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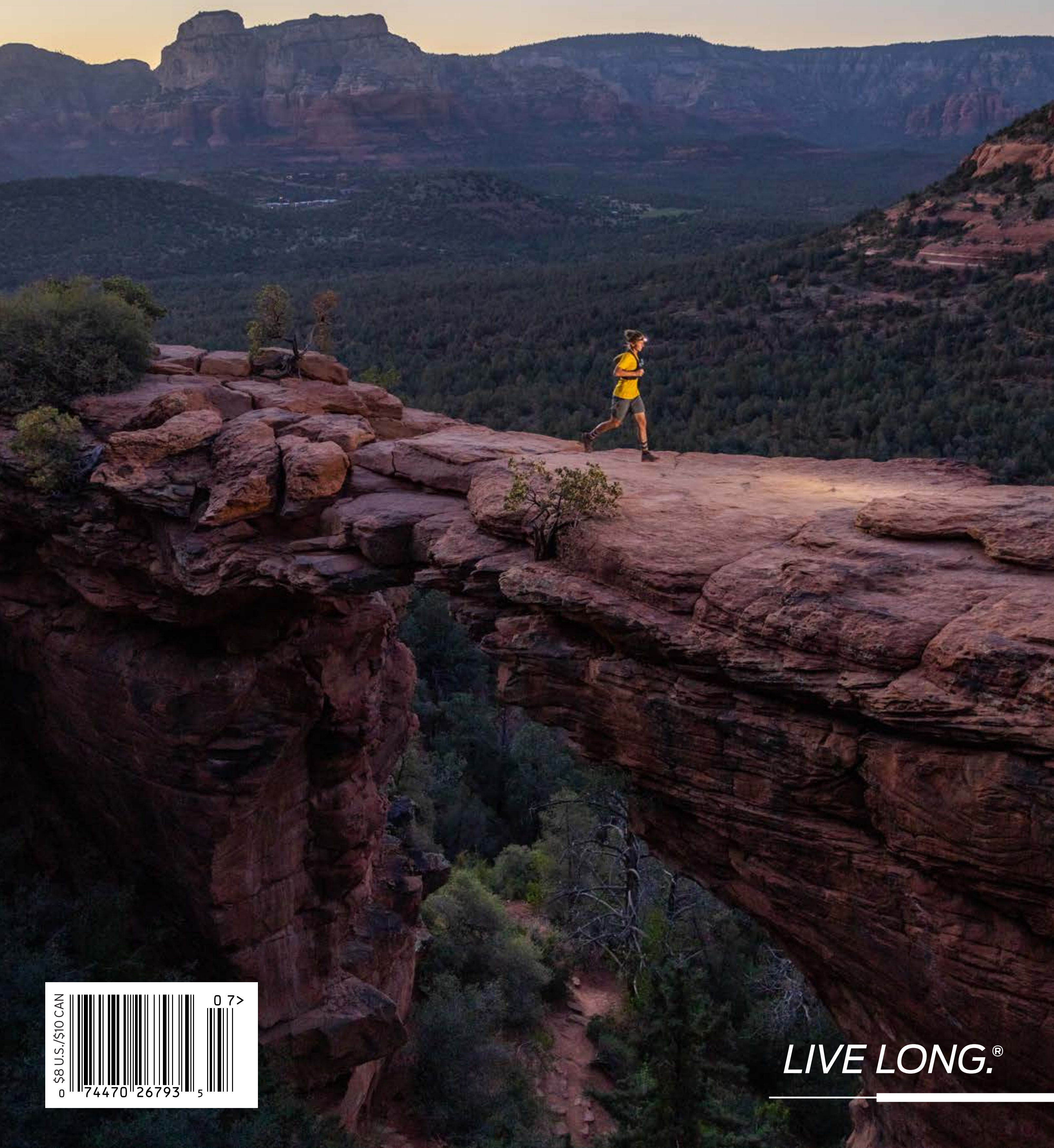

