITOR: Drs. Teppema and Berendsen (7) raise several points that highlight the complexity in interpreting how acetazolamide (AZ) and other carbonic anhydrase (CA) inhibitors alter breathing at high altitude and prevent acute mountain sickness (AMS). To the point that AZ does not increase hypoxic sensitivity of the peripheral chemoreceptors in man and, in fact, depresses it somewhat—this is universally the case when the drug is given before the onset of a metabolic acidosis, which occurs in roughly 4-6 h after the first dose and is maintained while the drug is continued on a regular twice daily schedule. Here, the published data demonstrate that when predrug PCO2 conditions are maintained in hypoxic ventilatory response (HVR) testing, the HVR increases with acetazolamide (2, 4, 8, 9).

More relevant to the situation at high altitude by contrast, if HVR is tested at the lower prevailing PCO2 and state of metabolic acidosis with drug dosing after 1–3 days, then HVR is largely unchanged (2, 6, 9). It is important, however, to state that despite an unchanged HVR, subjects taking acetazolamide still are better oxygenated. Thus these data on HVR under field-type conditions suggest that acetazolamide may still exert a negative effect on peripheral chemoreceptor responsiveness to hypoxia, but this is overwhelmed by the countervailing and stimulating effect of metabolic acidosis. Reflecting this, when ammonium chloride and acetazolamide, engendering roughly an equivalent degree of metabolic acidosis, were tested in the same subjects the increase in HVR was lower with acetazolamide (9). Clearly more work is needed and the careful and rigorous study by Teppema et al. (8) is an example of how this might be accomplished.

I entirely agree with their concluding point that the many CA inhibition-related effects as well as those unrelated to CA inhibition discussed in my review do make it difficult to assess how quantitatively the metabolic acidosis is responsible for the benefits of acetazolamide at high altitude. Given the complexities involved, experiments that compare other strategies of generating an equivalent degree of metabolic acidosis as acetazolamide are needed, but may be difficult to perform because the only feasible agent available is ammonium chloride, which itself has unpleasant side effects in some people, and in one study did not reduce AMS perhaps because its side effects mimic some of the same symptoms of AMS (1). One way to test the role of metabolic acidosis would be to quantitatively correct bicarbonate losses sustained by chronic dosing and thus eliminate its influence. I still believe it would be valuable to perform a placebo-matched lower inspired PO2 study to determine if acetazolamide has effects beyond simply improving arterial and tissue oxygenation. Another issue that has not received attention is whether some other means of replicating the small volume (diuretic and natriuretic) losses with acetazolamide by other mild diuretics (e.g., thiazides) or replacing the fluid losses sustained with acetazolamide would alter the incidence of AMS. It remains evident that despite five decades of use in AMS, we still lack a definitive explanation of its efficacy.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
Author contributions: E.R.S. conception and design of research; E.R.S. analyzed data; E.R.S. interpreted results of experiments; E.R.S. drafted manuscript; E.R.S. edited and revised manuscript; E.R.S. approved final version of manuscript.

REFERENCES