A Life at High Altitude: A Conversation With Todd Bull and Peter Hackett

In this special discussion for the PHA, Guest Editor Todd Bull, MD, spoke with Peter Hackett, MD, of the Altitude Research Center, Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Anschutz Medical Campus in Aurora, Colorado. Dr Hackett is a leading authority on altitude illness with years of experience in high-altitude settings both abroad and in the United States.

Dr Bull: It's a pleasure to be talking to Dr Peter Hackett, who is, without a doubt, one of the most renowned altitude researchers here in the United States, with a long and storied career. He has greatly contributed to what we know about the physiology and impact on humans as they ascend to higher and higher peaks. We're going to discuss aspects of his career and interests, exciting moments, and directions that we think the field is moving toward.

Dr Hackett, welcome. Let's start with a question about your early career. How did your work in altitude initiate? Where did your interest in the area stem from, and how early on did you find yourself investigating the physiology of high altitude in humans?

Dr Hackett: I've had a pretty unusual career. My love for the mountains is what propelled me into high-altitude medicine. That started at a young age when my grandparents took me to Colorado on a camping trip and I fell in love with the mountains. After medical school, I decided to go to San Francisco for my postgraduate training because it was close to Yosemite. Of course, during those years, I think I got 3 days off in my first year of training and was able to run up to Yosemite a couple of times.

After my internship year, I decided to take a break and went to Yosemite and became a helicopter rescue doctor. My training then was mostly in trauma and emergency medicine. I had a great summer fighting fires and doing rescues from this tiny helicopter. This was back in the mid-1970s, before it got very sophisticated.

One fellow I rescued, who had fallen on a climb and broken some ribs, owned a company called Mountain Travel, and he needed a doctor to go to Nepal with a trekking group for 3 months. At that time, I decided not to return to my medical training and went to Nepal. I ended up staying for most of the year, working as a volunteer doctor at this little aid post at 14000 feet on the way to Mount Everest. There were about 3 or 4 families in this tiny little village, and I stayed there for most of the year.

I saw all these people coming down with this weird virus on their way to Everest. When they got to about 14000 or 15000 feet, everybody started getting headaches and some nausea and vomiting, and they weren't sleeping and were short of breath. I couldn't understand what was going on until it finally dawned on me that this was altitude sickness. At that time, it was very little known. There was one paper in the *New England Journal of Medicine* from the experience of the Indian Army, Indira Singh, talking about altitude sickness, and that was about it.

I realized I was in a unique position to start collecting data and epidemiology and risk factors, and even treatment. I didn't quite know what I was doing, but I got a little help from John Dickinson, who was a British missionary doctor in Kathmandu at the time. When I eventually came back to the States, I had this box full of questionnaires and physical exams, and I took it to Drummond Rennie in Chicago; he had published on high-altitude physiology and retinal hemorrhages and a little bit on cerebral edema. I collaborated with him, and we wrote up a paper, and it was the lead paper in *The Lancet* in 1976, called "The Incidence, Importance and Prophylaxis of Acute Mountain Sickness." That launched my career, really. I became published at the age of 27 in a lead article, and it was a great opportunity. Then I had to make a decision about what I was going to do because I was developing a passion for the mountains and for altitude illness and keeping people safe.

I saw a number of deaths, and it really impressed upon me that perfectly healthy young people could go to altitude and die of pulmonary edema for no reason other than that they'd gone up a little too quickly. I was totally engrossed in this and decided I really needed to learn more about it. I approached Bob Grover and Jack Reeves, who were at the University of Colorado in the Cardiovascular Pulmonary (CVP) Research lab. They agreed to take me on as a fellow. A few months of that fellowship was taking them to Nepal to collect data and samples. We did hundreds of hypoxic ventilatory response tests manually with spirometry, and we had one of the early Hewlett-Packard ear oximeters, and we were able to do urine and plasma osmolality. We published a bunch of papers out of this research in Nepal, having to do with altitude illness.

With Grover and Reeves, I really learned about research, about how to critically review literature, how to do literature reviews, form hypotheses, how to test things, learned some statistics. That really was what launched my career in high-altitude medicine. After that, I worked clinically in emergency medicine and became boarded in emergency medicine, but I always had this interest in pulmonary physiology, especially the pulmonary circulation.

