

# The herd shot “round the world”

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Colorado is known for its “Fourteeners,” mountain peaks over 14,000 feet tall; there are more than 50 of them. One is Mount Evans, standing at 14,260 feet conveniently located just 60 miles west of Denver. I’m going to take you back in time so you may witness the remarkable adventure that played out near the summit of that mountain half a century ago.

My story begins on the third day of July in the year 1960. Early that morning, one could have seen Bill Wilson driving a heavily loaded, 18-wheel cattle truck as he began his ascent up the winding road that leads to the summit of the mountain. However, his destination was Summit Lake Flats (Fig. 1A), a broad stretch of tundra lying just below the peak but well above tree line at an elevation of 12,700 feet. He was carrying a load of 10 yearling Hereford steers, 12 Rambouillet/Suffolk spring lambs, and four tons of hay, straw, and pellet feed (Fig. 1B). Bill had been instructed to deliver his cargo to a portable corral that my colleague Jack Reeves and I had fabricated down in Denver. Estelle Grover, my wife, and Donald Will, a veterinarian and previous collaborator in 1958,<sup>[1]</sup> were coinvestigators on this project.

Assembling the corral within reach of Summit Lake, we now had a potential source of fresh drinking water for our livestock. Our next challenge was to find a way to establish a continuous supply water from the lake to the water troughs for the next two months; we took on this challenge by laying out 1,200 feet of flexible pipe that literally siphoned water out of the lake and over to the corral (Fig. 2). The process was smooth and efficient, except for the occasional night when it froze up; we hadn’t counted on that. As for electric power, we brought in a portable generator. We completed all of these preparations a few days before the truck arrived; the only thing left was to move the three tons of live cargo and four tons of food from the cattle truck over to the corral.

Using a four-wheel drive pickup truck to move the steers, one at a time, over to the corral gate, we turned them

loose into one section of the corral. As for the lambs, we unceremoniously hoisted them over the side of another section of the corral, while the hay, straw, and feed were packed into a separate section (Fig. 3). At the end of the day, we could say that we had successfully launched the high altitude phase of the project.

About now I hope you’re asking yourselves what in the world this is all about, placing cattle on a mountain top. Well, back in the late 1800s cattlemen moving west traveled to the Rocky Mountains where they discovered broad, intermountain valleys lush with tall grass, such as South Park in the shadow of Pikes Peak. Believing this area to be perfect grazing land, they imported thousands of cattle from low altitude, Texas, Oklahoma, Kansas: but they were soon in for a surprise. Within the first six months of ranching, 5% to 10% of their cattle died! While examining the afflicted animals, they noticed a strange swelling at the base of the neck and under the sternum. Meat-cutters call this area “the brisket of beef,” and so the cattlemen dubbed this ailment “brisket disease” (Fig. 4).

In order to better understand what was wrong with their cattle, they turned to the veterinary college at Colorado State University in Fort Collins, just north of Denver. When two veterinarians by the names of George Glover and Isaac Newsom drove up to South Park to examine the animals, they concluded that the cattle were in congestive heart failure. Furthermore, they were convinced that some aspect of the severe climate at high altitude environment was causing this heart failure. That was very perceptive. And so when they published their paper in 1915,<sup>[2]</sup> they subtitled it “dropsy of high altitude.” Rather quaint, isn’t it?

Now I want to tell you something absolutely confounding. For the next 35 years, there was absolutely no increase

