earlier, Edwards (10) in his initial study showed that subjects who had not been at high altitude long enough for good acclimatization had higher maximum blood lactate levels than well-acclimatized subjects.

The data in Fig. 1 predict that there would be no rise in blood lactate concentration on maximal exercise above the resting level at altitudes above ~7,600 m and indeed the highest data point (6) seems to confirm this. It is very extraordinary that under these conditions of extreme tissue hypoxia, blood lactate levels are so different from those seen in acute hypoxic exposure. Irrespective of whether this strange state of affairs does not occur in everybody (although the data in Fig. 1 are from a large number of subjects including both acclimatized lowlanders and high-altitude residents), and there may be some recovery of blood lactate levels with increased time spent at high altitude, this extreme reduction in blood lactate is certainly intriguing.

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COUNTERPOINT: THE LACTATE PARADOX DOES NOT OCCUR DURING EXERCISE AT HIGH ALTITUDE

Some 75 years of research has been undertaken studying lactate metabolism at acute and chronic exposure to altitude. Despite these endeavors there are no data providing either an explanation or convincing evidence for a change in muscle lactate production and accumulation in the blood during exercise at chronic exposure to altitude. The simple reason is that the lactate paradox does not exist. Hochachka (11) tried to explain the phenomenon. He suggested a reduced glycolytic potential and tighter coupling between ATP production and use, based on observation that Quechuas (altitude natives in the Andes) accumulated less lactate in blood than lowlanders and that they had a lower muscle lactate dehydrogenase activity (12, 13). However, these observations have been questioned as the subjects were anemic and the metabolic adaptation observed was due to anemia rather than to genetic or developmental hypoxia-induced adaptations (7). Indeed, we did not find any differences in muscle lactate dehydrogenase activity or isofrom or other proteins involved in acid/base balance or lactate transport in Aymaras compared to lowlanders (15). Moreover, maximal lactate levels were similar, pointing at a similar glycolytic potential in altitude natives. Since Aymaras
and Quechuas are closely related, it seems highly unlikely for genetic differences to explain the discrepancy in lactate dehydrogenase and blood lactate responses. In our study at Chacaltaya (Bolivia, 5,260 m), the lactate concentration and leg net lactate release were higher at submaximal but similar at maximal workloads compared to sea level after 9 wk of acclimatization. We wondered whether the altitude above that of permanent habitation or longer duration of acclimatization compared to most studies might have caused the lactate response to be similar as acute hypoxia after initially reduced levels. Our data were similar when the studies were performed after 2–8 wk at El Alto (Bolivia, 4,100 m), meaning that the lactate paradox does not exist (20, 25). In addition, the lactate concentration and net leg lactate release during continuous submaximal exercise were high after 4 wk of acclimatization (21) and confirmed the finding of Klausen et al. (18, 19).

Additional support for the normal glycolytic potential after acclimatization is the observation that when incremental exercise until exhaustion was performed with a small muscle mass, one legged knee-extensor exercise, the submaximal and maximal net leg lactate release was the same (25). These studies and others (5, 6, 7, 17–19) provide further evidence that there is no change in glycolytic potential with chronic exposure to hypoxia. Furthermore, the relationship between relative workload and either plasma lactate accumulation or net leg lactate release was maintained with acclimatization in lowlanders (25). This was already shown previously by Dill (6) in 1931. The study of Dill was used by Reeves et al. (23) as the first report of the lactate paradox, “blood lactate during exercise initially rose higher in one subject (THE, Edwards), than at sea level, but after several months residence, the concentrations were similar to those at sea level.” However, two other subjects, Talbot and Dill, did not show a change in submaximal and peak lactate accumulation with acclimatization similar to our observations (20, 25). Second, and more importantly, Edwards’ maximal lactate was actually unaffected with acclimatization, and the reason for his submaximal lactate levels nearing sea level values with duration of acclimatization was simply due to a shift of the lactate curves to the right caused by training. This meant that he was able to do similar work after 8 wk of acclimatization compared with sea level, which is actually discussed in the paper. Therefore, the Leadville expedition provides good support for the nonexistence of the lactate paradox, and it showed that at altitude the normal lactate to relative workload relationship is maintained, including that of Edwards.