From there, I eschewed academic departments. It wasn't consistent with my lifestyle of going on expeditions every year as well as interests in field research. That took me to places like Mount Lo-

gan in the Yukon with Charlie Houston, and I started a project at a 14000-foot camp on Mount Denali, funded by the National Institutes of Health, where we saw quite a few very ill climbers with pulmonary and cerebral edema. It was there that we did the first bronchoalveolar lavage in high-altitude pulmonary edema (HAPE) and also studied vasodilators for treatment. I was there for 8 summers. I was with John West and his American Medical Research Expedition to Everest in 1981, in which I summited Everest and collected data all the way to the top. We made quite a mark in the field of high-altitude physiology and published a large number of papers and a book that many of the American Thoracic Society people will be familiar with.

So that's how I got started. It was my love for the mountains and a burning intellectual curiosity. What is it about high altitude that causes people to develop these life-threatening conditions? How do we make high altitude a safer environment and practice clinical medicine in the mountains? It was a nice combination of a passion for wanting to help people as a physician and my love for the mountains and climbing activities and trekking.

Dr Bull: That's a fantastic story and intro, and actually, it highlights a couple of important points. One is that research favors the prepared mind. Here you were at a clinical station, and you noticed a series of events, this viral illness, and you decided to dig into it and developed questionnaires regarding it and looked into physical findings, leading to an important early publication. So your clinical observations and then curiosity launched this career.

The other fascinating aspect to me is that I imagine, after your fellowship, there was probably some pressure to move on to a junior faculty position and start writing grant awards and work your way up the academic ladder, but you followed your passion and went in a different direction that was highly productive and successful. Was that encouraged or discouraged? Did people say, "There's no way you'll stay in research if you go in that direction"?

Dr Hackett: I thought you might pick up on that as an academician. There are a lot of young faculty and trainees out there that, I'm sure, struggle with the pros and cons of academia. It's tough to be in academic research at a medical center and be both a clinician and a researcher. It was made clear to me at the CVP that a research track would involve junior faculty and writing grants such as an RO1 and being part of the Program Project Grant and advancing along the traditional academic track, but it was also clear to me that I wasn't really cut out for that. I had to spend time in the mountains, and a major expedition would take at least 3 months a year. I wasn't going to give that up.

Emergency medicine fit the best at that time because it was then a brand-new field, and it was easy to just leave a job and then come back and get hired again almost anywhere. The advantages of not being in an academic institution were that I didn't have all these meetings, didn't have to report to a dean or a chancellor. I could do my own thing and didn't have to be in committees. The disadvantage, of course, was that funding opportunities were more limited without university affiliation. I had to have institutional review board (IRB) approval, so I would always be affiliated with a university in some capacity so that I could use their IRB.

It's great if you have a colleague next door that you can talk to about the latest developments or hypotheses. That's tough when you're an outlier and not in an academic setting, but I was able to develop a good community of people I was working with in this field. If I had to do it all over again, I'm sure I would have been more productive if I'd stayed in academics. I'm sure I would have published more. I still have a lot of data I haven't written up, a lot of papers I haven't published yet. I probably would have been more efficient. On the other hand, I would not have had quite the same career enjoyment. There are definitely tradeoffs.

Dr Bull: What I tell my fellows, in talking about their careers, is that you have to find a passion, and then if you can build your research on the passion, that is the most successful way to contribute because it keeps your enthusiasm and excitement high. From my standpoint, it's about trying to find the balance between the clinical work many of us love, while also keeping the research going to help you answer the myriad questions that always arise when you are seeing patients, "keeping the prepared mind."

Then again, some will say you have to home in completely on research, but where the excitement comes, or the inspiration, is at the bedside, seeing the problems that occur and then trying to tackle them. It strikes me that you're saying you were doing what you loved to do but then saw clinical questions that would arise while doing that, though it's fascinating that you mention these sentinel papers, the *New England Journal* paper about altitude. Can you tell us a bit more about that? How did that come about and what data were you collecting?

Dr Hackett: So I'll put this into context. Studying humans at altitude, you can do chamber studies, where you put people into large tin cans for days or weeks at a time and reduce the pressure, which is very expensive and labor intensive but much more tightly controlled. You can do hypoxic gas studies, which are not exactly the same as hypobaric hypoxia, but it can be done, and you can do field studies, where you take humans to high altitude to study acclimatization. You can't ethically take people to high altitude to study pulmonary edema, but you can do what I did in Nepal and Alaska, which is sit by the trail and, as people come by sick, study them because they've already gotten themselves sick.