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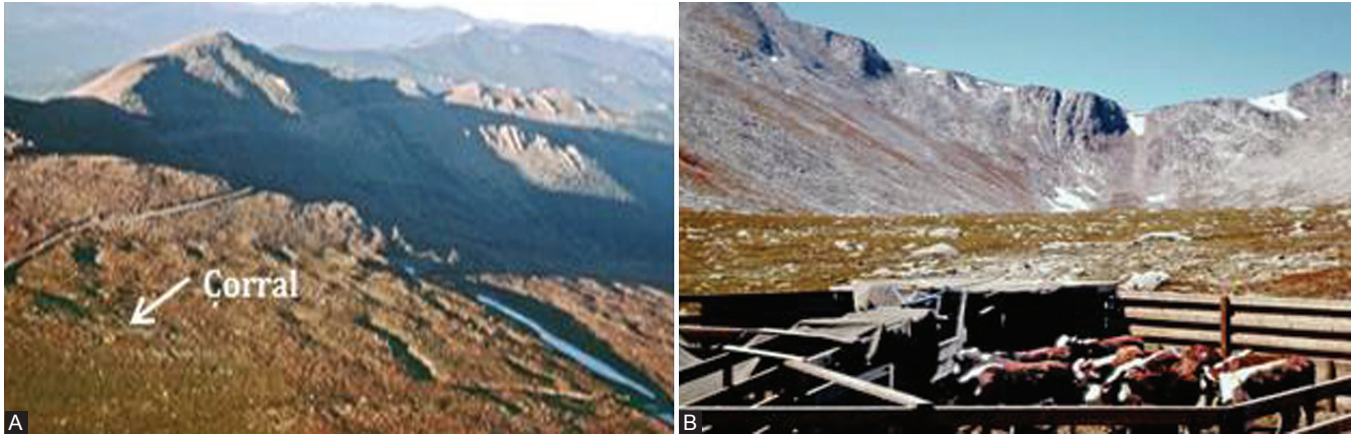
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**Figure 1:** Corral well above timberline at Summit Lake Flats, altitude 12,700 feet on Mt. Evans (A). Steers (and lambs) studied in this portable corral for 2 months (B).



**Figure 2:** Bob laying out 1,200 feet of flexible pipe to siphon fresh water from Summit Lake to the water troughs in the corral.



**Figure 3:** Bob standing on bathroom scale measuring body weight of lamb.



**Figure 4:** Steer at high altitude with *cor pulmonale* (brisket disease).

in the understanding of the pathophysiology of brisket disease. Nothing! Not until the early 1950s did Rue Jensen, a veterinary pathologist at Fort Collins, come to a fundamental conclusion while dissecting hearts of brisket animals. Jensen was the first to note two abnormalities:

(1) the significant and selective enlargement of the right ventricle; and (2) the marked dilatation of the trunk of the pulmonary artery. Combining these observations, Jensen concluded that something must be increasing the resistance to blood flow through the lung, placing an excessive pressure load on the right ventricle causing it to fail. Brisket disease was a form of *cor pulmonale*. A man of few words, Jensen titled his paper "Right Heart Failure."<sup>[3]</sup>

Now, neither Jensen nor his colleagues had a clue as to what was causing this pulmonary hypertension. Was it some toxic substance in the grass that grew in South Park?<sup>[1]</sup> Was brisket disease actually a disorder in blood coagulation causing the animals to develop pulmonary thromboembolism? Or maybe it was an excess intake of salt from the mountain stream drinking water?<sup>[1]</sup> I want to place emphasis on this line of speculation because in the mid-1950s the scientific community had absolutely no concept of the physiology of the pulmonary circulation. It was a blank page.

And now back to my story. This (the mid-1950s) was the time when Jack Reeves and I arrived on the scene. We were at the University of Colorado School of Medicine, Denver, working in the Division of Cardiology diagnostic heart catheterization laboratory, seeing children with various forms of congenital heart disease. We were intrigued by the fact that a number of these patients had significant pulmonary hypertension. One day in 1958, Giles Filley,<sup>[4]</sup> who worked just down the hall, told us that there were veterinarians just up the road at Fort Collins studying pulmonary hypertension in cattle in South Park.<sup>[5]</sup> Wow! We didn't waste any time getting in touch with those fellows, Arch Alexander and Don Will, and in a short period of time we were collaborating with them in South Park,<sup>[1,6,7]</sup> making the very first measurements of the severe pulmonary hypertension in brisket cattle.

Jack and I were already familiar with published reports on how the inhalation of hypoxic gas mixtures elevate the pulmonary arterial pressure.<sup>[8,9]</sup> This was only acute hypoxia; nothing was known about chronic hypoxia. So we suggested to our veterinary colleagues that, just possibly, the atmospheric hypoxia at high altitude might be causing brisket disease. To my knowledge, this was the first time that either of these gentlemen had ever heard of the concept of “hypoxic pulmonary hypertension.”

