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EDITORIAL

Reflections on the past three decades of high-altitude exercise research and the autonomic nervous system

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Introduction

When Pheidippides (530–490 B.C.) completed his run from Marathon to Athens, his goal was not physical conditioning but communication: to appraise the Athenians of their victory over Persia in the Battle of Marathon. Pheidippides exclaimed *chairete, nikomen* (greetings, we won!), and then collapsed and died. Two millennia later, marathon running has become part of an avalanche of exercise worldwide [1, 2]. Pheidippides completed 240 km of mountain roads in two days at an average speed of 5 km per hour, which is commonplace by modern ultra-running standards.

I will use the term "freestyle neurology" for research in which one practices what one preaches, engaging in sport and adventure that offers a chance to advance knowledge about exercise and the autonomic nervous system, unimpeded by the confines of federal funding or the commercial restrictions that come with funding from the pharmaceutical industry. To this end, I studied the autonomic nervous system at high altitude in the Andes, Ethiopia, the Himalayas, and New Mexico. These are demanding settings that offer rich research opportunities, because altitude sojourn activates the autonomic nervous system in lowlanders, while controls are readily available from local indigenous populations (Fig. 1).

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In combining exercise and autonomic medicine, I was inspired by Sir Roger Bannister (1929–2018), a record-breaking runner, who was also a pioneering neurologist and autonomic specialist [7]. Sir Roger and I became colleagues and friends after I arrived at Queen Square in 1961. He was awarded a Radcliffe travelling fellowship from Oxford University to Harvard, where he worked under the tutelage of Derek Denny Brown (1901–1981). Later, he got his medical degrees from Oxford and was appointed to the Order of the British Empire (CBE) in 1955 for his sub-4-min mile. Sir Roger had a lifelong interest in the autonomic nervous system. He was the founding editor of *Clinical Autonomic Research* and edited a book with Christopher Mathias titled "Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System", which went to its fifth edition in 2013. Amongst the research fellows, it was said that Sir Roger's mile spanned the world for in later years he was invited to lecture on running and the autonomic nervous system throughout Europe and the Americas. After his return from Boston he changed from an aloof upper class English man into a more approachable figure who would now talk to the fellows from around the world who came to learn clinical neurology at Queen Square from what was at the time the greatest assembly of neurological clinicians including Sir Charles Symonds (1890–1978) and McDonald Critchley (1900–1997). During my time at Queen Square, Sir Roger was a senior registrar, and we were both collaborators and competitors in our research endeavors. Before I left London, he arrived at my apartment with a large trunk, which he carried upstairs to my family's door. We used his gift to hold our belongings to travel to Boston, where I became a fellow at the Massachusetts General Hospital. On arrival at the Massachusetts General Hospital I was welcomed by C. Miller Fisher (1913–2020) and joined the brace of eight "stroke fellows" Miller accepted during his career. Miller insisted on making rounds during visiting hours so that he could interview his

Fig. 1 Freestyle neurology in action in the Himalayas, Peru, and Ethiopia. **a** Everest base camp in Tibet at 5,500 m, where the rowing machine provided a standard exercise test. **b** On the way to the base camp at a lower altitude ~ 3,800 m. Tibetan villagers watched the rowing machine in action before they in turn were tested at 5,500 m. **c** On a trail in Tibet. **d** A wedding in Cuzco, Peru. **e** A Tibetan yak herder. **f** At a monastery festival in Tibet, a tourist attraction. **g** Simien mountains, Ethiopia, the only research site requiring an armed guard. **h** Our armed guard needed to prevent marauding locals from pilfering our equipment at night. All images were taken by the author

patients' relatives. The interviews were lengthy but, thankfully, Miller insisted on driving me home, usually at about 2 am.