The Everest expedition, organized by John West, was funded by the National Institutes of Health and the Army and the American Lung and American Heart Association and National Geographic and all sorts of organizations. We had a large team. Our purpose was to study the process of acclimatization, especially cardiovascular physiology. This was in 1981. At that time, there were not really good noninvasive measurements of pulmonary artery pressure, but we did a lot of exercise, physiology,

and metabolism, and we looked at sleep at altitude and weight loss and hemoconcentration and hemodilution and lots of different issues.

One of the primary measurements we made was the determination of blood gases near the summit. We didn't actually get a summit value, but we got end-expired alveolar samples with the use of a special instrument on the summit. We would breathe into this instrument, and it would fill a pre-evacuated aluminum ampule and then rotate it. You pulled a trigger to activate it. We collected end-tidal air, and we also made the first measurements of barometric pressure on the summit, which was higher than expected based on the standard atmosphere calculations; this helps explain how it could be climbed without oxygen at that time of year but also explains why it may be impossible to climb in winter, since the pressure is at the very limit of human hypoxic tolerance, and the barometric pressure and PIO_2 are significantly lower in winter.

We were there in October, and like you'd expect, on all of these trips, whether it's Denali or Mount Logan or Everest or Kilimanjaro, there's always risk. There's always inherent risk in going to that kind of altitude and subjecting yourself to that kind of weather. We had a pretty tough time, and there was a lot of attrition; at the end of the trip in October, we still hadn't gotten to the top with our measurements. We had done a lot of good work at base camp at 18000 feet and in the Western Cwm at 21000 feet. At 21000 feet, the average oxygen saturation is in the high 70s, lower 80s, and we were doing fine despite that.

I was one of the few people left that still had enough stamina or drive toward the end of the trip to try for a summit bid. There were two of us, Chris Pizzo, a pathologist from Denver, and me, and two Sherpas. We set out for the summit and had a bit of an epic time. I ended up going to the top by myself because the Sherpa who was with me thought he was getting frostbite on his toes, so he turned around. Chris and his Sherpa were far ahead of me, and I couldn't catch up, so I ended up going by myself.

In those days, there were no ropes. It wasn't like it is now, with a rope all the way up to the top. It was a bit dangerous. Chris and his Sherpa made it to the summit, and on the way down they ran into me. I had just gone out of oxygen, and I said we should probably all go down together for safety. Chris said, "Peter, when are you going to be this close to the summit again?" I said, "Well, I'm out of oxygen." It turned out his Sherpa had hardly used any oxygen at all. He gave me an oxygen cylinder, and I continued up alone, making measurements. For example, my respiratory rate off oxygen was about 60, and on oxygen, it was more like 30 or 40, with tidal volumes at 2 L. The amount of hyperventilation is extreme. Based on the measurements we made, in these kinds of extreme hypoxic environments, the body chooses to defend alveolar PO_2 rather than defend pH. My pH, for example, was 7.57, with a PCO_2 of 7.5 and an arterial PO_2 of 24 or 26; extreme hyperventilation allows a shift in the oxygen dissociation curve to the left and loads more oxygen at the lung, which is beneficial.

I vividly remember getting to the summit after a bit of difficulty on the Hillary Step, which is a technical aspect of the climb. It's an 80° steep rock feature about 40 feet high, just below the summit. This is where there's often a lot of trouble, and we didn't have any fixed lines, but I was able to surmount it and realized two things: I was going to get to the summit because there's nothing else difficult on the way, and secondly, I might not ever be able to tell anyone about it because I had no radio and could possibly die on the way down. It's much harder to downclimb something like that than it is to climb up it.

I summited, and since I was by myself, I had to have a picture to prove I was there. I took a picture looking down on the north side just a bit. It was quite cold and windy, as you would imagine, and it was getting dark, about 4:30 in the afternoon, so I had to get out of there. On the way down, sure enough, I fell. I was headed for about an 8000-foot fall off the Hillary Step when my legs got caught behind a little piece of rock, and I was flipped upside down. It was a terrible situation. I was able to eventually right myself after doing what seemed about 10 sit-up attempts. I got my ice axe in a little piece of ice above me and then was able to work my way down to the bottom of the Step to Chris, who had been waiting for me a couple thousand feet lower down. We made it back to high camp together.