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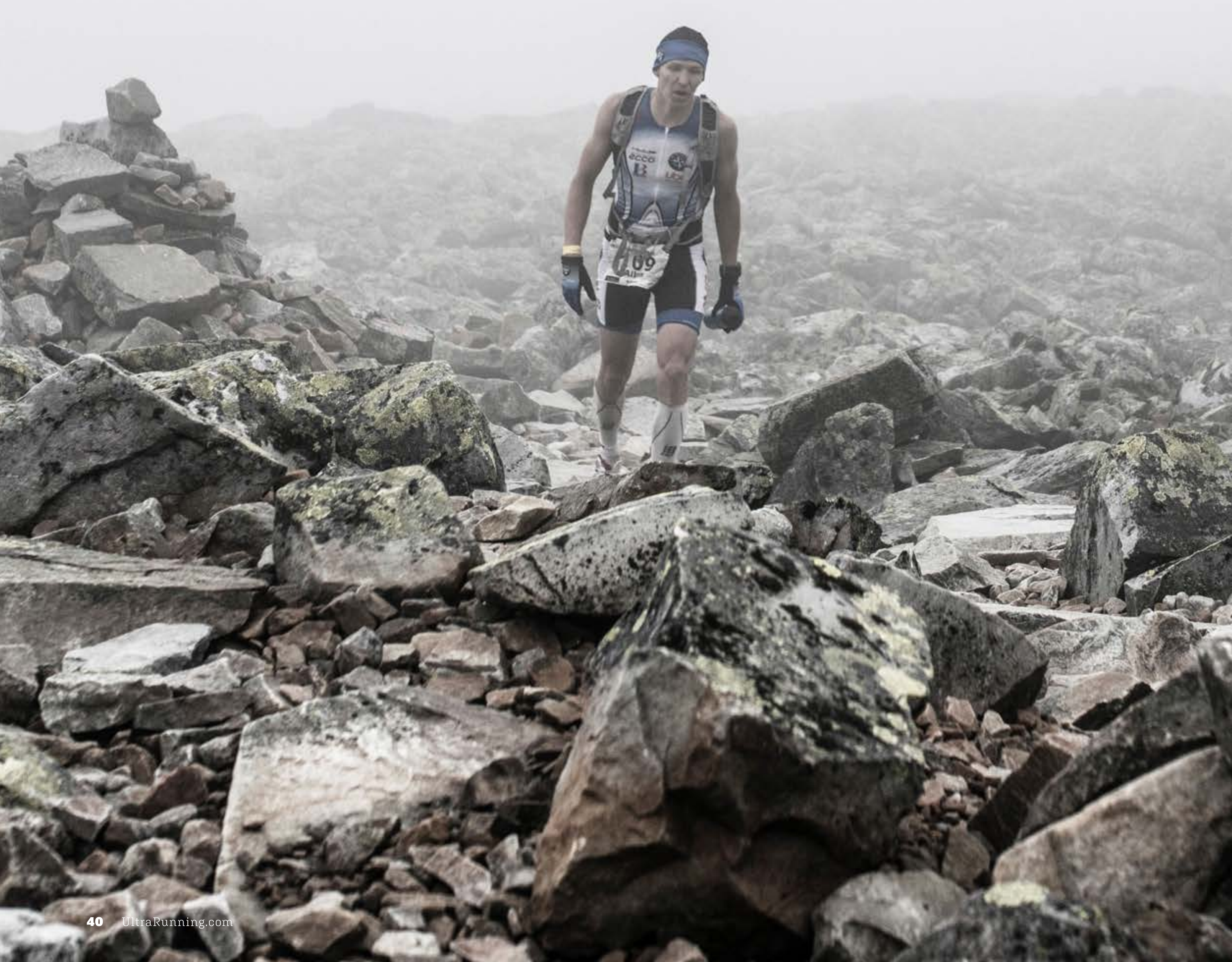
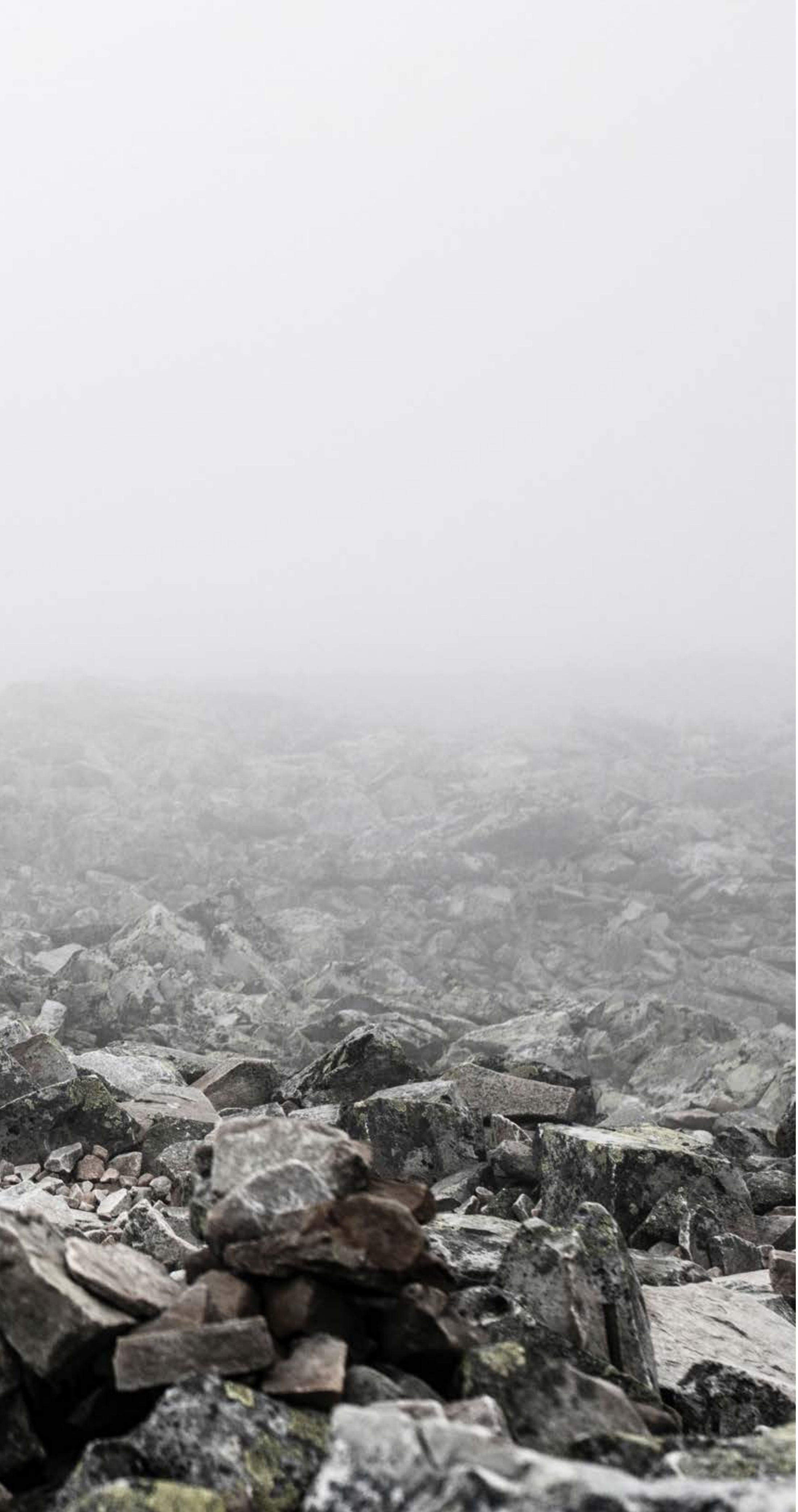
SCIENCE AT THE EXTREME