Jack and I were fascinated by the fact that the bovine species, cattle, appeared to develop more severe pulmonary hypertension than other species exposed to chronic hypoxia. Did they have a poor ventilatory response to high altitude (relative hypoventilation) resulting in a more severe hypoxic stimulus? Did cattle have unusually strong pulmonary vasoconstriction in response to alveolar hypoxia? To what extent was the increase in pulmonary vascular resistance due to vasoconstriction compared to structural changes (vascular remodeling) of pulmonary blood vessels? Would pulmonary hypertension develop more rapidly if the cattle were taken to a higher altitude (12,700 feet) than in the 1958 studies in South Park (10,000 feet), i.e., a more severe hypoxic stimulus? To address these questions (and others) we decided to expose a group of young steers to the chronic atmospheric hypoxia at 12,700 feet for two months and document the time course of their pulmonary vascular responses. In addition, we thought it would be interesting to simultaneously study lambs, a species known to tolerate high altitude very well. We selected lambs because Estelle and I had observed first hand sheep and llamas grazing side by side at an altitude of 14,000 feet in the Peruvian Andes during a visit with Alberto Hurtado late in 1959.

Now, just how do you go about collecting hemodynamic data from a 500-pound steer? I'll tell you. Jack and I decided to adopt techniques used by cattle ranchers, of which we had

become familiar with while working with the veterinarians (remember, Jack and I were both “city boys”). The first thing you need is this medieval-looking device known as a “squeeze chute” (Fig. 5A). In case you aren't familiar with their general disposition, steers do not eagerly volunteer to walk into this contraption, but after some “encouragement” they will. Pulling down on the lever, you will see the side of the chute swing up against the animal's torso, another contraption closes in around the neck, and now the steer is not going anywhere. Next, you will need to blind-fold him because you don't want these animals to be spooked by what is going on around them (Fig. 5B). Finally, you restrain the head to one side with a rope halter. Now you are ready to go to work.

Steers have jugular veins the size of your forearm; you can't miss them. Popping in a 10-gauge needle, a stream of blood spurts out, and then you need to thread in a catheter that goes directly to the right heart. To identify where the tip of the catheter is, you attach it to a pressure transducer which in turn will send a signal to a photographic oscillograph. When you look into the shielded viewing slot, a bright spot of light will move across a slit lens in response to changes in pressure. As soon as the catheter tip enters the right ventricle, the spot begins swinging back and forth and you know exactly where you are. A little farther on, the pressure contour changes to that of an arterial pulse and you know



**Figure 5:** Bob and his wife Estelle collecting expired air from steer (A). Jack (standing) and Bob (squatting) performing heart catheterization on steer restrained in squeeze chute (B).

you’re in the pulmonary artery. That spot of light is focused upon light sensitive photographic paper, pulled by a motor past the lens. To develop this recording, you must take it into a dark room, place it through the developer, the fixer, and the water bath; what you end up with is a very elegant analog tracing of the pulmonary arterial pressure in that steer. All that remains is to take a metric measuring device, sit down and measure the height of the pressures. With a stubby pencil, you write down the numbers in a data book. There was no such thing as automatic pressure recording during that time; it was all manual.

In addition to the pulmonary artery pressure, you will need to know the pulmonary blood flow at the time the pressure was recorded. The Fick principle<sup>[10]</sup> says that if you know the amount of oxygen going into the lung, and you know how much the oxygen content of the blood increases as it flows through the lung, then you can calculate the total blood flow or cardiac output. In practice, you will need to collect expired air for oxygen uptake, and for the blood a-v difference across the lung you will need samples from both the pulmonary artery and a systemic artery. But how do you collect expired air from a steer? Obviously, you need a face mask (Fig. 6). To construct one, take a length of inner-tube from a car tire, cement this onto a plastic disk, and attach a high-flow respiratory valve; the fit to the steer’s muzzle is quite snug! Then, you will need to connect the valve to a large rubberized Douglas bag, and with a stop cock and stopwatch you will need to collect expired air for exactly 1 minute (Fig. 7). Then to measure the volume of air you squeeze out the bag through a gas flow meter. During this process you also collect an aliquot sample of air for future analysis. For calculation, you must also know the temperature of the expired air as it was collected. This requires inserting a foot-long glass mercury thermometer into the steer just below the base of his tail; that was usually my job!