I hadn't had anything to drink at all that day because my water bottle was in my pack, frozen solid, and I couldn't put it inside my vest because I had all this monitoring equipment. I had a Respitrace and electrocardiogram (ECG) monitors and whatnot. That night, I had a hard time breathing. I started rehydrating and thought I had HAPE because I was in acute respiratory distress, and I thought I was going to die. I ended up coughing up a cast of my bronchial tree. Chris, being a pathologist, said, "Oh my God, that's one of the best bronchial casts I've ever seen!" I had this huge mucus plug that had compromised my ventilation, obviously. Once that cleared up, then I could settle down and survive the night and eventually the trip down to base camp. That was definitely one of my closest calls. I really felt like I should have died from the fall, and I was very, very lucky. John West is forever grateful that I didn't die because it would have ruined the whole expedition.

Dr Bull: [laughter] I'm glad he had his priorities in line there. That's quite a harrowing story. You really had an ECG monitor track what your heart rate was when you were hanging upside-down doing sit-ups on the Hillary Step?

Dr Hackett: It was very interesting. As you ascend to higher altitudes, the maximum heart rate drops, and the resting heart rate increases. The ability to do work is severely compromised at one-third barometric pressure, which is what the summit of Everest is. My maximum heart rate was about 132 at that altitude. It was almost 200 back home. When I fell, it didn't get much above that, but my resting heart rate was about 120, so I could only do about 12 heartbeats of work. Of course, it has to do with cardiac output, not just heart rate. The ECG showed a right bundle branch block, which I don't have at lower altitude. Interestingly, I was in an altitude chamber

at Duke with Richard Moon and Peter Wagner doing a study with a Swan-Ganz catheter at 16000 feet simulated altitude on a bicycle at max exercise, and I developed a right bundle branch block, and they thought it might have been the catheter hitting my right ventricle or some sort of iatrogenic thing, but then I went back and reviewed my ECG from Everest, and sure enough, I had a right bundle at 28000 feet as well.

Dr Bull: Did you say you were actually getting arterial blood gases on this ascent and doing arterial sticks as you were climbing to these high altitudes?

Dr Hackett: Actually, we didn't do arterial sticks. We collected a venous blood sample on the South Col at 26000 feet before going to the summit, and then we did the alveolar gas samples. Those were taken back to San Diego and analyzed along with controls. We feel that the data are quite reliable. We rushed the venous samples down to the blood gas analyzer at Camp 2, at 21000 feet, and then calculated the other values.

Subsequent to our expedition, Mike Grocott and his crew in a project called Xtreme Everest did do arterial sticks at around 27700 feet. They couldn't do them on the summit for logistical reasons. They published their studies in the *New England Journal* because it was so unusual, and they found the exact same things that we did: PCO_2 values less than 10 and arterial PO_2 values from 19 to about 28, and pH of 7.55 or so. It confirmed our data, and I have to hand it to them for doing femoral artery blood sticks under those circumstances.

Dr Bull: That's brave, being that high and letting someone poke your femoral artery, as well as hauling all that equipment up. Now that was the data that your group published in *Science* and other publications as well?

Dr Hackett: Yes. It actually ended up appearing in a few places. John West was the first author on many of those, and he also published a book called *Everest: The Testing Place*, altogether we published about 40 papers from the expedition.

Dr Bull: What other peaks have you climbed as part of expeditions?