Stories from the "Frontlines" of Applied Research

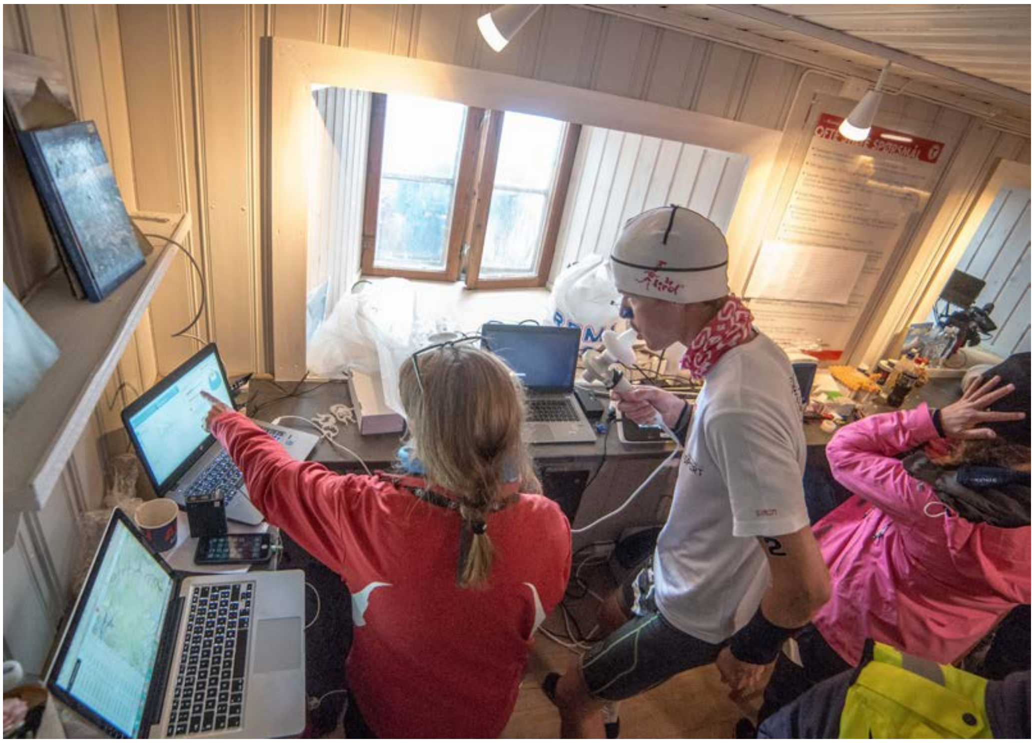
BY NICK TILLER, PHD, MRES





A box of mouthpieces slid across the floor of the minibus, crashing against the wall, and the light was fading fast, diminishing our window to make it to the base of the next climb. Consequently, the driver, an ex-Royal Navy serviceman, was unrelenting on the gas. The athletes gripped their seats as the vehicle twisted and turned through narrow, mountainous valleys. I held even tighter to the lung function device as Karl, one of the athletes, performed his breathing maneuvers. Making matters worse, the sky was dropping its payload on the tarmac, and it was becoming dangerously slick. My concern for the integrity of the data was being quickly overruled by the goblins of self-preservation. These were hardly conditions one associates with a 'controlled scientific experiment.' We were 14 days into a 25-day expedition to conquer 100 of the highest mountains in the British Isles, and the team's lung function values had been in steady decline for the last two weeks. And so, before they began the next climb, there was an imperative to take those measurements in our heavily improvised mobile laboratory. Fortunately, Karl—the team

Gausta Peak, 1,183m above sea level, is the final climb of the Norseman triathlon. From there, volunteers headed for the tourist cabin to begin their post-race medical assessments.
COURTESY OF JØRGEN MELAU



An athlete performs spirometry—a pulmonary function test which assesses the competency with which air can be moved in and out of the lungs as a function of time.
COURTESY OF JØRGEN MELAU

leader—was both sympathetic and spirited, and he performed his breathing tests just as valiantly as he summited the next peak.

