Lofty goals at high altitude: The Grover Conferences, 1984–2011

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ORIGIN

The first Grover Conference was held at the Lost Valley Ranch Conference Center in Deckers, Colorado, in 1984. Both the concept of the conference and the choice of the site were initiatives of John T. "Jack" Reeves MD (Fig. 1). At the time, there was no major conference dedicated to pulmonary circulation or pulmonary hypertension and a PubMed search for articles with the following key words detected <80 publications/year: pulmonary circulation, hypoxic pulmonary vasoconstriction, and pulmonary hypertension. By 2010, there were >900 publications/year with those keywords in their title (Fig. 2). Although the biannual Grover Conferences cannot take all the credit for this new interest in lung circulation, they have certainly contributed. The impact of the conference has been enhanced by the careful selection of new topics that are identified as areas of emerging opportunity (Table 1). Thus, new science is always on the "menu." Moreover, the invitation of scientists to a ranch that is literally in a "Lost Valley," with only a pay phone for communication with the outside world, has meant that these established and emerging scientific leaders are fully engaged. In addition, enduring camaraderie is derived from sharing cabins and enduring the terror of novices on horseback. The hypoxic majesty of the Pike National Forest at elevations of >7000 feet focuses the mind on hypoxia (especially as one pants up the inclines to cabins with names like "Huff n Puff"). A remarkable transformation of the intellectual elite occurs when they are wrapped in denim and plaid giving a talk using a fishing pole as a pointer. If that did not generate sufficient humility, Jack Reeves was ever ready with a deceptively simple question that would humble the arrogant and point out the need for more research.

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Dr. Reeves and his colleagues, Drs. Wiltz Wagner, Norbert Voelkel, Ivan McMurtry and Ken Weir (Fig. 3), recognized the need for an ongoing international, scientific conference devoted to the pulmonary circulation. The meeting in 2011 was the 15th in the series. Those who study the pulmonary circulation do not need to be reminded of its unique characteristics. However, the great majority of the non-medical public are still in the pre-Harveian era and do not know that there is an entirely separate circulation of blood to the lungs. Few of those who are medically trained, other than cardiologists and pulmonologists, remember the complex embryology that gives rise to the proximal, capacitance, pulmonary arteries. Many have forgotten that the pulmonary vasculature is a low-pressure system, accommodating the entire cardiac output and interfacing with the airways down to the level of the alveoli, with the bronchial circulation and with the lymphatics. Those who work in the area know that the lungs provide a large area of contact between the blood and endothelium and consequently, the lungs' metabolic activity is enormously important. Many endogenous substances are activated, such as angiotensin I, or inactivated, such as bradykinin; and yet others, such as nitric oxide and prostacyclin, are generated by the endothelium of the pulmonary vasculature. In most respects, the pulmonary circulation is quite different from the systemic circulation, as illustrated in terms of acute reactivity by hypoxic pulmonary vasoconstriction, in altered function by the potentially fatal condition, high-altitude pulmonary edema, and in chronic disease by idiopathic pulmonary arterial hypertension. It is clear from even a brief summary of

Access this article online	
Quick Response Code:	Website: www.pulmonarycirculation.org
	DOI: 10.4103/2045-8932.93550
	How to cite this article: Weir EK, Wagner WW, Archer SL. Lofty goals at high altitude: The Grover Conferences, 1984-2011. Pulm Circ 2011;1:501-7.

