Profiles in Pulmonary Hypertension

John Newman, MD, Tracks Pathogenesis of PH, From Exercise-Related Factors to Emerging Evidence on the Role of the Metabolic Syndrome



Considering how far research has brought the state-of-the-art treatment for pulmonary hypertension (PH), and how much current therapies have worked their way into daily clinical practice, one tends to forget how many clinicians were mystified by the disease at the beginning of their careers when no treatments were available. John Newman, MD, is one of those physicians, and he recalls vividly

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what it was like when he was an intern at the Columbia-Presbyterian Medical Center in New York City.

A young woman, still in her 20s, had come into the hospital with PH at a time when "no one had any understanding of the disease," he recalled. Dr Newman and others on the staff felt frustrated when the woman died soon after her admission to the hospital, an experience that hit him hard "emotionally and intellectually." Some of the early work on the pulmonary circulation had been done at Columbia-Presbyterian, and Dr Newman took that knowledge to the University of Colorado Medical Center in Denver where his mentors were Dr Robert Grover and Dr Jack Reeves, 2 legendary figures in PH research.

"They were doing the best work in the country on how hypoxia causes PH and I ended up working in their lab for 2 years, evaluating hypoxia and vasoconstriction and how the lung responds to low oxygen levels. A young researcher thus gets into a fraternity of clinicians, which was what happened to me as a Fellow. Grover and Reeves were pioneers in the study of high altitude PH." Another great researcher, Ivan McMurtry served as his lab mentor for 2 years before Dr Newman moved on to Vanderbilt where he has formed a long-lasting research partnership with Jim Loyd, MD.

For nearly 30 years, Dr Newman has moved into numerous areas of pulmonary circulation research, including the genetic basis of PH, an interest that started in 1980 when he and Dr Loyd encountered their first cases of familial PH and continues today. The author of over a hundred articles in scientific publications and numerous books, book chapters, and review papers, Dr Newman continues to be an investigator on many trials that examine such issues as gene-to-gene interactions in PH, the role of phosphodiesterase type 5 (PDE5) as a modulator in right ventricular (RV) failure, and gender and endothelin determinants of RV function in PH.

The research interests have also ranged to various aspects of lung inflammation, work on oxygen toxicity, sepsis damage to the lung, and the effect of exercise on PH. "We have been especially interested in how the lung stays dry during exercise. Since there is so much flow and pressure in the lung during exercise, we tried to determine how the lung does not get into pulmonary edema."

More recently, Dr Newman has helped coordinate a registry supported by a \$25 million award that was set aside as a result of the phen-fen class action suit. As Chair of the foundation overseeing the registry, Dr Newman said, "We set up a unique study to harvest lungs from patients who are undergoing lung transplantation. We are preserving cells, tissue, DNA, and serum, and we are conducting histology studies, sending the material to a variety of scientific centers around the country. The problem has been that no single transplant center performs enough transplants to obtain a high volume for scientific research so we decided to set up a national consortium of transplant centers. It has been going on for 3 years and is just beginning to flourish. We have high hopes that a lot of important information will come out of this."

The recently established Pulmonary Vascular Research Institute, a loosely affiliated international group of investigators and practicing clinicians, is also benefiting from Dr Newman's input and guidance. "We are trying to promote education and management and encourage people internationally to interact as part of an effort to push the field of PH research forward."

One of the most understudied areas, according to Dr Newman, remains the genetic and environmental pathogenesis of PH. Recognizing that women are 3 times more likely than men to develop PH and that the familial form of PH is 3 times more likely to appear in women, Dr Newman and his colleagues Dr Anna Hemnes and Eric Austing are considering the hypothesis that testosterone may offer a protective effect. "We do not know why estrogens may work in this regard. We do know that there is a promoter for the *BMPR2* gene that has an estrogen response feature. There may be some effect that makes *BMPR2* work in the wrong way."

Future directions for Dr Newman are also exciting, particularly work with Dr Ivan Robbins on the association between the metabolic syndrome, a constellation of cardiovascular risk factors frequently seen in diabetic patients, and PH. "We know that the metabolic syndrome damages systemic vessels. We are hypothesizing that the metabolic syndrome damages pulmonary artery vessels as well." Still in its early stages, this work at Vanderbilt will focus on whether insulin resistance could be a factor in the pathogenesis of PH. He notes that a group at Stanford University has verified that insulin resistance occurs in PH. "We are looking at a special group of patients who appear in our clinic with the full-blown metabolic syndrome. Since we know that they already have insulin abnormalities we are trying to figure out how that translates into inflammation of the pulmonary system."