Primary pulmonary hypertension (PPH) is a rare condition characterized by neointimal vascular occlusion of small pulmonary arteries that leads to circulatory failure and death (1–3). Severe pulmonary arterial hypertension with identical pathologic obliteration of the pulmonary vasculature is also seen in patients with familial pulmonary hypertension, human immunodeficiency virus, liver cirrhosis, scleroderma syndrome, systemic lupus erythematosus, and in patients who take diet pills (1,4,5). At present there is no medical cure for pulmonary hypertension, and, untreated, the disease is progressive, with a median survival of three years after diagnosis (6).

Pathologic pulmonary hypertension is associated with excessive expression of vasoconstrictors such as endothelin and thromboxane (7) and with deficiency of vasodilators such as prostacyclin (2,8). The expression of endothelial nitric oxide synthase in patients with pulmonary hypertension was reported by one group to be decreased (9); other investigators reported no decrease or an increase (10–12). The imbalance of vasoconstrictors and vasodilators in pulmonary hypertension provided the rationale, over the past two decades, for therapies principally directed at augmenting pulmonary arterial vasodilation. Such agents include calcium channel blockers, prostacyclin and its analogs (intravenous epoprostenol (13), subcutaneous treprostinil (14), inhaled iloprost (15), oral beraprost (16), endothelin receptor antagonists (17), and phosphodiesterase inhibitors (sildenafil) (18). Approximately 15% of patients identified as those with an early vasodilator response have a significant long-term therapeutic response to calcium channel blocking agents (19). The mainstay of treatment for most patients with advanced PPH who lack an early vasodilator response is long-term administration of prostacyclin (13). Because PPH is an aggressive disease with a poor short-term survival rate, many studies of new therapies in PPH involve treatment periods that are three months or shorter in duration (13–17).

Prostacyclin is a potent arterial vasodilator with anti-thrombotic and anti-proliferative effects (20). Prostacyclin is synthesized in endothelial cells and acts through G-protein-coupled prostacyclin receptors on the surface of vascular smooth muscle cells to elevate intracellular cyclic adenosine monophosphate and produce vascular relaxation. Prostacyclin and its analogs suppress proliferation of vascular smooth muscle cells in vitro, with treprostinil (UT-15) demonstrating 10-fold greater potency than beraprost (21). Continuous administration of intravenous prostacyclin (epoprostenol) has been associated with improved survival, exercise tolerance, and heart failure class (13,22–26). Most patients initiated on epoprostenol infusion do not demonstrate an early vasodilator response, yet achieve clinical benefits after several months of continuous infusion. These benefits are thought to arise from anti-proliferative effects and beneficial pulmonary vascular remodeling in response to epoprostenol. Although some benefits of epoprostenol treatment accrue over time, sustained reversal of established disease has been difficult to demonstrate. Sitbon et al. (24) showed, in 107 patients treated with epoprostenol infusion, that the major improvement in hemodynamics was achieved in the first three months, without further improvement detected at 12 months. Continuous intravenous administration of epoprostenol through an indwelling central venous catheter carries a risk of bacteremia (13,25), and the therapy is inconvenient for patient use. An oral medication that is effective therapy for PPH would represent a significant advance.

Contributions of the current article. In this issue of the Journal, Barst et al. (27) present data on the effects of the oral prostacyclin analog beraprost sodium in patients with PPH. This study, performed over 12 months, represents the longest controlled clinical trial performed in PPH. Beraprost therapy was administered in escalating doses and, compared with placebo, was associated with benefits. Beraprost produced a significant improvement over placebo in the primary outcome measure (disease progression) only at the six-month time point. The secondary outcome measure was exercise endurance, and compared with placebo, beraprost significantly improved the 6-min walk distance at 3 and 6 months; however, there was no statistical difference at 9 or 12 months. The results suggest that studies that are longer than three months might be useful in assessing the efficacy of new therapies for pulmonary hypertension, because benefits that are apparent at three months might not be apparent with longer duration of therapy. The result is important because several therapies have been accepted into common practice based on their effects on exercise tolerance over periods of three months or less (14–17).

There are several possible explanations why benefits were demonstrable at 3 and 6 months but not at 9 and 12 months. First, this discrepancy could be attributed to a type 2 error (failing to reject the null hypothesis when it is false), in which the study design (in particular, the population size and heterogeneity) fails to demonstrate a statistically signifi-
significant difference when a true difference does exist (28). Factors that influence whether a statistically significant difference between therapies is reached include the number of subjects in each treatment group (in this study, a smaller number reached 12 months due to premature discontinuation of the study by the sponsor), the variability in the outcome measure (in general, biologic measures are less reproducible over time) (29), and the magnitude of the treatment effect related to the standard deviation of each group (30). The notion that a difference between beraprost and placebo exists but did not reach statistical significance at both nine and 12 months is supported by the trend in this study toward improvement in 6-min walk distance that was still evident at both nine and 12 months but did not reach statistical significance.