Table 1: The Grover Conferences on the Pulmonary Circulation, 1984-2011

		Publisher	Conference Director
1984	Pulmonary Vascular Reactivity	Chest 88: 199S-272S, 1985	E.K. Weir, I.F. McMurtry, J.T. Reeves
1986	The Role of Lipid Mediators	Am. Rev. Respir. Dis. 136: 196-224; 782-788, 1987	E.K. Weir, J.T. Reeves
1988	The Control of Cellular Proliferation	Am. Rev. Respir. Dis. 140: 1093-1135; 1446-1493, 1989	E.K. Weir, J.T. Reeves
1990	The Diagnosis and Treatment of Pulmonary Hypertension	Futura, New York, NY	E.K. Weir, S.L. Archer, J.T. Reeves
1991	The Pulmonary Circulation and Gas Exchange	Futura, New York, NY	W.W. Wagner, E.K. Weir
1992	The Role of Ion Flux	Plenum Press, New York, NY	E.K. Weir, J. R. Hume, J.T. Reeves
1994	The Role of Radicals	Futura, New York, NY	E.K. Weir, S.L. Archer, J.T. Reeves
1996	The Pathogenesis and Treatment of Pulmonary Edema	Futura, New York, NY	E.K. Weir, S.L. Archer, J.T. Reeves
1998	The Fetal and Neonatal Pulmonary Circulations	Futura, New York, NY	E.K. Weir, S.L. Archer, J.T. Reeves
2000	The Blood and the Pulmonary Circulation	Futura, New York, NY	E.K. Weir, H.L. Reeve, J.T. Reeves
2002	Proinflammatory Signaling Mechanisms in the Pulmonary Circulation	Humana Press, Totowa New Jersey, NJ	J. Bhattacharya
2004	Genetic and Environmental Determinants of Pulmonary Endothelial Cell Function	http://www.groverconference.org/grover_past_conft.htm	T. Stevens
2006	Rho Family GTPases in Pulmonary Vascular Pathophysiology	http://www.groverconference.org/grover_past_conft.htm	K. Fagan, I.F. McMurtry
2008	Membrane Receptors, Channels and Transporters in Pulmonary Circulation	Humana Press-Springer, New York, NY Adv. Exp. Med. Biol. Vol. 661	J.P.T. Ward, J.X.-J. Yuan
2011	Risk Factors in Pulmonary Hypertension	Pulm. Circ. Vol. 1-2, 2011-2012	M.R. MacLean, N.W. Morrell, K. Fagan

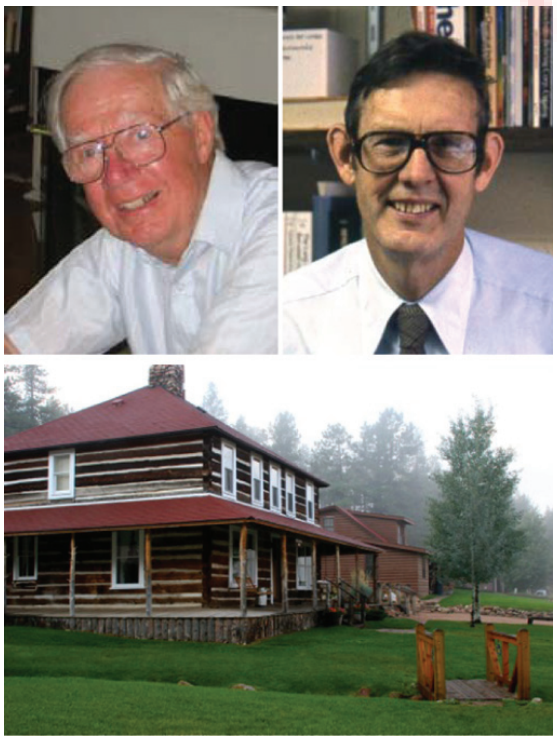

Figure 1: (Left, right and bottom) Bob Grover, Jack Reeves, and the Lost Valley Conference Center at Sedalia, Colorado where the Grover Conferences are held since 1984.

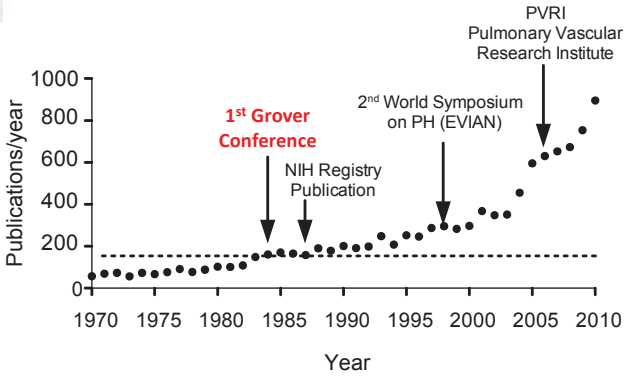

Figure 2: Key meetings in the development of the study of pulmonary circulation. Although association is not causality, the Grover meeting in 1984 clearly occurred at the first deflection point in the field, as evident by the subsequent growth in what had been a niche area of research. Many other important events occurred that also stimulated interest, including the Evian meeting in which a modern classification of pulmonary hypertension was developed, the publication of the NIH's PPH registry and, most recently, the creation of an international PVRI, which engages scientists from countries around the world in pulmonary vascular research (HYPERLINK "http://www.pvri.info" www.pvri.info).

some of these features of the pulmonary circulation that a dedicated, ongoing conference was, and remains, necessary.