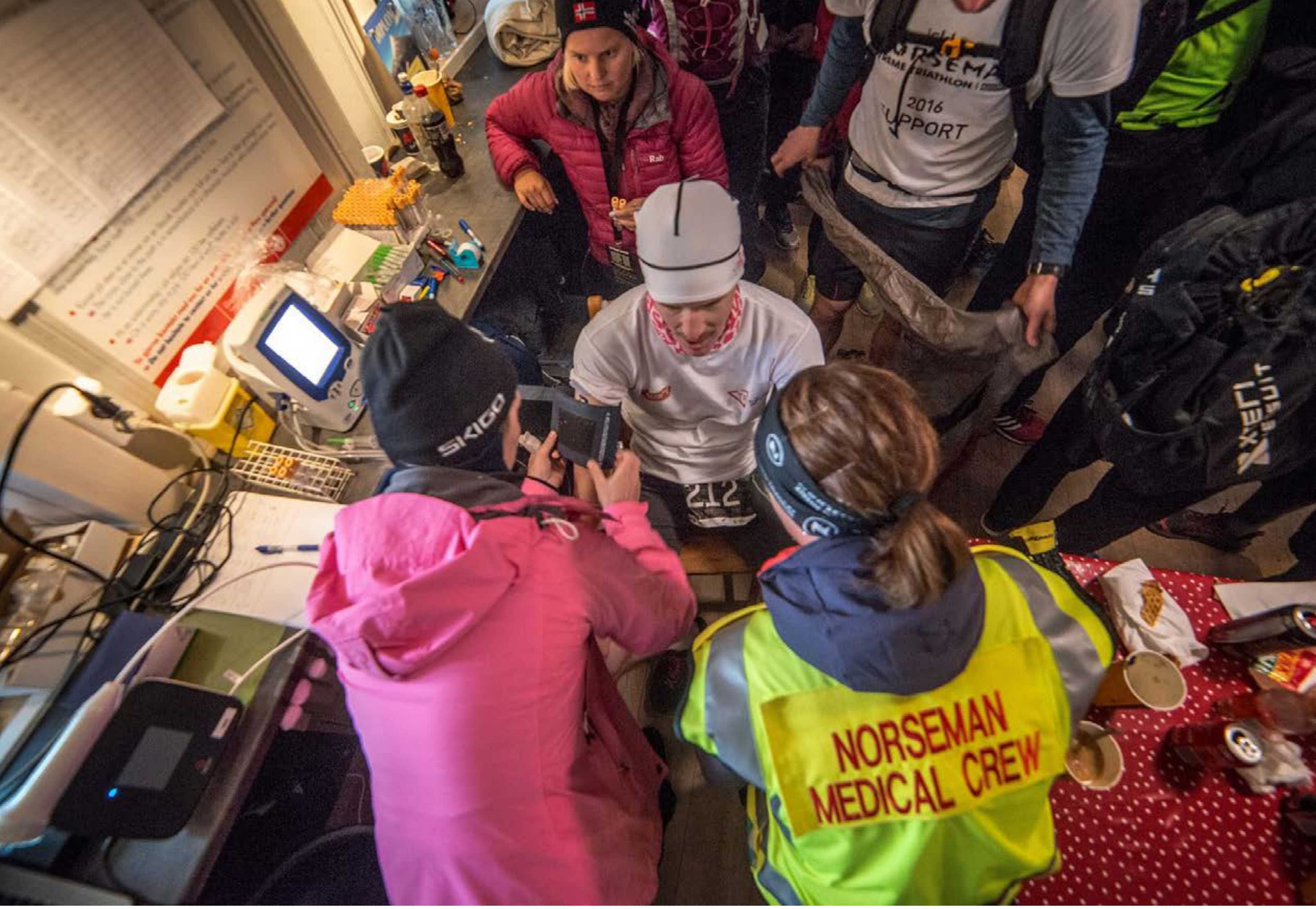
SCIENTISTS HAVE BEEN EXPLORING the physiology of extreme exercise for nearly a century. Many of the studies contributing to our understanding of this complex area have been conducted in the field: at the start/finish lines of races, in makeshift laboratories and even on the trails themselves. These experiments, performed on the 'frontlines' at some of the world's most notorious races, have slowly dismantled the barriers between science and practice, and have refined our understanding of how the cardiopulmonary, musculoskeletal, renal and digestive systems respond to ultramarathons (or ultra distances). We know more about the sport's physiology and pathophysiology than ever before. But it hasn't come easily. In their pursuit of deeper insights, researchers have had to overcome considerable challenges such as the logistics of transporting fragile equipment to remote locations, motivating exhausted athletes to perform demanding medical tests and facing the same unsociable hours and sleep deprivation that afflict the athletes themselves. All must be tackled while maintaining the integrity of the data. For many remarkable feats of ultra endurance, there's a research team behind the scenes having an adventure of their own. Here are some of their stories.

These experiments, performed on the 'frontlines' at some of the world's most notorious races, have slowly dismantled the barriers between science and practice.

Exploring physiological responses to the 100 Peaks Challenge was a true test of my commitment to scientific research. With technical equipment in hand, I followed the team to various locations around Great Britain. We camped in fields by the country's highest peaks, including Ben Nevis in Scotland and Scafell Pike in the Lake District. I took lung function measurements in the wind and rain and endured the height of "midge season" which threatened to derail data collection with a plague of insect bites. But I didn't choose the 100 Peaks Challenge just to pacify my scientific curiosity. For Karl, this was a deeply personal journey—one that he'd arranged to honor his brother, Lloyd, who'd been killed in action on the 25th day of his third tour of Afghanistan. Seeing Karl endure the physical toll of the challenge, in addition to valiantly bearing its emotional weight, was a privilege. Indeed, witnessing the resolve conjured by contestants of this ludicrous sport is one of its most inspiring features.