**Figure 6:** Bob pulling tight-fitting face mask over the muzzle of steer for gas collection.

For the blood samples, while you already have a catheter in the PA you will still need oxygenated arterial blood. Jack’s solution was to take a 10-inch long needle and thread it between muscles in the animal’s neck, puncturing the carotid artery. The needle in place, you will need to withdraw the pulmonary arterial and systemic arterial blood samples, simultaneously. Once all of the gas and blood samples from several animals have been collected, one member from your research team will need to put them in his pick-up-truck and drive nine miles down the mountain to a permanent facility operated by the University of Denver at Echo Lake. Here, we had set up a temporary analytical laboratory for our technicians, consisting of VanSlyke machines for analyzing blood samples and a Scholander apparatus for analyzing the composition of expired air.

And now for one more chore: To measure the magnitude of the hypoxic stimulus to which the animals were exposed, we needed to measure the oxygen pressure (tension) in arterial blood (PaO<sub>2</sub>). Furthermore, this analysis had to be made on-site without delay. And so while Jack had his needle in the carotid artery, he withdrew a second sample of blood and handed it to Estelle. She took it to her mini-laboratory, a mere closet shelter from the elements, where she submerged the syringe of arterial blood in a water bath at the animal’s body temperature. With a low-power microscope to read calibrations on the syringe, she measured PaO<sub>2</sub> by the now-obsolete Riley Bubble technique<sup>[11]</sup> (Severinghaus blood gas electrodes had yet to be perfected). Our 12 lambs were studied by the same techniques, except that we had to construct a mini-squeeze chute of plywood because it is critical that lambs (and sheep) be studied in their normal standing position; held on their side or back, they will die!

These techniques, while dated now, were all state-of-the-art during the 1950s and 1960s. Cardiac Catheterization Laboratories were popping up all over the country, and in



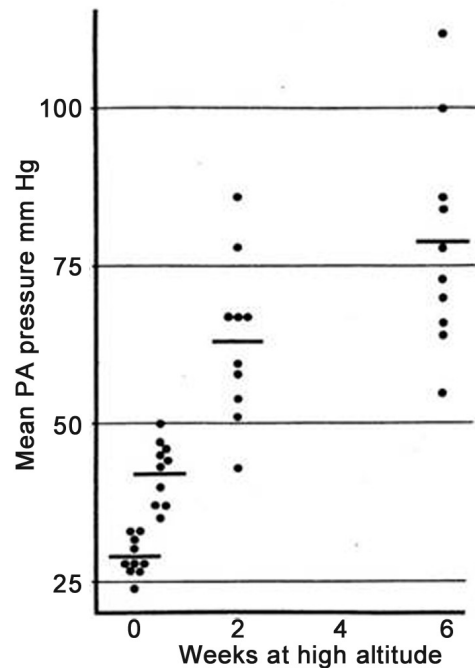
**Figure 7:** Jack with bag of expired air being pushed through gas meter to measure volume.

every single one they used exactly these same techniques; very labor intensive but they gave good data. Technology really has come a long way.

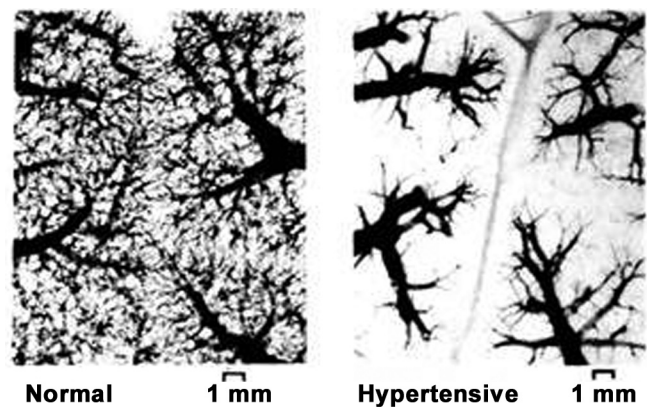
Now, what did we learn? Let's begin with the PA pressure data from the 10 steers (Fig. 8). Each dot represents the mean PA pressure from a single animal so at each time period there is a collection of 10 points. At low altitude in Denver, they clustered around 25 mmHg. But as soon as they were exposed to the hypoxia of high altitude, the pressures began to rise relentlessly. After six weeks the average pressure for the whole group had tripled to 75 mmHg. At the same time, you will notice there is tremendous variation among individuals in how much hypertension they actually developed. One steer's pressure was only 55 while most steers had pressures up around 60, 70, and 80, and two steers had pressures above 100 mmHg;<sup>[12]</sup> it's no wonder that one of them went into heart failure.

