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Mountains to Climb

New medications to fight the altitude sickness suffered by mountain climbers promise to aid peak performance. But the same drugs could also yield new treatments for people with breathing disorders. **Brendan Borrell** meets one man at DARPA, the US Defense Department's research agency, who's trying to move mountains for a new therapy.

Michael Callahan was racing south on California's Highway 395 in a rented Chevy station wagon. It was early one morning in late August this year, and the night before he had faced down thunderstorms on his way back from Colorado's Maroon Bells, two peaks that measure about 4,300 meters high. Now, he was cruising along the eastern side of the Sierra Nevada mountain range to Bridgeport. There, he would lead a joint training session at the US Marine Corps Mountain Warfare Training Center between the military and the legendary Yosemite Search and Rescue team, a group he had volunteered with as a lanky, long-haired climbing bum back in the summer of 1989.

"They are just over the mountain from each other, and they've never met!" Callahan says in disbelief.

Making such connections is precisely what Callahan excels at: digging into his seemingly limitless social and scientific network to advance medical practice, vaccine development, drug discovery and national security. Along with his rounds at the infectious diseases unit at Massachusetts General Hospital in Boston, where he works part time, Callahan has juggled snakebite antivenom trials in Vietnam and tracked the spread of bird flu in Russia for the US State Department.

It's an impressive resumé for one man, says Hill Harris, a gastroenterologist at the Denver Health Medical Center who has known Callahan since their medical school days. "Mica"—a nickname the 48-year-old Callahan has embraced since his youth—"has already lived two or three lives."

Callahan's name rarely appears in the pages of high-impact journals. But as a program manager at the Defense Advanced Research Projects Agency (DARPA), a division of the US Department of Defense, he has become one of the nation's most influential and wide-ranging emergency medicine doctors. At the same time, Callahan has never lost focus of his lifelong pursuit: to conquer mountaintops. It's a goal he brought with him to DARPA in October 2005, and they eagerly supported him, given the US's increased involvement with mountain warfare.

The agency has committed millions of dollars this and next year to find a pharmacological way to speed acclimatization and prevent the headaches and dizziness associated with acute mountain sickness, along with less common, but potentially fatal, conditions, such as high-altitude pulmonary edema. Callahan's research program could also have a wider influence on medicine, as it could provide insights into a slew of hypoxic disorders, such as chronic obstructive pulmonary disease (COPD), and problems faced by patients struggling on ventilators.

Callahan also wants volunteers to put new mountain sickness medications to the test within the next year, an aggressive timeline considering the typical path from discovery to market takes 12 years. His funded teams will benefit from access to safety assays that use primary cells, assistance enrolling volunteers around the world and DARPA's backing for expedited review of their Investigational New

Drug applications at the US Food and Drug Administration. Yet even his best scientists are keeping their fingers crossed. “Most people in the industry would look at it and say, ‘No way,’” admits physiologist David Irwin, of the University of Colorado Health Science Center in Denver, who collaborates with Callahan. “But if I’m going to be in this program, I have to put on my poker face.”

Breathtaking concerns

The challenge of trekking to high altitude is not just that there’s less oxygen available, but that the body becomes less capable of making use of it. In the fall of 1981, a physiologist named John West led the American Medical Research Expedition to Mount Everest, where he was able to track the progression of six experienced climbers and six climbing scientists as they pursued the 8,848-meter summit[1]. At the start, they took about 20 breaths per minute, and as they ascended this rate increased to compensate for reduced oxygen levels. But at about 40 breaths per minute, the brain cuts off this compensation mechanism, and, even with supplementary oxygen, climbers tend to remain in a chronic state of hypoxia.

Faster breathing also causes carbon dioxide levels in the blood to plummet, driving up pH. The classic drug for preventing acute mountain sickness, acetazolamide (Diamox), forces the body to dump bicarbonate into the bloodstream and normalize the pH. Unfortunately, acetazolamide is a diuretic, which aggravates the problem of dehydration at high altitudes. Moreover, it is a sulfa drug, which can cause Stevens-Johnson syndrome, a life-threatening allergic reaction that causes the skin to slough off.

At very high altitudes, blood vessels constrict, shunting blood from the lungs and causing pulmonary hypertension. So climbers on Mount Everest have been known to take acetazolamide in conjunction with sildenafil (Pfizer’s Viagra), which keeps blood vessels dilated[2]. Although sildenafil has a modest ability to improve exercise ability in patients with pulmonary hypertension, it mostly relaxes smooth muscle in the penis, resulting in increased local bloodflow.