From the four finishers of the challenge—which, each day, demanded 5.5 hours of exercise and around 3,000 calories—only Karl's data was sufficiently complete and precise enough to make it to publication. Despite the less-than-optimal conditions, we eventually published our data as a case report in the journal *Frontiers in Physiology* (Tiller et al., 2019). We made measurements throughout the challenge and anchored the study with medical tests before and after. A key finding was that Karl's lung function steadily declined. By the end of the event, he was unable to fully inflate his lungs (a condition referred to in pulmonary medicine as a "restrictive pattern"), and he had a diminished capacity to absorb oxygen through his lungs and into his blood. We can only speculate on the causes, but it may have been due to mild fluid accumulation in the lungs. Extreme exercise is also known to cause muscle damage and oxidative stress, resulting in a generalized inflammatory state. By day 14, this manifested in Karl as increased endotoxin concentrations in the blood (a condition termed "endotoxemia") and an upper respiratory tract infection that gave him a sore throat and wet cough. As unpleasant as these symptoms may sound, none of them were of immediate clinical concern, and they scarcely slowed our intrepid explorer. In fact, he recovered relatively quickly after the challenge. This is a testament to his excellent baseline health and fitness, as well as the physical and psychological resilience of the human body.

However, resilience is not infinite. Extreme conditions, poor preparation and bad luck can coalesce to reveal cracks in the façade. A recent report published in *Wilderness and Environmental Medicine* highlighted four cases where runners needed to be



Blood samples and vital signs being recorded.
📷 COURTESY OF JØRGEN MELAU

hospitalized after the Western States Endurance Run (WSER) (Pasternak et al., 2023). The athletes—three males and one female—suffered serious running-related conditions including rhabdomyolysis (severe muscle damage causing muscle proteins and electrolytes to leak into the blood), hyponatremia (low blood sodium concentrations) and severe kidney injury that required weeks of dialysis. Medical tests also highlighted the physiologically important, but often ignored, "cardio-renal axis," which is the synergistic relationship between kidney and cardiac damage. "Serious kidney damage during ultra-marathon is rare," said Dr. Andrew Pasternak, WSER medical director and lead author of the study, "but it still happens if athletes aren't careful. Western States, being one of the more extreme 100-mile footraces, taking place in very hot conditions, increases the risk of medical problems. We urge our runners to minimize the risk of kidney injury by staying hydrated, managing their electrolytes and avoiding NSAIDs (non-steroid anti-inflammatory drugs)." While all four individuals thankfully recovered, one is yet to return to competition.

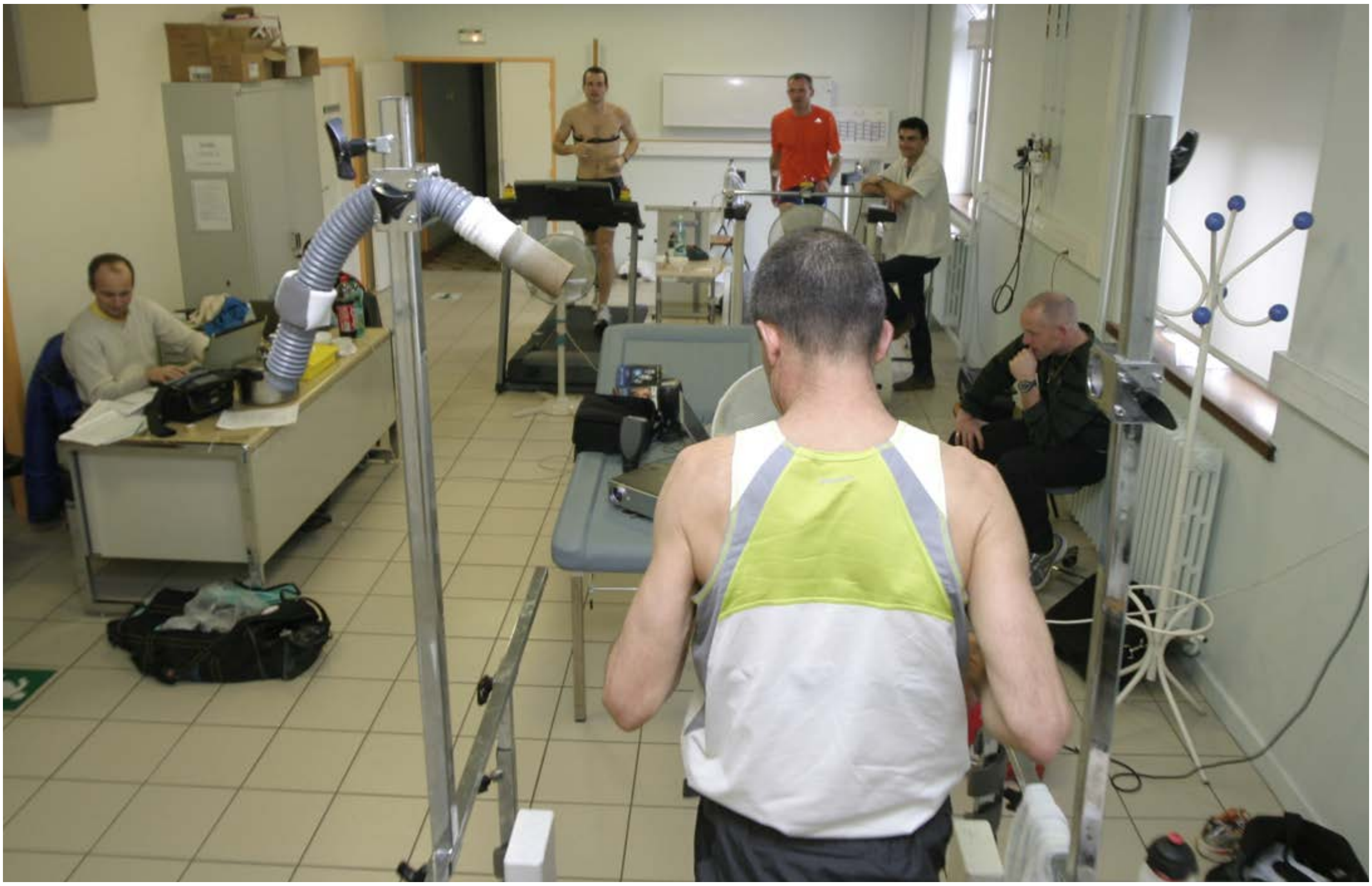
ANOTHER OF THE WORLD'S MOST GRUELING ULTRA MARATHONS, the Ultra-Trail du Mont Blanc, takes place each year in the French, Swiss and Italian Alps. In 2019, I had the opportunity to spend two weeks in Chamonix, France, collaborating with a team from the Mayo Clinic to collect data at both UTMB and the shorter CCC. Before the experiment could begin, there was the simple task of transporting our fragile measuring devices—ultrasound scanners, lung spirometers, blood sampling apparatus—from the United States to Geneva, and then onto Chamonix via minibus. It then took 5 hours to turn three bare rooms at the National School of Mountain Sports, our home for the duration of the project, into makeshift physiology laboratories, ready to accept research participants.