Histology of the lungs showed marked thickening of the media of the small muscular arteries, or vascular remodeling, as described previously by Alexander.<sup>[13]</sup> But if you really want to get the feel of vascular remodeling, look at these arteriograms (Fig. 9).

Having seen these spectacular responses in the cattle, don't forget that we also had 12 lambs living side by side with the steers, exposed to exactly the same hypoxic stimulus, and they developed absolutely no pulmonary hypertension (Fig. 10). After six weeks, their PA pressures were no higher than they had been at low altitude at the start of the study;<sup>[14]</sup> I believe this to be one of the most provocative findings from the entire Mount Evans study. In cattle, lungs had multiple vasoreactive mechanisms, vasoconstriction, together with vascular remodeling, while in lambs these mechanisms appear to be totally absent. What is this all about? Subconsciously we think that because something exists it must therefore serve some purpose, and usually it must do something good for the individual; thus, people speculated on the importance of hypoxic pulmonary vasoconstriction. One school of thought is that it serves to match local perfusion to local ventilation ( $V/Q$ ). For example, if you have an unventilated region of lung (e.g., lobar pneumonia) and you constrict the arteries within that area, that will divert blood to better oxygenated parts of the lung and the lung becomes more efficient at gas exchange. But when you start applying this to multiple sections of the lung, as in patients with COPD, this response becomes disastrous; it creates heart failure and the patient dies. So that is not such a good explanation, I don't think. Another school of thought says, no, the purpose of hypoxic vasoconstriction is to minimize perfusion of the fetal lung before it becomes functional. This would reduce the workload on the heart



**Figure 8:** Rapid development of hypoxic pulmonary hypertension in 10 steers at 12,700 feet altitude. Note marked variation among individual steers in the severity of hypertension after six weeks.



**Figure 9:** Pulmonary arteriograms of normal and pulmonary hypertensive steers. Note extreme narrowing of distal blood vessels causing hypertension. Prepared by Wiltz Wagner.

of the fetus, and then right after birth when oxygen enters the lung, the vessels relax, perfusion begins, but the mechanism doesn't go away. So when you find it in the adult, it is a legacy from fetal life. It is excess baggage that we have to carry around for the rest of our lives and it may end up killing us. Where is “the wisdom of the body” that Walter B. Cannon<sup>[15]</sup> spoke of? Maybe Shakespeare had the right idea hundreds of years ago, in that “each of us carries within him the seeds of his own destruction.”<sup>[16]</sup> Hypoxic pulmonary vasoconstriction seems to be one of those seeds of destruction. We simply have to deal with it, try to understand it, and maybe, just maybe, we can do something about it.

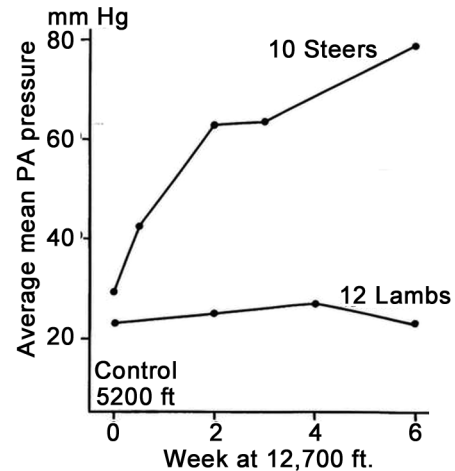
This is where the investigators of recent decades come in. They are the ones who have explored the pathophysiology of the lung circulation. They are the ones who have discovered an amazing array of mechanisms, the HIF's, the PDGF's, Rho/Rho kinase, and now something called an autophagia, all unimaginable back in 1960; we were groping in the dark back then. Once the intimate details of these mechanisms have been worked out, the information can be given to pharmacologists and clinicians who may then proceed to develop effective modes of therapy. A classic example is the recent work of Ivan McMurtry and his colleagues<sup>[17]</sup> who have shown that Rho kinase inhibitors are more effective pulmonary vasodilators than conventional agents such as nitric oxide, prostacyclin, and nifedipine. Such observations have great potential for therapy of pulmonary hypertension.<sup>[18]</sup>

I feel a great sense of pride when I think of the accomplishments these investigators have produced for us. Thanks to them, we now have an impressive body of knowledge assembled through their scientific acumen and imagination. They have written many chapters on the blank pages of 50 years ago. But sometimes I wonder, if in their scientific careers, they have had as much *fun* as Jack and I had on that mountain top half a century ago (Fig. 11).

