

# How It *Really* Happened

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## High Adventure in Pulmonary Hypertension Acute and Chronic Hypoxia Are Not the Same

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High adventure—that is what it was at 12,700 ft above sea level. The adventure involved chronic hypoxic pulmonary hypertension, and in 1960 it led to building a corral for cattle on an isolated tundra above tree line near Summit Lake on Mount Evans, Colorado (Grover, RF, Reeves JT, Will DH, and Blount SG Jr. Pulmonary vasoconstriction in steers at high altitude. *J Appl Physiol* 1963;18:567–574). The findings were so rewarding, that this project began my life-long research career in pulmonary circulation. Research, like life itself, can be high adventure for those fortunate enough to do what they enjoy. And the pleasure of research need not be confined within laboratory walls.

That I would study cattle began almost by accident in 1957. I was a fledgling research fellow at the University of Colorado School of Medicine, Denver, with Gil Blount, Chief of Cardiology. In those early years, Blount was Czar of cardiology in the Rocky Mountain West; his domain included all of pediatric and adult cardiology, cardiac catheterization and angiography, and pre- and postoperative cardiac care. His eclectic interests included pulmonary circulation. On my arrival in Denver, he assigned me to the heart catheterization laboratory, over which he maintained control, but the day-to-day operation of which was directed by Bob Grover. Late in 1957, one of our pulmonary faculty, Giles Filley (known for steady-state lung diffusion of carbon monoxide and acid-base balance), whose office was next to the fellow's office where I had a desk, happened to give a lecture in Fort Collins. There he had learned that veterinary scientists at Colorado State University were finding pulmonary hypertension in cattle at high altitude. He said Grover and I should look into it, and we did. We found that pathologists Rue Jensen and Arch Alexander with physiologist Don Will were using primitive methods, but were indeed finding surprisingly high pulmonary arterial pressures in cattle at 10,000 ft in South Park, Colorado.

We were fascinated and also felt we could help improve their methods. Perhaps we could bring essential components from our human laboratory to study cattle. Rather than a mercury column supporting a cork and needle, we proposed electronic transducers. Rather than the needle scratching a smoked drum, we suggested a photographic recorder having a light beam reflected off a mirror on a string galvanometer. In addition to pulmonary arterial pressure, we suggested measuring wedge pressure, oxygen uptake, blood gas compo-

sition, cardiac output, and to use these to calculate pulmonary vascular resistances. Compared with today's methods, the micro-Scholander analyses of expired air and the van Slyke analysis of blood were time-consuming and primitive, but they would provide accurate, reliable data needed to describe lung circulation.

We also suggested hypoxic pulmonary vasoconstriction as a possible mechanism for the pulmonary hypertension, given von Euler's 1946 report that acute hypoxia raised pulmonary arterial pressure in cats. While we knew something about hypoxia and lung circulation, Alexander and Will were current on everything known about right heart failure in cattle at altitude, a disorder known to ranchers as "brisket disease." As a result, our discussions moved rapidly, and we soon came to the idea that chronic residence at altitude might elevate pulmonary arterial pressure more than acute hypoxia, particularly in cattle. So why not join forces and test the idea that hypoxia directly and profoundly raised pulmonary arterial pressure in cattle residing at altitude? We could provide the latest methods and they knew how to study cattle. It was a perfect fit.

Together we conducted a preliminary study, which actually was the first-ever prospective study of chronic hypoxic pulmonary hypertension, and possibly of chronic pulmonary hypertension from any cause. We brought cattle born at low altitude to South Park, Colorado at 10,000 ft (Alexander AF, Will DH, Grover RF, Reeves JT. *Am J Vet Res* 1960;21:199–204). Over a period of 6 months, some animals developed severe pulmonary hypertension, but the question remained, "Did chronic hypoxia cause high pulmonary arterial pressures simply because of sustained vasoconstriction, or had there been some basic change in the walls of the pulmonary arteries?" Some colleagues suggested that pulmonary arteries had been "exercised" by hypoxic vasoconstriction and had become stronger, just as muscles in the blacksmith's arm become stronger by much use. However, we wondered if there might be an additional factor. What if the pulmonary arteries not only constricted at high altitude, but also they could not relax?