Dr Hackett: I've done clinical research to the summit of Mount Kilimanjaro with volunteers, doctors' groups mostly, and Pikes Peak in Colorado. That's not an expedition because you can drive right up there, but it has advantages since you can get there so quickly; people get reliably ill. Other expeditions were to South American peaks, Aucanquilcha to study the world's highest living humans, and Denali in Alaska, where we did a huge project. We flew in there with military airlift support every year on May 1 and came off every July 1. We'd be there for 2 months. Rob Roach from the University of Colorado and I did that together. We were able to get quite a bit of work done there. We looked at the effect of nifedipine on pulmonary artery pressure in people with HAPE and controls. We almost killed people by testing nitrates in HAPE, which turned out to be a very bad idea. We tested beta blockers in HAPE, which is also not a good idea. Brownie Schoene did the first bronchoalveolar lavage in HAPE patients. Ben Levine from University of Texas Southwestern flew in with Medtronic's echocardiography device, and the quartz crystal quickly froze, so we had to get a new one airdropped and take better care of it [laughter]. Denali is such an extreme environment; the low daily temperature was typically −40° in May and −25°F in June. It's 62° north; it's the highest polar mountain in the world, so a lot of our time was spent trying to survive. We had to build igloos to stay out of the wind, and we had very, very ill patients that we had to take care of, but it was all very exciting and productive, as was the Mount Logan project with Charlie Houston in the '70s. We would fly onto Mount Logan at 17500 feet, some directly, and others would stage the ascent to avoid getting severely ill. One of our studies from there was published in the *New England Journal*. The background was interesting. I flew into 17500 feet directly, and that night, we monitored my oxygen saturation with the Hewlett-Packard ear oximeter and found incredible desaturations into the 50% and 60% level. The next night, I took acetazolamide (Diamox), and we found that it almost totally eliminated the severe central sleep apnea and the periods of severe hypoxemia. In the *New England Journal* article, the graph showing the 2 sleep traces—one on acetazolamide and the other without it—is of my oximetry study. You know, that was a very dangerous operation; there were plane crashes. Fortunately, nobody was killed, but flying and landing on a glacier at 17500 feet is radical. Charlie was very bold, as was John West. These were very risky expeditions, and we were really lucky that nobody died.

Nowadays, well, you may be familiar with the big altitude chamber that just opened up in Bolzano, Italy, where you can control the wind, the temperature, the humidity; you can make it snow. You can take people to 30000 feet in a highly controlled environment. Obviously, it's a much safer thing to do. For the future, however, for those who are interested in high-altitude medicine, I think the field is really wide open. If your interest is in pediatrics or neurology or obstetrics or trauma, there is so much that can be done in terms of both clinical and basic research.

There's the bench research, obviously, looking at basic mechanisms, and look what's happened with Hypoxia Inducible Factor (HIF) biology, which had a lot to do with high-altitude work. There is the clinical work with either hypoxic gas breathing in animal models or humans. There's the hypobaric hypoxia exposures, either in a chamber or in the field. There is so much to be learned about people living at high altitude here in Colorado. We still don't know the prevalence of pulmonary hypertension due to the altitude in our resort communities. We don't know the prevalence of central sleep apnea and, in general, sleep-disordered breathing in these communities. We don't know about the relationship between sleep-disordered breathing and pulmonary hypertension. We don't know how many people have to leave the mountains because they just get breathless and lose their exercise capacity as they age, and we don't know the exact mechanisms involved there, but I take care of a lot of those people,

and some of them I send to you at the University of Colorado Pulmonary Vascular Disease program for workups to look at their pulmonary circulation. There's a lot to be done, and if your passion is any of these things that could be combined with high altitude, or you'd like to be in the mountains, then it can be a great combination.

Dr Bull: What other advice do you have for those entering the field now?

Dr Hackett: The best advice I can give is to get the best training possible, to start with, and find the best mentors available. It's not easy. There are not many people doing high-altitude research, and there's not a lot of funding for it, so it takes motivation to go after the funding sources and find the right mentors and get the necessary experience.

Clearly, if one is going to do research, they need some training in research methodology and statistics and all that goes along with it. My advice, if someone is really serious about making a contribution by doing clinical or basic research, is to really buckle down and get some training in research before trying to do it or while establishing themselves.

Dr Bull: What are the major obstacles right now in terms of investigative work or research in the field?

Dr Hackett: Major obstacles, as with other areas, have to do with funding opportunities. High-altitude medicine has been a bit of an orphan field. It probably hasn't gotten a lot of respect in the past. It's more respectable now, but it has to overcome this perception that doctors who do high-altitude research are just looking for an excuse to go play in the mountains. The way to get around that is with solid foundations in research and really good, quality work because there is some truth to that criticism.

That's why I make a plea for getting really trained in research. That's one obstacle in addition to funding; and then there's the time it takes for field studies, the dangers, the problems with IRBs. You can't ethically get people critically ill with HAPE, but you can take care of them if they get it on their own, if you are in the right spot at the right time, which is where my work came in and why fieldwork was successful.

Hypobaric facilities are also very expensive and limited. Hypoxic gas studies are a great way to go because they can be much less expensive and give you much more control, but we still haven't worked out the exact differences between hypobaric and normobaric hypoxia. That's a great study in itself.

