Identification of mutations in the bone morphogenetic protein receptor-2 (BMPR2) in the majority of cases of familial pulmonary arterial hypertension (FPAH) has been a major advance in the elucidation of the pathogenic sequence in pulmonary arterial hypertension (PAH) (1,2). However, fewer than 20% of individuals with a BMPR2 mutation develop FPAH, and most individuals who develop PAH do not have an identifiable mutation (3); accordingly, it is likely that other factors, including genes and environmental stimuli, are needed to initiate the pathological sequence that leads to vascular injury and the pulmonary hypertensive state. Both the role of these other factors in initiating the vasculopathic process and the mechanisms through which they interface with genetic abnormalities are unknown (4).

Various cellular pathway abnormalities have been described that may play important roles in the development and progression of PAH (5–9). These include altered synthesis of nitric oxide, prostacyclin and endothelin, impaired potassium channel and growth factor receptor function, altered serotonin transporter regulation, increased oxidant stress, and enhanced matrix production. However, the relative importance of each of these processes is unknown, and the interactions between these various pathways should be explored. Additionally, the intermediate steps involved in the transduction of signals related to BMPR2 are unknown; clarification of these pathways will lead to a more complete understanding of how impaired BMPR2 signaling leads to hypertensive pulmonary vascular disease (10,11).

**THERAPY OF PAH**

Less than a decade ago, the treatment of PAH was based on a limited understanding of the disease pathogenesis and was largely empiric and usually ineffective. The treatment of PAH has advanced dramatically since then, with a number of well-designed clinical trials demonstrating efficacy of several therapies that target specific abnormalities present in PAH (12–15). Furthermore, the complexity of these treatments has evolved from continuous intravenous (IV) delivery to oral and inhaled modes of drug delivery. Despite these successes, the response to therapy of PAH is not universal and is often incomplete. Future studies targeting newly identified alterations in endothelial and smooth muscle cell function, including phosphodiesterase-5 (PDE5) and angiotensin activity, vasoactive intestinal peptide synthesis and activity (16), and the serotonin pathway (9,17) may provide novel treatments.

Drugs currently marketed to treat other conditions may have effects that are beneficial in PAH as well. For example, the hydroxymethylglutaryl-coenzyme-A reductase inhibitors manifest pleiotropic effects that have been suggested to be responsible for a component of their benefit in atherosclerotic disease (18), and these agents attenuate the pulmonary arteriopathy induced by the administration of monocrotaline to experimental animals (19,20). Formal clinical studies with the statins may, therefore, be appropriate. Similarly, currently available platelet inhibitors (i.e., aspirin) and newer antithrombotic agents may have a role in the treatment of PAH, in light of the beneficial effects (and inherent risks) of anticoagulation with warfarin in idiopathic PAH.

As with other diseases with a complex pathogenesis, targeting a single pathway in PAH is unlikely to be uniformly successful. With the development of several pathway-specific therapies, the opportunity exists for evaluating multidrug therapy in PAH: for example, studies combining an endothelin receptor antagonist with a prostanoid or a PDE5 inhibitor may lead to either a more aggressive first-line treatment strategy combining several drugs, or to a strategy of layered therapy for disease progression, or both.

**MEASURING OUTCOMES AND MONITORING THE COURSE OF THERAPY**

The development of treatments for PAH has prompted the challenge of how to best assess and monitor the efficacy of long-term therapy. Because it is believed that randomized, placebo-controlled trials using survival as an end point would be unethical to perform in PAH, alternative strategies are required to measure and compare the relative effects...
of the available treatments. Similarly, noninvasive markers of disease severity, either biomarkers or physiological tests, are needed that can be widely applied to reliably monitor clinical course. Studies that assess the value of these outcome measures, alone or in combination, will enable physicians to time and select therapy in a more structured fashion.

Conclusions. Although major advances in our understanding of the mechanism of disease development and in the treatment of PAH have been achieved over the past decade, substantial gaps in our knowledge remain. Bringing together physicians and scientists representing multiple disciplines and expertise, all sharing an interest in PAH, afforded the opportunity to explore areas of mutual interest and collaboration that will, it is hoped, narrow these gaps of knowledge in the future. Ultimately, the success of the Third World Symposium on Pulmonary Arterial Hypertension will be best measured by the progress achieved in understanding and treating PAH over the next few years.

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