Maximal lactate levels are difficult to determine since that last 30–60 s of an incremental max test will make a big difference in lactate concentration due to the exponential nature of blood lactate accumulation. Therefore, the two studies of Brooks and coworkers published in a series of papers (1–4, 22) are the most convincing support for the lactate paradox, as they showed reduced arterial lactate levels during 40 min of continuous exercise at 50% \( \dot{V}_{\text{O}_2} \text{max} \) after 3 wk at Pikes Peak (4,100 m) compared with acute hypoxia. Unfortunately, the first report (1, 2, 4) has serious methodological problems. The two-legged glucose uptake and lactate release exceeded up to above 200% of the systemic glucose disappearance and lactate appearance. In addition, to determine lactate oxidation rates, an inappropriate tracer was used and the required tracer bicarbonate prime was omitted. Therefore, the conclusions from these papers should be ignored. Of note is also that in both studies from Brooks and coworkers, no difference in leg net lactate release was found between acute hypoxia and 3 wk of acclimatization, thus there were no differences in muscle lactate production similar to our findings (20, 25). This may suggest that in their study the rate of lactate clearance from the circulation was increased, causing the reduced arterial lactate accumulation.

Another area with conflicting results is the activity in the sympathetic nerve system. It has been suggested that sympathoadrenal activity is reduced with acclimatization (22), but this was dismissed by direct muscle nerve activity determination (9). Consistent with these findings we have observed much higher blood levels of epinephrine and norepinephrine levels with acclimatization (20, 25). Despite the controversy on sympathetic activity it does not seem to be related to blood lactate levels, implying that it does not play a major role in muscle lactate production during exercise (20, 22, 25).

If we are so certain that the lactate paradox does not exist, why does an important review on the topic (23) and in Handbook of Physiology (8) show a graph with data suggesting the existence of the lactate paradox? The graph is assembled from two studies that were designed to investigate pulmonary gas exchange with simulated altitude, not lactate accumulation. Nevertheless, Reeves et al. (23) used the lactate concentration of acute hypoxia data from Wagner et al. (27) and the chronic hypoxia data from the study of Sutton et al. (24). For the following reasons, the acute and chronic hypoxia data cannot be compared: 1) different and inappropriate discontinuous exercise protocols to study the lactate paradox phenomenon; 2) different simulated altitudes (429 Torr and 347 Torr) for acute and chronic hypoxia, respectively; 3) different subjects; 4) chronic hypoxia was not prolonged exposure to a certain level of hypoxia since altitude was increased continuously (14).

In conclusion, we feel that there is more than reasonable doubt for the lactate paradox to exist and that no special adaptation occurs in the regulation of glycolysis to chronic hypoxic exposure. The studies that report a lactate paradox phenomenon might suffer more from confounders related to field studies in remote areas or hypobaric chambers, which cause lactate to be decreased with acclimatization not related to prolonged exposure to hypoxia per se. One could wonder whether the words of the Nobel Prize laureate A. V. Hill (10) in the preface of his last book are applicable to those who still believe in the lactate paradox, “It is odd how one’s brain fails to work properly when pet theories are involved.”

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REBUTTAL FROM DR. WEST

I am sorry to report that I do not find Dr. van Hall’s statement convincing. First, much of it concerns possible explanations for changes in blood lactate concentrations. For example, he refers to Hochachka’s work (1) and argues that the metabolic adaptations there could be explained by anemia rather than genetic or developmental causes. He also cites evidence that the glycolytic potential is unaltered when only a small muscle mass is exercised. Finally he discusses the controversy about the role of the sympathetic nervous system. However, the subject being debated is not the mechanism of the changes in blood lactate but whether the lactate paradox occurs. Therefore these sections of his statement are really irrelevant.

Second, I sympathize with the plight of Dr. van Hall because basically he is in a no-win situation. It is extremely difficult to prove that something does not exist, and simply listing situations where the lactate paradox is apparently not seen is insufficient. By contrast, if it can be shown that the paradox does occur under some conditions, the debate is over. In my previous statement I cited some 21 references to demonstrations that the lactate paradox does exist. I also added that perhaps the lactate paradox does not occur in everybody, perhaps the lactate concentration falls with acclimatization but then tends to recover, and perhaps the paradox is best seen at very high altitudes. But these qualifying statements do not negate the proposition the lactate paradox does occur during exercise at high altitude, which is the subject of the debate.

Two specific points in Dr. van Hall’s statement should be responded to. I thank him for referring to the publications of Brooks and colleagues, which I had overlooked. There may be some methodological questions about these studies, but overall the results certainly look convincing to me. Dr. van Hall refers to the Chacaltaya study (2), which was one of the first to challenge the existence of the lactate paradox, but a flaw in this study was the omission of any lactate measurements prior to the ascent.

In conclusion, there may be some situations where the lactate paradox does not occur. However, as Fig. 1 in my earlier statement shows, there is overwhelming evidence that the lactate paradox does occur during exercise at high altitude under some conditions, and it would be a brave man who ignored all this evidence.