For a person who wants to get involved in this field, they need to find a chairman of their department, or senior faculty, who shares the interest or can at least get enthusiastic about high-altitude medicine. It's very difficult to go into a department where you don't feel supported or you don't feel that there are like-minded people. There are not many places doing high-altitude research currently. A young investigator needs motivation and passion to get it going and develop their own program and break trail, as we say in the mountains.

Dr Bull: And where do you think the biggest opportunities are right now? What do we really need to understand or know right now in the field, if you could focus a research question?

Dr Hackett: The current important questions range from molecular biology to epidemiology. One could take their pick, but one of the more fascinating things is HIF biology. Humans at altitude offer a great model because they're perfectly healthy, just hypoxemic. It offers great opportunities. The Holy Grail in high-altitude medicine in some aspects is to find breakthroughs by using these models of healthy humans at altitude or sick humans at altitude for your work in the intensive care unit (ICU). That really hasn't materialized. HIF is obviously a link. There's a lot of genetic work going on, looking at the relationships of illness at altitude and acclimatization and people with acute respiratory distress syndrome and survival and that sort of thing and finding common genetic patterns. That's one big area, formulating a question you might have from the ICU and figuring out how you could use humans at altitude as a model to help answer that, a common factor being hypoxemia.

Then you've got whole population studies. You've got hundreds of thousands of people living above 7000 feet in Colorado and very little information on what happens to their blood pressure, for example, and what's the best medication for control. Is atrial fibrillation really more of a risk living at 8000 or 9000 feet than at sea level? Nobody knows. I get calls all the time from cardiologists around the country, and there is not a reliable answer. There's a tremendous amount of important work to be done, helping people live healthier in the mountains so they can enjoy their chosen lifestyle, or helping those in ICUs or at sea level with hypoxic diseases or anemia or other problems of oxygen transport. Those are two main themes.

Dr Bull: I think understanding the physiology of hypoxia and pulmonary vascular disease at altitude could certainly help solidify what we're doing or help point us in new directions for helping those who get hypoxemic or develop pulmonary vascular diseases.

Dr Hackett: I think another idea for a research project is looking at whether exaggerated physiologic pulmonary hypertension is a limiting factor in exercise performance at high altitude. I'm convinced from my clinical practice that hypoxic pulmonary vasoconstriction or physiologic high-altitude pulmonary hypertension can cause a decrement in exercise performance in certain people and that, if you relieve it with pulmonary vasodilators, exercise can markedly improve. I'm talking about people living in Summit County or in Telluride. Such a study has never been done. The only studies to date in hypoxia or high altitude with phosphodiesterase inhibitors, for example, were not in selected patients complaining of impaired exercise performance, only in nonselected subjects, and they showed no real benefit on average. It's still an important clinical question ripe for research.

Dr Bull: I'd also like to get your thoughts on COVID-19. There were statements to the effect that this was like HAPE, something where altitude could inform us. I'd like to get your view on whether or not that is the disease state we're looking at with COVID hypoxia.

Dr Hackett: There has been some literature and a lot of discussion about whether COVID-19 pneumonia is the same as HAPE. Obviously, they're both noncardiogenic pulmonary edema with severely impaired gas exchange. There are similarities, but the pathophysiology is entirely different; one is a hydrostatic edema due to exaggerated hypoxic pulmonary vasoconstriction with patchy or uneven vasoconstriction, as far as we understand, and the other is a viral infection with inflammation and maybe loss of hypoxic pulmonary vasoconstriction in areas with resultant shunting, or perhaps with vascular thrombosis as well.

My colleagues and I published articles on that, and Eric Swenson and Steve Archer and others have also addressed that. As for treatment, the best therapy for HAPE is oxygen, and it's also valuable in COVID-19 pneumonia for improving oxygenation, but while oxygen resolves HAPE, since it reduces pulmonary vascular resistance, pulmonary artery pressure, and edema formation, it does not address the pathophysiology of COVID-19 pneumonia. Suggestions that pulmonary vasodilators that are useful in HAPE might be useful in COVID-19 pneumonia or acute respiratory distress syndrome are dubious at best and potentially dangerous. I think where the altitude community has failed the clinicians on the front lines is in helping them recognize that, like at high altitude, these severely hypoxemic patients may not be hypercapnic and may not need mechanical ventilation, but rather correction of the hypoxemia with oxygen therapy, at least initially. In addition, these patients may be tolerating hypoxemia better than expected because they have had some time to "acclimatize" to it, similar to persons at high altitude. I think with COVID-19 patients, if it takes more than 3 or 4 days to slowly develop hypoxemia, they could tolerate it pretty well as long as they're not hypercapnic and they're not in true respiratory failure. Clinicians with altitude experience are accustomed to seeing people with SpO_2 values in the 70s and 80s, levels of hypoxemia that may be entirely normal for the inspired PO_2 for the altitude and without clinical adverse effects. Obviously, there are differences, and COVID-19 patients have other organ system involvement, but understanding the extent to which people can tolerate hypoxia is helpful.