The possibility also remains that beraprost is no different from placebo after nine months of therapy. There are at least two distinct (but not mutually exclusive) biologic explanations for such a result. First, there might be a loss of drug efficacy due to altered natural history of disease. Newly diagnosed subjects might respond well to therapy, but subjects with more severe or a longer duration of disease may not. This concept is supported by the survival advantage of subjects with New York Heart Association (NYHA) class I and II severity of disease, compared with subjects with NYHA class III and IV disease, particularly when treated with intravenous epoprostenol (22). The second possible explanation is drug tolerance (in which repeated administration of a drug after a period of time leads to a decrease in its effectiveness) or a failure to increase the drug dosage to reach therapeutic efficacy. The latter may be an important possibility in this study because patients who take intravenous prostacyclin generally increase the administered dosage to achieve therapeutic efficacy (25). The question remains whether therapies that have a proven benefit after three months and are currently widely prescribed should be re-evaluated for efficacy during long-term (>6 months) administration. Currently, little is known about the long-term effects of endothelin antagonists, subcutaneous prostacyclin analogs, or sildenafil on exercise tolerance or survival.

**Genetic insights and the potential role for anti-proliferative therapies in PPH.** The recognition of familial PPH, with clinical presentation and pathology identical to sporadic PPH, and autosomal dominant inheritance, led to the breakthrough identification of a genetic basis for hypertensive pulmonary vascular disease (31–33). Mutations in the coding region of the bone morphogenetic protein receptor type II (BMPR2) occur in 50% of patients with familial PPH and 26% of patients with sporadic PPH. Bone morphogenetic proteins and their receptors are important for development and regulation of the cardiovascular system. The BMPR2 gene encodes a transmembrane receptor with protein kinase activity, which is a member of the transforming growth factor receptor superfamily. The BMPR2 protein serves to transmit anti-proliferative signals to vascular endothelial and smooth muscle cells. Mutations in one allele of BMPR2, causing haploinsufficiency and defective anti-proliferative signaling, appear to predispose individuals to development of pulmonary vascular disease (34). Atkinson et al. (35) demonstrated a reduced expression of BMPR2 protein in pulmonary vessels of patients with PPH, even in those PPH patients with no detectable mutation in BMPR2 coding sequences. Together, these results strongly support a role for the BMPR2 signaling pathway and abnormal regulation of vascular proliferation in the development of PPH and other pulmonary vascular diseases, such as pulmonary veno-occlusive disease (36). Newman et al. (34) analyzed a large kindred and determined that PPH developed only in 15% of individuals who carry a mutation in BMPR2, implicating other factors, likely environmental, immune, or hormonal factors, as necessary for development of PPH (37).

The new insight that significant numbers of PPH patients carry a genetic predisposition to vascular proliferation correlates with morphologic characterizations demonstrating inappropriate neointimal proliferation of vascular smooth muscle cells within small pulmonary arteries in this disease (4) and exuberant expansions of endothelial cells in plexiform lesions (38). Recent work by Launay et al. (39) demonstrates potentiation of hypoxia-induced vascular proliferation in mice that receive desfenfluramine. These effects appear to be mediated through 5-HT2B receptors because both genetic and pharmacologic inhibition of this receptor inhibits this response in mice. Humbert et al. (40) recently demonstrated a significant increase in the incidence of BMPR2 mutations in patients who developed PPH after exposure to fenfluramine. More precise characterization of pleiotropic factors that can induce inappropriate vascular proliferative responses to injury may eventually lead to effective anti-proliferative therapies for prevention and treatment of PPH. To this end, experimental models of PPH have been established in which rats develop neointimal vascular occlusion, pulmonary arterial hypertension, right ventricular hypertrophy, and death (41). The development of disease in this model mimics both the pathophysiology and pathology of human disease, and furthermore, the pulmonary hypertension can be attenuated by anti-proliferative or pro-apoptotic compounds, such as rapamycin (42) and simvastatin (43). The exciting implication is that anti-proliferative compounds, rather than vasodilators, may provide the new wave of therapies for patients with PPH (44) and prevention of PPH in susceptible individuals (45).

The current 12-month study of oral beraprost by Barst et al. (27) demonstrates the challenge and importance of performing clinical trials in PPH. Beraprost improved exercise performance at three and six months but not at nine and 12 months. Beraprost is likely to be producing its modest effects through vasodilation rather than through substantial anti-proliferative properties (21). This current study provides important data on the natural history of...
PPH, both treated and untreated. The data reveal that, in the absence of therapies directed at reversing the pathologic process of pulmonary vascular occlusion, pulmonary hypertension remains a progressive disease.

The recognition that vascular obliteration in PPH is associated with genetic abnormalities in anti-proliferative signaling suggests the importance of evaluating new therapies directed at preventing pathological vascular proliferation in vivo. Future clinical trials in PPH should be designed to identify those agents or combinations of agents that will provide sustained efficacy combined with safety. Such therapies will inhibit and reverse vascular occlusion and pulmonary hypertension and extend survival. We should not be complacent with therapies that provide short-term benefit; rather, we should use these data as further impetus not only to study the pathogenesis of PPH but also to search for a cure.

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