Performing the experiment meant navigating several issues that threatened to derail our data collection. To capture acute responses to the event, we needed to shuttle athletes to the labs as soon as possible after they'd crossed the finish line. Often, they were physically and emotionally drained, having covered up to 171k on foot, climbed around 32,800 feet, faced intermittent exposure to altitudes above 8,000 feet and endured extreme temperature swings from 86 degrees at sea level to 21 degrees near the glacial peaks. It required patience and empathy to cajole exhausted and sometimes delirious runners, some of whom needed medical assistance, through the technical tests. We also wanted to capture responses from the full spectrum of competitors: from the first of our athletes who finished the CCC at hour 15, to the last of our athletes who finished the UTMB at hour 45. This meant maintaining lab operations for about 30 hours. It was exhausting work but also incredibly rewarding. We were inspired by the feats of endurance we witnessed and felt appreciation from the athletes that we were contributing to the science of their sport. *Our* sport.

To date, we've published two papers from the experiment. In the first (Stewart et al., 2019), we found evidence of "heart damage" in athletes who finished the race, together with a diminished ability to transfer oxygen through the lungs and into the blood—similar cardiopulmonary "dysfunction" that we saw in Karl after his 100 Peaks Challenge. This time, using ultrasound scanners, we identified fluid accumulation in the lungs of a small handful of runners (a condition known as pulmonary edema). We're yet to identify the factors that predispose some runners to clinically meaningful responses to ultrarunning, but there's likely to be a genetic component. In the second study (Tiller et al., 2022), we sought to test the idea that females might be better able to tolerate the stresses of extreme exercise owing to their potentially superior fatigue resistance. From our final sample of 53 runners, there were only eight female finishers. We then selected a group of eight males whose finish times most closely matched the female average. We were surprised by what we found when comparing the physiological responses of the groups. Across multiple variables, including markers of cardiac, musculoskeletal, renal and respiratory function, it was the male group that experienced more frequent perturbations and with larger effect sizes. Despite the small sample, our preliminary study is one of the first to suggest that females might be more physiologically "robust" to endure the stress of ultramarathon racing.

FEW PEOPLE KNOW CHAMONIX AND UTMB like Professor Guillaume Millet. Since 2009, he and his team have conducted three large experiments at the race, testing close to 150 athletes on numerous occasions and producing at least 20 independent papers to do justice to the data. But it's a unique study that his team conducted at their lab at UJM-Saint-Etienne in 2011 that I was particularly fascinated to explore (Millet et al., 2011). They managed to convince 14 ultrarunners to run "as far as possible in 24 hours" on a motorized treadmill, without payment. All while being pushed and prodded in the name of science.