I think clinicians in New York and other places at sea level don't have that experience of seeing people that are hypoxemic and are fine. They're used to seeing hypoxemia associated with hypercapnia, respiratory failure, loss of neuromuscular activity, or severe chronic obstructive pulmonary disease or other things. I do think that the altitude community should be better informing these clinicians. It's just the fact that humans can tolerate hypoxemia; give them oxygen, and you don't necessarily need to intubate them. Does that make sense?

Dr Bull: Yes. The global critical care society I think has evolved to watching from how we have treated acute respiratory distress syndrome in the past; the decision to intubate is made based on looking at the patient and taking in information, whereas when COVID-19 first hit, although there was much discussion after seeing what was rolling out of China, not knowing what we were dealing with led to intubating much earlier. I think there have been investigators and clinicians across the country looking at that again.

I do think it's an important point. If I can go back to the early days of COVID-19 and say, "Hey, we didn't necessarily need to put them on the vent when they hit 8 L of oxygen or 10 L of oxygen," part of that, too, was that we were trying not to put on heated high-flow or CPAP, BiPAP because we worried about aerosolizing the virus and putting others at risk, but we learned that the protection to ourselves was okay.

One last question I was going to ask is, looking back, what are you most proud of to date?

Dr Hackett: I think increasing the awareness and improving the safety with respect to altitude illness for people going into the mountains. My paper in *The Lancet* in '76 was seminal, and it brought attention to a wide readership that perfectly healthy people do get sick when they go to the mountains, and they can die. At that time, there were a lot of deaths. Through research, publications, lecturing, through helping to found the Wilderness Medical Society and the International Society for Mountain Medicine and running the International Hypoxia Symposia, I feel that I've really helped to make going to altitude safer for people around the world, not just for mountain climbers, but for skiers and workers and everybody visiting or living at altitude.

I think I also turned the attention from respiratory physiology to the brain in the '90s when I started writing about the pathophysiology of mountain sickness, and since then, research has focused on what's going on in the brain, not just oxygen transport. Being a thought leader in the field has been rewarding. I feel good about what I've been able to offer in that respect. One of my guiding ideas is that people are going to help save the environment, to save our forests and our mountains, only if they get out there, enjoy these spaces, and love the experience. People protect what they love.

In terms of regrets, I don't know what researcher doesn't regret not getting projects across the finish line into publication. There are still unpublished studies in the queue. More importantly, maybe because I wasn't in academia, I didn't develop a cadre of young physicians or researchers coming up in this field to take over and continue with clinical as well as basic high-altitude research. There are many young docs wanting to get into the field, and there aren't many opportunities now for lack of strong programs at academic centers, and that's probably my main regret. If I had been in academics, we could've developed, hopefully, a strong program with a lot of

younger people coming up in the field, but there are still myriad opportunities and interesting applications. Being an expert in high-altitude medicine opens all sorts of doors; professional sports groups that are going to play at altitude and need advice, for instance. I have been a consultant with NASA on space sickness and published with Jim Bagian the only paper on cerebral blood flow and space sickness. I consulted on high-altitude ballooning projects, including the world's first nonstop around-the-world balloon flight and the first nonstop flight around the world in an unfueled aircraft, as well as a hang glider expedition to Everest, and many other interesting efforts. For all these fascinating things taking place at high altitude, people are looking for expertise in high-altitude medicine. One of them was the world's best rock and roll band going to play in South America wanting advice on dealing with the altitude; that got me hooked up with them, and I've been one of their doctors now for many years. That's been a gas, as they say in the rock and roll business. You never know; it's fascinating how the world of high-altitude medicine can take you so many places.