Editor's Memo

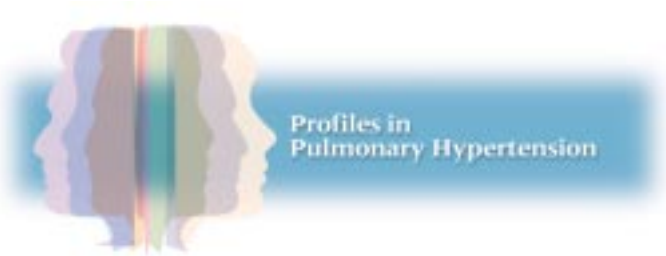
Predicting Future Directions in Pulmonary Hypertension

The future of the diagnosis and treatment of pulmonary arterial hypertension (PAH) is uncertain, but it is much more promising than it was a decade ago. Intravenous prostacyclin has changed the course of this disease, and now one oral agent is approved for use and clearly has an impact on PAH.

Our experts took aim in this issue at what may come to be—in terms of understanding the pathobiology, possible advances in therapy, and new thinking on end points. So much of the effort driving new approaches to therapy stems from the hope that a yet-to-be discovered agent could unlock the secret of reversing the disease process, addressing the core issue of cell proliferation. How convenient it would be if we could identify switches that might be turned off, thereby directing the vasculature to reverse proliferation as we solve the riddle of restoring vessel architecture and lung function. These topics and much more are addressed in the Roundtable discussion.

I wish to thank two esteemed colleagues who served as guest editors, Sean Gaine, MD, and Richard N. Channick, MD, not only for organizing the Roundtable but for recruiting the experts who contributed their articles as well. Many of the advances foreseen by our experts are still theoretical, yet some are tantalizingly imminent. We need translational research to turn them into clinical applications. Although work is progressing swiftly to find a cure for PAH, this issue of *Advances in Pulmonary Hypertension* seeks to "freeze" the moving target, at least for the moment, or for as long as is required to read these pages. After that, the elusive target will move on, as will our relentless effort to find and hit it.

Victor F. Tapson, MD
Editor-in-Chief



In the Pantheon of PH Research, Tim Higenbottam Sets the Pace

Tim Higenbottam, MD

He vividly remembers the first patient—a woman about 30 years old with primary pulmonary hypertension (PH) and unstable angina, "very blue," and hardly any measurable cardiac output. She was among the patients seen in the early 1980s at a Cambridge, United Kingdom, hospital who were dying, the focus of frenetic activity by Tim Higenbottam, MD, FRCP, and his colleagues in a lung transplantation program.

Unable to find a donor soon enough, they turned to prostacyclin, an investigational drug at that time for peripheral vascular disease. The woman consented to its being used experimentally over the long term for her primary PH, and soon after its initiation she showed dramatic improvement. Dr Higenbottam and a colleague devised an infusion pump through a subclavian line to continue the delivery of prostacyclin and they monitored her progress for the next 13 months. At that point they decided other patients with primary PH deserved a similar trial of prostacyclin, and this pioneering experience with the drug is among the major achievements establishing Dr Higenbottam as one of the giants among researchers into the disease. After more than 2 years the woman chose to receive a lung transplant, but the remarkable turnaround with prostacyclin had set the stage for the worldwide use of the drug in subsequent trials in the United States.

Building up a cohort of patients and generously supported by the Wellcome Company, Dr Higenbottam expanded on their observational work that paved the way for the larger randomized controlled trials of prostacyclin. In a career that has spanned the introduction of lung transplantation medicine, Dr Higenbottam has exerted a profound influence on colleagues worldwide. Among his achievements:

- Discovery of the benefits of inhaled nitric oxide in PH.
- Introduction of the 6-minute walking test as a noninvasive technique to assess improvement in PH.
- Authorship of the International Guidelines for Lung Transplantation and for PH.
- Introduction of transbronchial lung biopsy for diagnosing lung rejection.
- Development of inhaler devices and the application of mathematical modeling and simulation of breathing to optimize inhaled drug delivery.

Currently Senior Principal Scientist and Associate Director of Global Clinical Science at Astra Zeneca R&D in the United Kingdom, Dr Higenbottam described how his initial studies of prostacyclin led to further approaches of using the drug. "We used prostacyclin to protect the lung in the donor when the donor had died and was going to undergo an operation to obtain the graft. That process has enabled us to go from doing the operation on the donor and recipient in the same hospital to actually extending the ischemic time to about 2.5 hours."

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Profiles

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The discovery of the efficacy of nitric oxide was based on Dr Higenbottam's work in physiology. "We were using inhaled nitric oxide to measure the lung diffusion capacity alongside carbon monoxide. We had PH patients inhale the same concentrations that we had used for the gas diffusion studies and we were able to show that nitric oxide is a selective pulmonary vasodilator. We then developed a device for use in ambulatory patients because prior to that they could not use it except through a ventilator. The new technique involved a pulsing device delivering nitric oxide every time they breathed."

In his new role at Astra Zeneca, Dr Higenbottam remains on the frontier of new approaches to lung disease. "My job is to apply some of these thoughts on disease and make the final link between the molecule and affecting the disease process itself." In PH, "the major problem is how to restore function to the chronically damaged lung, enhancing the reparative process. This will lead us to the next generation of treatments—looking at growth factors and various signaling systems that work not only in the exogenous stem cells but on endogenous stem cells in the organ. Growth and repair are the main issues in chronic lung disease. The current generation of treatments is beneficial in terms of the horrendous pathophysiology. The treatments are improving the circulation of the blood through the lung, but we need to move beyond that. We need to ask, how we can restore some compromised vessels back to normal."

The introduction of bosentan has been a major advance. "It has profound effects, and the approach of endothelin-1 antagonism is a very strong one, clearly addressing a persistent abnormality present in all forms of PH. Bosentan in this regard is probably the best, because it is oral, but it's in the same category as other agents—it's just better.

"We need to think in terms of real function, not just vessels where there's a narrowing as a result of a particular deficiency, but actually restoring the structure and architecture of the vessels to normal. I believe that in the next 5 to 10 years we will have that therapy. The key will be restoring the blood vessel and airway back to normal."