The Himalayas

The Himalayas were a fertile field for research for they provided easily reachable high altitude for the activation of the autonomic nervous system as well as friendly locals eager to participate in the "fun." For example, we tested the effects of blood viscosity on exercise performance [10]. Blood viscosity increases at high altitude due to increased red cell production, and we wondered whether higher viscosity would impede athletic performance. Contrary to our hypothesis, we found that those with lower viscosity performed worse at high altitude than those with normally increased viscosity, probably because the tachycardia induced by the altitude accelerated blood transit through the lungs, thus decreasing the available time for oxygen uptake. We also examined the effects of blood viscosity on autonomic functions such as reperfusion of fingertips after compression, a measure of skin blood flow [3], and found similar results; reperfusion was faster in people with lower blood viscosity.

Cerro de Pasco, Peru

In Cerro de Pasco, Peru (altitude: 4,338 m), numerous research endeavors led to advances in the understanding of hypoxia, exercise, and the autonomic nervous system. For example, native highlanders from Peru are extremely resistant to the effects of orthostasis when compared to lowlanders [3]. Many suffer from chronic mountain sickness. The prevalence of chronic mountain sickness among young adults (20–29 years) is around 7% but it can reach 33% in elders (> 60 years). We found evidence of altered mitochondrial morphology and function in the cultured neurons of subjects with chronic mountain sickness. We also saw increased cell death under the hypoxia prevailing in Cerro de Pasco due, in part, to altered mitochondrial dynamics [6, 8, 12].

Simien Mountains, Ethiopia

In the Simien Mountains, Ethiopia (altitude: 4,533 m), we camped just below the summit of Ras Dashen at an altitude similar to that of our sites in Peru and the Himalayas, and collected blood samples from villagers. Laboratory analysis of their cells enabled us to compare the expression of a small subset of genes ($n=8$) in these Ethiopian highlanders with the expression of the same genes in Andean and Himalayan populations. Whereas normoxia-induced gene expression changes were previously found in Andeans, those changes were absent in Ethiopians, as they are in Himalayans. This is consistent with physiologic studies finding no increase in cerebral circulation and hypoxic ventilatory drive in Ethiopians and Himalayans at high altitude, and with the absence of chronic mountain sickness on the East African altitude plateau [5], as in Tibet—and in contrast to the Andes [11, 12].

Sandia wilderness crossing research run, New Mexico

I organized the *Sandia Crossing*, an annual wilderness run in the Sandia Mountains (close to Albuquerque, NM) near my home—an extreme event that posed a physical challenge for me and other participants and also a chance to study the neurological effects, especially on the autonomic nervous system, of intense, sustained exertion at high altitude. This was a 46 km annual trail run that reached an altitude of 3,300 m, starting and finishing about 1,800 m [4]. The Forest Service allowed 50 runners and uniformed employees counted runners as they passed through a checkpoint. There was no entry fee, but participants were expected to cooperate with research projects, and they always did. All runners received a specially minted medal irrespective of finishing place. The record for a male finisher still stands at 3 h and 29 min. Among the numerous scientific "firsts" from data collected over 13 years was the discovery that running led to an increase in circulating endorphins [9]. At the finish line, it was noted that runners had constricted pupils, suggesting an endogenous opioid had been released during the run. We later instilled naloxone drops, an opioid antagonist, at the finish, which caused considerable pupillary dilatation. At the next annual race, we obtained blood; we had to hire mules to carry the samples on ice out to the boundary of the National Forest where it was spun and the serum driven to the laboratory. Indeed, the level of endogenous opioids was significantly higher at the finish when compared to the levels at the start; this discovery revealed also the possible biological basis for the storied "runner's high [1]." Such collective "freestyle neurology" endeavors, unfortunately, are not possible during the times of the COVID-19 pandemic.

Conclusion

Pheidippides' run two millennia ago inspired a change of lifestyle and, ultimately, a field of research that has provided some of the most rewarding moments in my study of the autonomic nervous system. Over the decades, I have watched the neurobiology of exercise change from an informal pursuit on the edge of neurology to one that is squarely in the mainstream.

Conflict of interest

The author declares no conflict of interest.

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