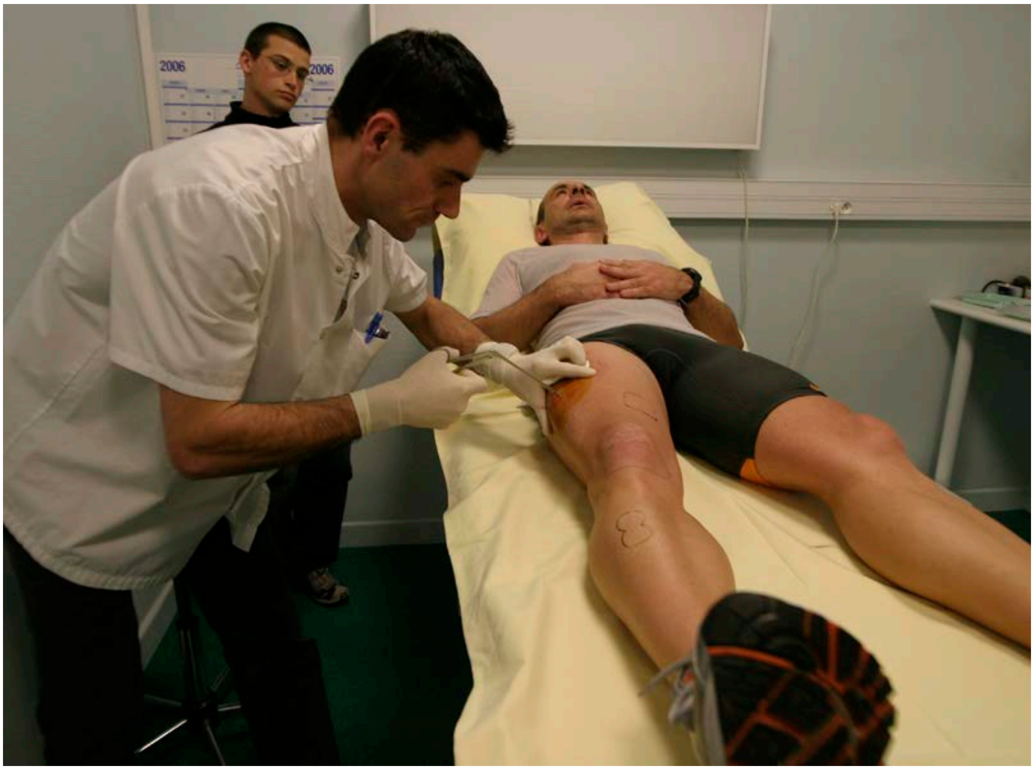
The setup was such that two or three athletes ran simultaneously on adjacent treadmills, each with his/her



Three athletes contest the 24-hour time trial as the research team provides ongoing moral and technical support.
COURTESY OF GUILLAUME MILLET

own support crew providing nutrition, hydration and moral support. Far from stoking the fires of competition, the grueling challenge in the artificial space cultivated a unique camaraderie within and among the crews. One might expect it to have been difficult to convince 14 runners to contest an unpaid 24-hour time trial on a treadmill. On the contrary, Guillaume found his participants very forthcoming. “We had more volunteers than we were able to test. One athlete from Belgium wanted to participate so badly he was willing to pay for his own travel and accommodation. He was fueled by his passion for the challenge, to have a unique experience and to contest something inaccessible to others.”

The researchers wanted to know how well physiological and biological variables predicted performance in the 24-hour time trial. They extracted muscle biopsies from the athletes’ thighs and assessed the samples for aerobic enzyme activity and blood vessel density. They then measured gas exchange during a maximal treadmill test to determine running economy and maximal oxygen uptake. The average distance covered during the challenge was 149k (range 128-173k)—an impressive feat considering the frequency with which athletes were stopped for the scientific tests. The distance was most strongly correlated with maximal oxygen uptake (VO2max), which predicted 82% of the variance in performance. A highly developed blood vessel network in the muscle and a good running economy were also important factors. Although perhaps not applicable to all race types and distances, the data reaffirms the importance of “maximal aerobic fitness” in successful ultramarathon performance.



One of the research team members extracts a sample of muscle tissue from an athlete's right thigh before the time trial begins.
COURTESY OF GUILLAUME MILLET

Despite Guillaume's famously demanding studies, he rarely has difficulty recruiting subjects. Why? Because he's a highly credentialed ultramarathon runner in his own right, having placed fourth at UTMB. Being a runner and a researcher offers unique insights into the trials and tribulations of racing. It enables scientists like me to empathize with participants who might be exhausted, dehydrated or injured after crossing the line. Guillaume even participates in some of his own experiments. "I'd prefer the athletes know me first as a runner, and then a scientist," he explains, "It helps develop trust and mutual respect. When athletes volunteer for one of my studies, they know they'll be treated like runners and not lab rats." Ultramarathon research is unique in that, by volunteering for research, runners can contribute to the understanding of the physiology but simultaneously share in the experience with scientists who are oftentimes equally passionate about the discipline.

THE START LINE OF AN ULTRA-ENDURANCE EVENT is, invariably a frenzy of excitement. At the Marathon des Sables, the renowned race through the Sahara Desert that I contested back in 2011, hundreds of runners from around the globe assembled at a large, inflatable arch as AC/DC's "Highway to Hell" boomed over the speaker system. It's symbolism that wasn't lost on the competitors as they charged across the start line into the scorching desert expanse. At UTMB, thousands of supporters line the promenade, feverishly cheering the athletes who, invigorated by the crowds, tear off into the mountains. And at the Western States start line, as the digital clock counts down to zero, an hour before the sun rises over the mountains, athletes and spectators cheer enthusiastically as the race begins to a kaleidoscope of camera flashes. At the start of the Norseman, arguably the world's toughest Ironman-distance triathlon, it's so quiet you can hear the zippers being fastened on each individual wetsuit.

