over time. These newer tools may also enhance predictive accuracy when used in combination with the "standard" testing modalities. Many of these variables have been shown to correlate with one another; thus, which parameters will prove to be the most useful in assessing disease severity requires further investigation. Importantly, all of the above studies evaluated idiopathic PAH patients but not patients with PAH related to connective tissue disease, congenital heart disease, anorexigens, HIV infection, or portal hypertension. Thus, these parameters must be applied cautiously to PAH patients in whom comorbid factors may contribute significantly to overall outcome, eg, in general, patients with PAH related to connective tissue disease have a worse prognosis than idiopathic PAH patients, whereas patients with PAH related to congenital heart disease have a much more slowly progressive course than do patients with idiopathic PAH.

In conclusion, PAH is diagnosed by following a careful series of investigations that include tests that are regarded as essential in making the diagnosis, as well as additional tests that may help clarify the category of pulmonary hypertension present. Disease severity can be evaluated by several modalities that are complementary and that together are useful in helping to choose therapy and evaluate the response to therapy. Close follow-up at a center specializing in pulmonary hypertension is recommended, with careful monitoring at frequent intervals of the course of the disease. ■

Overview of Genetics as presented at the PAH Symposium in Venice

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Medical scientists have achieved three major goals proposed by the 1998 Evian task force on the genetics of pulmonary hypertension. First, mutations in the gene that codes for bone morphogenetic protein receptor 2 (BMPR2) are linked to familial primary pulmonary hypertension. BMPR2 mutations are detectable in approximately half of the families affected by primary pulmonary hypertension. The gene that codes for BMPR2 is large (13 exons) and already more than 26 mutations are described. Second, many patients with apparently sporadic primary pulmonary hypertension have mutations of the gene that codes for BMPR2. This observation, combined with observations of common ancestors among patients with apparently sporadic primary pulmonary hypertension, indicates that an inherited basis underlies many cases of primary pulmonary hypertension. However, the relatively low penetrance of these mutations (only 15% to 20% of persons carrying a BMPR2 mutation develop clinically evident disease in their lifetime) makes identification of familial disease difficult. Third, BMPR2 mutations are rare in other classifications of pulmonary arterial hypertension, eg, pulmonary arterial hypertension associated with CREST, HIV infection, or fenfluramine exposure. Rare cases of pulmonary arterial hypertension with BMPR2 mutations and fenfluramine exposure raise the possibility of disease triggered by genetic predisposition and an environmental trigger.

The exact pathogenesis of familial primary pulmonary hypertension remains elusive in spite of the identification of BMPR2 mutations. The identification of abnormalities in other TGF beta receptors [ALK-1; TGF beta R2, and BMPR1A (ALK3)] suggests that dysfunctional TGF beta receptors are important in the pathogenesis of familial primary pulmonary hypertension. Indeed, TGFB represents a classic pleiotropic mediator to the vascular system by modifying growth, differentiation, and death of vascular cells. Nevertheless, other genes and/or environmental factors must also be important in order to explain the reduced penetrance of BMPR2 mutations. Genes that control nitric oxide synthesis, serotonin transport, or prostacyclin may prove important to the expression of disease. Animal models (eg, mice) allow study of genetic alterations of BMPR2 as well as other pathways, eg, serotonin. Inactivation of BMPR2 in mice leads to pre- and perinatal mortality because of abnormal mesoderm formation, illustrating the potential of BMPR2 mutations to cause vascular disease. To date, scientists have not been able to reproduce primary pulmonary hypertension in mouse models, but this remains an important goal for future research.

The discovery of mutations in the gene that codes for BMPR2 makes genetic testing and counseling possible. In the future such tests may corroborate diagnostic impressions and provide estimates of an individual's risk to develop primary pulmonary hypertension. The use of such tests requires an understanding of the meaning of the test results, as well as the risks and benefits of this knowledge to those who are tested and to other family members. Before and after the tests, education and counseling will be necessary, especially because the penetrance of known BMRP2 mutations is low and because the results may prove psychologically (eg, depression, anxiety) or socially (eg, employment barriers and effects on insurability) harmful.

For these reasons genetic testing for BMPR2 mutations will require adherence to basic rules. Informed consent is essential when a test can be linked to an individual. The consent should be voluntary, without coercion or intimidation; and patients should be assured that their care is unaffected by decisions to forego genetic tests. In addition confidentiality of results must be assured.

Genetic tests for mutations associated with primary pulmonary hypertension are not available in the United States. The BMPR2 gene is large, making tests expensive unless the test is directed at a known mutation. For these reasons the task force concluded that genetic testing needs development and is not ready for widespread implementation. ■