Despite these challenges, people ultimately do have some ability to adapt to high altitudes. Over days and weeks, human physiology naturally acclimates to living thousands of meters above sea level; a kid from Texas will show many of the same adaptive features as a Sherpa highlander. The problem is that this natural process takes weeks. And no one knows how to speed it up—yet. That’s where DARPA’s investigations come in.

Rock on: Above, Michael Callahan helping with a vertical rescue of an injured climber off Vedauwoo rock climbing range in Wyoming in 1986; top right, Callahan at El Capitan in California’s Yosemite National Park in 1988.

When Callahan first launched the earliest incarnation of the effort, called Rapid Altitude Acclimatization, in 2005, it was, in his words, “a loser.” “We had lots and lots of interest, but no talent,” he says. He was hoping to involve not only scientists from university laboratories but also small-molecule discovery teams from major drug companies. The problem was that his drug development program lacked a market: 100,000 servicemen and a bunch of skiers in Colorado wasn’t going to cut it. Then he had a revelation: the same biochemical pathways relevant to altitude are also important to general medicine. “The military is one percent of the market,” he says. “We have to be the tail that wags.” In other words, Callahan believes his work on physiological changes in extreme conditions will lead the way to new treatments for hypoxic disorders in everyday settings.

“The spinoff of what you learn from treating altitude disorders would certainly apply to respiratory illnesses and vice versa,” says Tejvir Khurana, a physiologist at the University of Pennsylvania in Philadelphia who is not involved with the program. He’s not alone. Peter Barnes, head of respiratory medicine at Imperial College

London, says that new ways to dilate pulmonary blood vessels are always welcome, but the chief challenge of Callahan's hunt will be finding a way to do that without reducing systemic blood pressure. If successful, Barnes estimates that a new therapeutic could immediately be helpful in the 5% of patients with COPD in whom pulmonary hypertension is a problem.

The wider benefits for patients in the hospital might be far off, but drug companies have signed on to the project by offering compounds that mimic mountain sickness for testing. One such test takes place inside the laboratory of Thies Schroeder at the Duke University School of Medicine in Durham, North Carolina. Schroeder's previous work has looked at the role of hypoxia in cancer, asking what happens when tumor cells are deprived of oxygen. It turns out that proteins known as hypoxia-inducible factors (HIFs) boost hemoglobin levels and natural levels of erythropoietin, best known as a performance-enhancing drug abused in the Tour de France.

Schroeder has used DARPA support to set up 16 rodent-running motorized wheels inside a hypobaric chamber simulating more than 4,000 meters of altitude. Over a two-week period at sea level, Schroeder's rats are trained to maintain their position in the running wheel until they reach exhaustion after about an hour. Then, they must face a high-altitude challenge in the chamber while medicated with one or several of the 50 drug candidates discovered by the researchers or supplied by several companies DARPA has inked confidential agreements with.

About 5–10% of the drugs interact with HIFs, and an additional 5% target HIF-induced proteins. Half the drugs have been tested in humans for other conditions. These include beta-2-adrenergic agonists, used for asthma, and calcium channel blockers, given for high blood pressure and other reasons. The other drugs given to the rodents are simply intriguing compounds from 'Big Pharma's' coffers that, for instance, may not have made the cut for the next blockbuster erectile dysfunction drug but are still good vasodilators.

The hope is to double the time it takes before the rats reach the point of exhaustion, and, just months into the experiment, Schroeder's team is already boasting one good lead. His team, which works in the Duke radiology department, has also perfected an unpublished technique allowing them to implant a window on the rats' chests and visualize blood flow and blood oxygen transport *in vivo* in response to drugs. Drug candidates will be tested for efficacy and safety in dogs before moving into human trials with 20 volunteers by July 2011, Schroeder says.

Getting high

Callahan's fascination with the mountains began at a young age. Born in Boston in 1962, he conquered a challenging route up New Hampshire's Mount Washington, the highest peak in the northeastern US, at age 14.

In 1993, while in medical school, he came up with a scheme to study a team of climbers on Denali in Alaska to understand a high-altitude wasting disease called cachexia. Even with adequate nutrition and oxygen, studies had shown that people at high altitude lose lean body mass. Callahan invited David Irwin—then a star ice climber and aspiring engineer he knew from his Yosemite days—to come along for the project. However, the National Park Service balked at the proposal, so the duo were allowed to take blood samples only from themselves.