Nervous energy suffuses the air, creating an unsettling silence. At 5 a.m., a ferry carries the athletes into the middle of the Hardangerfjord in central Norway to begin the race. The sky is dark, and the water is darker. Athletes bunch together in the limited space and, like paratroopers jumping one-by-one from a moving aircraft, they make a leap of faith into the blackness.

Athletes bunch together in the limited space and, like paratroopers jumping one-by-one from a moving aircraft, they make a leap of faith into the blackness.

Hitting the frigid water causes skin temperature to drop rapidly, triggering a reflex that results in constriction of the airway muscles, making it harder to breathe (Illidi et al., 2021). In 2017, as the athletes exited the fjord about an hour after the start, entering the first transition where they impatiently stripped their wetsuits, Dr. Illidi and her team were waiting to take their first set of measurements. "We wanted to see how the cold water affected their body temperature and also assess the interaction between the tough environmental conditions and the physiological strain of the race," said Dr. Illidi. From small electronic "tablets" that athletes had swallowed several hours earlier, the researchers were able to track core body temperature wirelessly using handheld devices. Later, the post-race measurements took place at the finish line, 3,881 feet above sea level at the summit of Gausta Peak. "To meet athletes after the race, we had to hike up the mountain with all our equipment—mobile gas analyzers, temperature sensors, laptops—and create a makeshift lab in a cabin at the top." There, jagged rocks, low-lying clouds and slippery shale met the athletes at the conclusion of an effort that lasted an average of 15 hours. From there, they stumbled into the lab where they were wrapped in blankets and readied for the experiment. "Many of the athletes needed medical attention before, during and after the physiological assessments," said Dr. Illidi. "All the athletes and their support crews were using the space. It was crowded and noisy, and we had to yell our instructions." Their sample of 57 finishers included the first and last-place participants, making their testing day more than 18 hours long.

Nearly every athlete experienced a significant decline in their lung function following the race, probably due to a combination of the cold water and the grueling physical effort. In fact, the team's findings suggest a potent airway obstruction, probably due to an inflammatory response causing airway narrowing and mucous production. Lung function still hadn't fully recovered 24 hours after the race. The data highlights why it's important that athletes with respiratory symptoms are thoroughly examined by a doctor before competing in such extreme exercise (Stensrud et al., 2020). Accompanying the diminished lung function, the team found that the percentage of red blood cells bound to oxygen had decreased by approximately 5%, a condition known as exercise-induced arterial hypoxemia. This was partly due to the final climb that finished at moderate altitude. All changes were transient. “It was a truly profound experience,” said Dr. Illidi, who is a former elite triathlete. “Being able to explore the science of a sport about which I’m so passionate inspired me to become a full-time exercise science researcher.”

Showcasing these studies and the stories behind them exemplifies the commitment and sacrifices made by researchers in their ongoing pursuit to reveal the complex physiology of ultra-endurance sports. Scientists face many challenges in this quest and must balance several opposing forces. They must carefully tread the line between producing applied data that reflects real-world phenomena and data that is trustworthy and robust. Too much emphasis on the former leads to high error rates and non-replicable studies which, in turn, undermine public trust in science. They must also strive to do their work with a detached objectivity but also employ empathy and compassion when dealing with the athletes. It requires tremendous skill to consolidate these contradictory aims, and it isn’t always accomplished. Kudos to those who manage it.

In sharing these stories, I also hope to inspire readers to participate in research studies when opportunities arise. There’s a profound shortfall in volunteers for ultra-endurance research—it’s not always well-paid and yet asks a tremendous amount from runners who have already invested much time and effort to make it to the start line. Nevertheless, the data we obtain can be tremendously important for our community. Through research, we can elucidate the various predictors of performance, helping runners to optimize their training and nutrition strategies. In addition, understanding the multidimensional stresses imposed by a given event can help us improve competitive longevity and help medical professionals and race directors make ultrarunning safer. And although the number of studies on “ultra endurance” has doubled in the last decade, much of the research is of poor quality, characterized by small sample sizes and superficial measures that gravely undermine our confidence in the findings. Part of the solution is to derive a larger athlete pool.

We especially need more female ultramarathon runners. Females make up only 10-20% of runners in a given race (Tiller et al., 2021), and this exacerbates the existing issue of female underrepresentation in exercise science research (Mujika & Taipale, 2019; Nuzzo, 2021). There have been numerous exceptional, record-breaking performances by female athletes in ultrarunning in recent years, increasing speculation that they might be predisposed to success in such events. But a failure to consider the clear anatomical and physiological differences between males and females may limit the effectiveness of training programs and negatively affect efforts at promoting competitive longevity. Females won't reach their true potential in the sport until the participation numbers become more comparable.

Lastly, while I cannot claim to speak for all ultra-endurance researchers, I know that many of us are equally as passionate about the sport as we are about the science. At its core, racing is about overcoming obstacles. Research is the same. And being able to meld professional and personal interests, to be on the frontlines doing research as the trials and tribulations of racing unfold, is a rare and privileged benefit of this extremely unique, exciting, intense and ridiculous sport of ours.

NICK TILLER, PHD, MRES is a senior researcher in exercise physiology at Harbor-UCLA, an experienced ultra-runner, and author of the award-winning book "*The Skeptic's Guide to Sports Science*". If you have a question that you would like answered in the column, send it to the Editor amyc@ultrarunning.com, or contact Nick directly at nbtiller@hotmail.com quoting "Ask The Physiologist" in the subject line.

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