Editor's Memo

The Prostacyclin Story: From Discovery to Future Directions

Until recent years, the concept of treating pulmonary arterial hypertension through a variety of mediators and mechanisms seemed beyond our grasp. As much as it is routinely done in other illnesses, the possibility of applying this concept in pulmonary hypertension was remote. This picture has radically changed, however, with the introduction of new agents that may be used in conjunction with prostacyclin and its analogs. The revolution in therapy started with the man profiled in this issue, Sir John Vane, a Nobel Prize winner recognized for his work in prostaglandin research.

Perhaps the theme of this issue should be that the revolution continues. After paying a debt of gratitude to Dr Vane, our story about prostacyclin continues throughout this issue. We explore the need to develop prostacyclin analogs to overcome the limitations of the epoprostenol delivery system, elaborate on the intriguing work with inhaled iloprost, and round it up with a roundtable discussion ranging across the spectrum of issues involving prostacyclin. We are also grateful to Bruce Brundage, MD, president of the Pulmonary Hypertension Association, who provided the images for this issue's cover.

Slowly, but with encouraging progress, we are getting to the point where we will better understand how to treat pulmonary arterial hypertension through a variety of mediators and mechanisms. There is still much to be discovered about prostacyclin—for example, how precisely does the medication work? When we discover its true mechanisms and determine how it can be used in combination with other treatments, perhaps the revolution in therapy will have achieved its goals.

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Editor-in-Chief

Profiles in Pulmonary Hypertension

A Nobel Prize Winner Who Triggered a Revolution in Therapy

Winner of the Nobel Prize in medicine. The researcher who discovered prostacyclin, the most widely prescribed drug in pulmonary hypertension. The pioneer who uncovered the mode of action of aspirin. Knighted in 1984 for his contributions to medical research. These achievements of Sir John Vane and the accolades received for them tend to dwarf those of even the most highly respected investigators in pulmonary hypertension.

It's been 20 years since Dr Vane shared the Nobel Prize for his studies of prostaglandins, and his discovery of one of them, prostacyclin, eventually ushered in a new era in the treatment of pulmonary hypertension. Ironically, the initial research involving the drug took a different direction.

"The first clinical trials on prostacyclin were not in pulmonary hypertension. They were in peripheral vascular disease," recalled Dr Vane during a recent interview from his office in the United Kingdom. Dr Vane was cited by the Nobel committee for his "discovery of the prostaglandin known as prostacyclin in 1976, and for analyzing its biological effects and function." Yet it was years before the drug epoprostenol (Flolan) was first used in pulmonary hypertension after Timothy Higenbottam, MD, documented its efficacy in the disease in 1987. Initially, however, Polish researchers who spent time with Dr Vane in his UK laboratory took a different track with prostacyclin when they returned to Poland.

"They reported striking and prolonged benefits following intra-arterial infusion of prostacyclin in five patients with advanced atherosclerotic lower-limb peripheral vascular disease. Rest pain disappeared, previously refractory ulcers healed, and muscle blood flow as measured by $Xenon^{133}$ clearance was significantly increased for at least 6 weeks after prostacyclin infusion. They later reported striking improvements in some of 55 patients with advanced peripheral artery disease of the lower extremities."

With the benefits also observed in pulmonary hypertension and Dr Vane later serving as Group Research and Development Director of the Wellcome Foundation, the path was cleared for the introduction of Flolan. Since the introduction of the drug, longer lasting analogs have been introduced, but no one has produced a compound with a half-life of more than 2 hours and this remains a barrier still to be overcome with the use of such agents.

Addressing this problem, Dr Vane said, "the answer must be that the prostacyclin molecule is unstable, and no matter what you do to it to try to add stability, you can't add all that much. Since the analogs have to be based on the original structure of prostaglandin, they are going to have relatively short half-lives."

Dr Vane's research on other medications are also milestones in the development of more effective treatment for a wide range of disorders. These include his discovery of

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