To answer this question, Grover and I designed a study of cattle maintained in a corral high on Mount Evans, 36 miles as the crow flies, west of Denver. Mount Evans also had a road to the top. Will agreed to join us. The project was so ambitious there would inevitably be "bumps in the road." Although Grover had sketched a clever design for a corral, we had to build it. So, beginning in January of 1960, from 6:00 to 7:30 A.M., Grover and I could be found at the Denver Stockyards, sawing, hammering, drilling, and bolting to make panels for the corral. In June, when it was finished and the snow had melted, we hauled it to the Mount Evans site, with a load sixteen feet high on a rented truck, being sure to avoid tunnels and low overpasses. We then set it up,

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bolting and nailing the panels in place, installing the troughs for feed and water, fixing in place the "squeeze chute" to restrain 500 pound steers, and providing a swinging gate and alley so we could drive the steers into the chute for study. Then on July 3rd, a livestock trucker with a tractor-trailer hauled tons of hay, grain, and animals to the corral over the narrow, winding mountain road. After we had unloaded the livestock, the driver simply let his rig roll down the mountain, careening around the curves as though in a race car, and terrorizing tourists who were driving uphill. Somehow, no one died.

Perhaps it was the bracing mountain air, or the spectacular view from the corral, but our livestock enjoyed marvelous appetites, requiring great quantities of hay and grain. And whatever went into their mouths appeared somewhat altered at the other end in amounts that defied the law of conservation of mass. Shovels became essential laboratory instruments. Water for the animals was siphoned to the troughs from a lake on the other side of the road four hundred yards above our site. The water pipe often froze overnight and the siphon vacuum had to be restored. We towed a substantial gasoline powered 15 KW generator to the site to operate the scientific equipment. Being above tree line, the corral required a lightning rod because of frequent electrical storms.

There were other issues. Because we had only one pressure recorder and we needed the technicians for blood and expired air analysis, the clinical heart catheterization laboratory had to be closed when we were studying the cattle. While Blount, our chief, did not block the project, he did not bless it either. A functioning clinical cardiac catheterization laboratory at the University Hospital in Denver was to be strictly maintained, and all work in cattle had to be done outside normal laboratory hours. Thus, the experiments on Mount Evans were on weekends. The "cath lab" was transported to the cattle on Friday evenings, and back to the humans on Sunday nights. Because the budget was limited, the cost of the livestock had to be retrieved at the end of the study, and the animals were sold to a commercial meat packer with the stipulation that we could have the heart and lungs for research.

I look back upon those days on Mount Evans in amazement that I remained unfazed by all these obstacles. Was it youth or the advantage of being only a research fellow? As principal investigator, Grover shouldered the problems. Grover had to maintain harmony among the laboratory technicians, some of whom were not happy to be working on the mountain. Grover had to provide our chief with reassurances that cattle were not obstructing the operation of the clinical laboratory. And Grover was the final arbiter of research quality as well as of all expenditures from our limited re-

sources. As a research fellow, I was free to wander, enchanted, through the new field of hypoxic pulmonary hypertension, but he had the responsibility.

And yet it was an adventure for us all. Being young, we almost relished the challenges. We were energized by novel findings in our cattle on Mount Evans, such as their increase in clotting time, their failure to increase their hemoglobin or ventilation, and their much greater increase in pulmonary arterial pressure than occurred in the other species studied simultaneously. Our project had yet another reward. Grover's wife Estelle and my wife Carol worked beside us when we were on the mountain. It being before the days of convenient electronic blood gas instruments, Estelle had mastered the tedious, capricious "Riley bubble method" for  $PO_2$  and  $Pco_2$ . She ignored the danger of lightning strikes and worked right through thunderstorms in a little shed attached to the corral. She also did more than her share of handling the shovel. Because we worked weekends from early morning till late at night, Carol maintained the living quarters at our "base camp," the Echo Lake Lodge at 10,000 ft, where she cooked the meals while at the same time minding our two small daughters.

What was our main scientific contribution? We reported that the pulmonary hypertension of chronic hypoxia was initiated by hypoxia but, "At the same time additional vascular changes were developing which could not be immediately reversed by the administration of oxygen." It was these "additional" vascular changes—the thickening of the vessel wall and impaired ability of the vessel to relax—that were our most important and novel findings. They are also the key components of fatal chronic pulmonary hypertension in clinical medicine. Chasing these two villains—wall thickening and impaired vascular relaxation—accounts for much of our subsequent research (and that of many others). The research has shown the extraordinary susceptibility of the newborn to pulmonary hypertension, the genetic component of pulmonary hypertension, the important interactions between the vessel wall and blood in maintaining elevated pressure, and the integrated response to injury of all the layers, cells, and tissues within the vascular walls. Thus, blood, the intima, media, and adventitia, the matrix, the bronchial circulation, and even the nerves are all interrelated components contributing to wall thickening and impaired vasodilation in pulmonary hypertension. While some of the mechanisms of pulmonary hypertension are analogous to those in systemic vascular disease, many are unique to the lung. Thus, our studies of chronic pulmonary hypertension in cattle opened new fields of inquiry. And in addition, for me personally, they opened my eyes to medical research as high adventure. That changed my life.