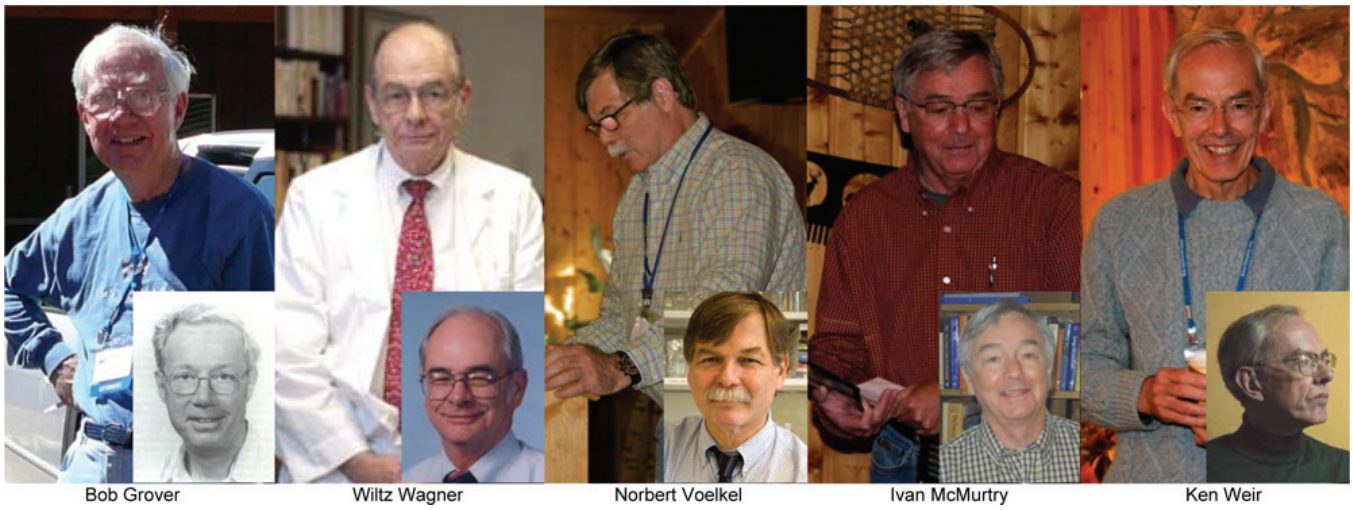

Figure 3: Bob Grover and his colleagues, Wiltz Wagner, Norbert Voelkel, Ivan McMurtry, and Ken Weir.

The conference is named for Robert F. Grover MD PhD in recognition of his many contributions to our understanding of the physiology and pathophysiology of the pulmonary circulation. His studies of chronic hypoxic pulmonary hypertension in cattle (brisket disease) were among the first describing this condition (1963).[1] He instigated or performed many studies on factors that influence acute and chronic hypoxic pulmonary hypertension, differences between species (1963),[2] sympathetic activity (1968),[3] genetic differences (1974),[4] endotoxins (1974),[5] prostaglandins (1976),[6] L-type calcium channels (1976),[7] acetylcholine (1976),[8] platelets (1976),[9] ethyl alcohol (1978)[10] and cold (1978).[11] Dr. Grover was one of the first to demonstrate a component of reversible vasoconstriction in patients with congenital heart disease.[12] He performed the first measurements of pulmonary arterial pressure in normal North American residents of high altitude.[13] He was involved in studies of pulmonary vascular reactivity in subjects who had had an episode of high-altitude pulmonary edema,[14] and also in pregnant women.[15] All these studies demonstrate the breadth of his interests in the pulmonary circulation and also illustrate many of the puzzles that continue to stimulate our research.

Dr. Grover was also an inspirational mentor and the conference celebrates both his scientific interests and his tradition of mentorship. In the first three decades of its existence the Grover Conference has become a retreat to which mentors return to see their mentees shepherding a new generation of scientists in the search to understand the lung circulation and its diseases. The sense of community and the excitement for discovery are perhaps 2 of the greatest benefits of this meeting, both very consistent with Dr. Grover's legacy. At the 2011 Conference, he gave a stirring summary of the high-altitude adventures that led him and his protégé, Jack Reeves, to understand the basis for brisket disease as both excessive HPV and exuberant remodeling of the pulmonary vasculature. In Figure 4a, the young friends, Reeves and Grover, are seen on the slide while the adventure of research is evident in Figure 4b, which summarizes cardiac catheterization of normal teenagers at high altitude, showing they too may have pulmonary hypertension. The talk ended with an emotional standing ovation (Fig. 4c), both for the talk and for the legacy of mentorship.

The conference's proceedings, published in a series of books and journal issues, bear witness to many discoveries which have changed our understanding of hypoxic pulmonary vasoconstriction, the pulmonary vascular effects of high altitude, the causes and treatment of pulmonary arterial hypertension, and the latest information of the role of gender in pulmonary hypertension. The publications arising from the conference are listed in Table 1. However, even more compelling are the areas of research that were begun and the collaborations and friendships that were launched during these conferences.