## HISTORICAL NOTE

The results of this 1960 study on Mount Evans were first presented to a scientific audience in 1962.<sup>[19]</sup> This was a conference titled *Normal and Abnormal Pulmonary Circulation*, the fifth in a series of Annual Conferences on Research in Emphysema founded by Jack Durrance, Roger S. Mitchell and Giles F. Filley, held in Aspen, Colorado. In 1961 they invited me (RFG) to organize the 1962 conference on the subject of the pulmonary circulation. I had never organized any conference in my life, so I was unencumbered by any previous knowledge of such prosaic matters as funding.

Given free rein, I proceeded to invite experts not only from the United States of America but also from around the world. And I even asked Nobel Laureate Andre Cournand to prepare the summary of the conference! It proved to be a wonderful exchange of information among persons who otherwise might not have had this remarkable opportunity to meet. For example, based on Estelle's and my visit to Lima, Peru, I invited Dante Penalozza to present his fascinating information on pulmonary hypertension in Peruvian natives living at 15,000 feet in the Andes. It proved to be the very first time this information had been presented outside of South America. Arch Alexander,<sup>[13]</sup> the veterinary pathologist from Colorado State University in Fort Collins, presented his beautiful work on the pulmonary vascular changes in brisket disease to renowned



**Figure 10:** Species variation in pulmonary vascular response to the same hypoxic stimulus, severe hypertension in steers versus virtually no response in lambs.



**Figure 11:** Jack and Bob still collaborating on high altitude research 30 years after Mt. Evans.

pathologists including Jesse Edwards from the Mayo Clinic, CA Wagenvoort from the Netherlands, Averill Liebow, and Javier Arias Stella from Peru. Geoffrey Dawes from England spoke on the fetal lung circulation. John Severinghaus, John West, Abe Rudolf, Al Fishman – it was a stellar cast.

In his summary, Cournand remarked “This conference, I would say without blushing, is the best that I have ever attended. The program was superb.” It was in this illustrious setting that we fledgling investigators, Bob Grover and Jack Reeves, presented our work. Thomas Karger, president of S. Karger AG, Basel, Switzerland, offered to publish all of the individual papers from this conference in their journal *Medicina Thoracalis*, Vol. 19, followed by a monograph in 1963;<sup>[19]</sup> we accepted.

## BIOGRAPHICAL NOTES

Robert F. Grover was born in 1924 in Rochester, NY. After three years of active service in the US Army during

WWII, he completed his education including a PhD in Physiology in 1951, and an MD in 1955. Following his internship and fellowship in Cardiology, he joined the faculty of the University of Colorado School of Medicine in July 1957 on the first rung of the academic ladder, that of Instructor in the Division of Cardiology. He was assigned to the diagnostic cardiology catheterization laboratory, a component of the broader Cardiovascular Pulmonary (CVP) laboratories. This soon functioned as a combined diagnostic and research facility under Dr. Grover's direction. In 1965, the research facility became independent as the CVP Research Laboratory with its own research training program that Dr. Grover directed for 19 years until his retirement in 1984.

John T. (Jack) Reeves was born in Hazard, Ky. in 1928. After completing his studies at MIT and the University of Pennsylvania School of Medicine, he was accepted as a Fellow in Cardiology at the University of Colorado School of Medicine in July 1958. His first assignment was the CVP laboratory where he and Bob Grover met. Thus began a life-long friendship and collaboration between Bob and Jack that lasted 47 years until Jack's untimely death in 2004. Jack spent four years in Denver until 1961 when he returned to Lexington, Ky., but he and Bob remained in constant contact and collaboration. In 1972 Bob was able to offer Jack a faculty position and he eagerly returned to Colorado where they worked together for the rest of Jack's life.

Thus, at the time of the study on Mount Evans, Bob had worked in the CVP laboratory just three years and Jack only two. Bob was 36 and Jack 32, hardly "seasoned investigators."

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