They went up with seven days' worth of food, and, at nearly 5,500 meters, just below Denali Pass, they were pounded by bad weather, so they holed up in their bivy sack shelters. After exhausting their food stores, they scavenged for canisters left over from expeditions years earlier. By the time they descended about a

Hanging tough: Above, hikers often rely on oxygen masks; top left, a US Marine partakes in a mountain warfare drill.

Immune to the high: Naturally elevated blood levels of nitric oxide seem to help Tibetan highlanders cope with elevated altitudes.

dozen days later, Callahan had lost 19 pounds. "I couldn't feel my feet for a while. It took me two months or so to recover," he says. "My wife still thinks I have neurocognitive defects." The research expedition may have failed, but Callahan's enthusiasm compelled Irwin to apply to graduate school in physiology at Colorado State University in Fort Collins. "I got really fascinated by the basic science," he says.

Callahan's life did not slow down after obtaining his medical degree in 1995. He was doing his residency in infectious diseases at the New England Medical Center in Boston, but he co-founded an organization called Rescue Medicine that performed emergency evacuations around the world. "He was the only person we knew who took residency calls from Africa," says Michele Johnson, who met Callahan through her involvement with the Wilderness Medical Society.

The attacks on 9/11 suddenly put Callahan's unique combination of skills in high demand. "He's been extremely good at connecting the military environment with mainstream public health," says Richard Danzig, Secretary of the Navy under President Bill Clinton and one of Callahan's first high-level links to the military. The attacks also elevated conflict zones to a new level, literally. By Callahan's count, there are currently 19 war zones in mountainous areas, including the Hindu Kush in Afghanistan, where US soldiers must rapidly acclimate to altitudes above 4,000 meters to fight an enemy with a home-turf advantage. Agencies such as DARPA needed his know-how, and Callahan was eager to sign on to take our understanding of mountain sickness to new heights.

Setting sights

It is rare for program managers at most granting agencies to outshine the star researchers they fund, but Callahan, with his brio and creativity, has managed to leave a mark on every program he leads. "He's not a passive program manager," says William Warren, president and chief executive of VaxDesign, a Florida company with a primary cell–based assay for testing drugs and vaccines at pre-clinical stages and that grew out of a DARPA program. "He doesn't just come and assess things. He comes and innovates with you."

Duke's Schroeder is just one part of a two-pronged approach that Callahan is pursuing. Schroeder's team is also indicative of what is so unique about DARPA—and Callahan. In seeing the strengths of different researchers early on, Callahan linked Schroeder with his old friend Irwin for the high-throughput wing of the effort. Irwin has been studying the causes of blood vessel leakage in high-altitude pulmonary edema. His studies recently linked leakage to the reactive oxygen species-HIF-1–vascular endothelial growth factor (VEGF) pathway[3], and he says one of the compounds, which he would not disclose, blocks VEGF and reduces leakage by 50% in rats. In Irwin's view, a preventative treatment for pulmonary edema is within reach in the next two years, but tackling acute mountain sickness or cerebral edema may be more far fetched.

Meanwhile, Callahan's program is also funding a more focused effort led by Jonathan Stamler, a cardiologist at Case Western Reserve University in Cleveland who has shown that nitric oxide binding to hemoglobin regulates the dilation of blood vessels. High levels of bioactive nitric oxide are thought to help explain the healthy blood flow of Tibetan highlanders at elevated altitudes[4]. But, as it turns out, getting nitric oxide into the blood is not as simple as inhaling it, which can have toxic side effects.

In 2002, Stamler showed that inhaled ethyl nitrite is converted to the bioactive form of nitric oxide in the blood, without the side effects. The approach has been used to alleviate pulmonary hypertension in newborns[5]. In pilot experiments he submitted to DARPA last year, Stamler demonstrated that inhaled ethyl nitrite can improve blood oxygenation. Further trials are planned in humans and animals both at rest and during exercise at high altitude.

Callahan, for his part, is not sitting on the sidelines. In exchange for providing clinical support and human volunteers to foreign investigators studying performance-enhancing compounds on Mount Everest, Callahan negotiated unrestricted access to their blood samples. He is also running his own observational studies on soldiers and climbers, which have taken place on Mount Kilimanjaro in Tanzania and Mount Aconcagua in Argentina. Last year, Callahan's team identified a new inflammatory mediator that seems to be linked to people at highest risk of developing acute mountain sickness, which he hopes to follow up on.

This month, he is packing his bags yet again for more work on Kilimanjaro, and he sees many more ascents on his horizon. "We really need better places to conduct these studies," he muses, "which means more people and higher mountains."

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