CONFERENCE EVOLUTION

In the 27 years since the first Grover Conference there have been enormous changes in our understanding of the pulmonary circulation but, Our improved basic science understanding has not been translated to cost-effective treatment. It is fascinating to read the description given by Robert Furchgott (co-winner of the 1998 Nobel Prize in Physiology or Medicine), at the 1984 conference, of endothelium-derived relaxing factor (EDRF)[16] (Fig. 5). He reported that EDRF was released from intrapulmonary arteries by acetylcholine and bradykinin causing vasodilatation, probably through an increase in cyclic GMP. He demonstrated that hemoglobin would inhibit EDRF and speculated about the identity of EDRF,

Figures 4: (a) Bob Grover at the 2011 meeting, summarizing the pioneering work he and Jack Reeves, then a Cardiology Fellow at the University of Colorado, performed in discovering the basis for brisket disease (b) Bob Grover describing how the work in cattle was quickly replicated in normal volunteers in the high-altitude community of Leadville, Colorado (c) A tribute to a fine after-dinner talk and an even finer scientist and mentor.

Figure 5: (Left to right) Jack Reeves, future Nobel Laureate Robert Furchgott, and E. Kenneth Weir, at the inaugural (1984) Grover Conference.

including "the free radical nitric oxide" among other candidates. Other presentations in the initial conference included Kees Wagenvoort describing fenestrations in the internal elastic lamina of small pulmonary vessels seen on electron microscopy which he suggested might facilitate communication between the endothelium and smooth muscle. Sami Said discussed vasoactive peptides in the lung and, in particular, the vasodilator activity of vasoactive intestinal peptide (VIP). Among many papers on pulmonary vasoconstriction, David Harder reported that hypoxia caused membrane depolarization in pulmonary artery smooth muscle cells, and Lew Rubin reviewed the use of calcium channel blockers in the treatment of primary pulmonary hypertension (now called IPAH, idiopathic pulmonary arterial hypertension).

Most relevant to the 2011 Conference was the paper by Jimmy Sylvester on "Prostaglandins and Estradiol-induced Attenuation of Hypoxic Pulmonary Vasoconstriction."[17] In the isolated perfused sheep lung he found that estradiol pre treatment reduces the normoxic control pulmonary vascular resistance by a mechanism unrelated to the production of prostaglandins. Further, estradiol reduces HPV by a mechanism that does involve prostaglandins. Meanwhile, an important presentation by Milton Packer cast doubt on the efficacy of vasodilator therapy in the treatment of primary pulmonary hypertension.[18] This was an early shot in the continuing debate over the role of vasoconstriction in the etiology of IPAH. The ensuing discussion of his paper reflected the recognition that the

response to vasodilator agents would be determined by the underlying histology, being poor in those patients with plexiform lesions.

The titles of the subsequent conferences are given in Table 1. The fact that the third conference (1988) was devoted to the control of cellular proliferation in the pulmonary circulation indicates the early understanding that the effective treatment of pulmonary hypertension would include the inhibition of cellular proliferation. The fifth conference (1991), directed by Wiltz W. Wagner, Jr., was the most memorable in a historical sense. Many of the pioneers of research into the pulmonary vasculature described their personal development and work in the field (Fig. 6). To mention a few highlights, Bob Grover spoke eloquently of his introduction to physiology, the history of research into the effects of high altitude on the pulmonary circulation, and his early work with Estelle Grover and Wiltz Wagner.[19] Donald Heath described his induction into the world of pulmonary vascular pathology and the histology of the small pulmonary vessels of men and animals at high altitude.[20] Peter Harris gave a talk, illustrated by many of his own line drawings, reporting experiments on sheep, goats, cattle and yak in the Himalayas.[21] Ewald Weibel talked about the insights that morphometry, and electron microscopy in particular, provide to our understanding of lung physiology.[22] In the course of their lectures, both Johannes Piper and Kees Wagenvoort described their experiences as young men during the Second World War.

The publications derived from the Grover Conferences stand as a unique record of the progress of research into the pulmonary vasculature and pulmonary hypertension. Over the course of the conference, the scientific reports have appeared in books, published initially by Steven Korn with Futura and more recently as articles in the journal Pulmonary Circulation, edited by Dr. J. X.-J. Yuan, Dr. Harishrishnam S. and Dr. N.W. Morrell (who helped organize the 2011 Conference). The idea that there would be a journal dedicated to pulmonary circulation was unthinkable when the first Grover Conference occurred, and bears testimony to the maturation of the field.

LOGISTICS

All the Grover Conferences have been held at the Lost Valley Ranch Conference Center. It provides the ideal environment for such meetings, fostering opportunities for formal and informal discussion between those attending. This is a rare conference in which forced isolation creates focus and creative collegiality. Along the winding dirt road to the Lost Valley, "Big City" scientists lose their suits, put on jeans and are soon sharing communal bunk houses, speculating on grizzly bear traffic in the valley and commiserating about the saddle sores they acquired during the daily horseback ride. In the beginning, the conference was a "do-it-yourself" enterprise and guests from around the world were greeted at the old Stapleton Airport by Rosann McCullough and driven up the mountain by faculty and fellows from the University of Colorado's legendary CVP lab. The JVL™ Lost Valley Ranch is an intrinsic part of the meeting. The Foster family who owns and operates this working ranch have embraced the city slickers who return to the ranch with a welcoming Ooh-Ah every 2 years. The Grover Conferences have been a catalyst for

Figure 6: Three generations of scientists at the 5th Grover meeting (1992). Front row (left to right): Robert A. Klocke (on one knee), James R. Snapper, Mark N. Gillespie, Wiltz W. Wagner Jr., Almas Aldechev, David J. Riley, Anne Clark, Gwenda R. Barer, Troy Stevens, Grant deJ. Lee (looking down), Tawfic S. Hakim, John N. Evans, Robert F. Grover, Norman C. Staub, Lynne M. Reid, J. Michael Kay, Michael R. T. Yen, Vaclav Hampl. Middle row (left to right): Robert E. Forster II, Claire Doerschuk, J. Usha Raj, John B. West, Aubrey E. Taylor, Solbert Permutt, Christopher A. Dawson, Roy G. Brower, J. T. Sylvester, C. A. Wagenvoort, Donald Heath, Serge Adnot, Gerald Simonneau, Phillipe Herve, Peter D. Wagner, John T. Reeves, David Badesch, Barbara O. Meyrick, Norbert Voelkel, A.N. Other, E. Kenneth Weir, Bertron M. Groves. Back row (left to right): Albert L. Hyman, Stephen Archer, Inder Anand, Peter Harris, Nicholas S. Hill, John A. Linehan, A.N. Other, Robert G. Presson, Stephen J. Lai-Fook, Robert L. Johnson, Jr., Robert Capen, Leonard Latham, John Butler, Lorna Moore, Gregory J. Redding, Ewald R. Weibel, Y. C. Fung, Walker Long, Keith Horsfield, John H. Newman, Thomas Jacobs.

Figure 7: Grover attendees 2011. Taken in front of the ranch house where science and life are discussed.

established scientists. It has also been an inspiration for new scientists. It holds the memories of friends departed and the promise of new friends and colleagues, as evident in the 2011 photograph (Fig. 7).

There are between 33 and 43 speakers and chairs, with a total of up to 90 participants at each meeting. The fact that the conference site is isolated encourages everyone to be present throughout the four days of the meeting. Almost all of the conferences have received grant support from the National Heart, Lung and Blood Institute (NHLBI), and most have been supported by the Cardiopulmonary and Critical Care Council of the American Heart Association, the American Thoracic Society and the Pulmonary Circulation Foundation. Additional funding has been received from many pharmaceutical, instrumentation and publishing companies. The process of selecting a subject for the next meeting initially rested with Drs. Weir, Wagner, McMurtry, Voelkel and Reeves. The stewardship for the meeting passed to the Leadership Committee of the Pulmonary Circulation Assembly of the American Thoracic Society in 2005. This logistic formula has provided a cost-effective method of achieving vigorous discussion of topical issues, from basic science, through translational studies, to current clinical treatment. The publications that contain the proceedings of the Grover meetings (Table 1) are a unique record of progress in pulmonary vascular research.

The legacy of the Grover meeting continues to be written but the chapters recorded to date are rich with the best traditions of science. Lectures honor figures who have been key to the spirit of the meeting, including the Estelle Grover Lecture, The John T. Reeves Lecture and the Terry Wagner Lecture. As each new generation of scientists picks up the torch, the stories of conferences past are shared. At the Lost Valley Ranch, curiosity, mentorship and camaraderie fuel the pursuit of better understanding of the pulmonary circulation, pulmonary hypertension and oxygen sensing. It seems that lofty goals are best pursued at high altitude.

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Source of Support: None declared, **Conflict of Interest:** None declared.