NIH Conference Charts Future Directions in Identifying Patients at Risk for Primary Pulmonary Hypertension

This report is based on information presented at a conference sponsored by the National Institutes of Health (NIH) earlier this year to identify trends in diagnosis and management of the disease.

As diagnostic and treatment approaches to pulmonary hypertension evolve over the next few years, clinicians may look back at an NIH conference held earlier this year as a watershed, a meeting where many of the new directions in care were charted.

The meeting, ***Translational Research in Primary Pulmonary Hypertension,*** was sponsored by the National Heart, Lung and Blood Institute and brought together leading experts to explore ways in which basic research may translate into clinical trials and related investigative work. Organized by Dorothy B. Gail, PhD, Director of Lung Biology and Disease in the Division of Lung Diseases at the NIH, the meeting provided a venue for reviewing new data and concepts, including recent findings in genetics and molecular medicine, as investigators discussed results from studies in transgenic mice and data about modulators for angiogenesis. One of the goals of the meeting was to provide the NIH with information on the kinds of research it may want to encourage, according to John H. Newman, MD, Professor of Medicine, Pulmonary Critical Care Division, Vanderbilt University School of Medicine, Nashville, Tennessee. The talks ranged across a broad spectrum of topics but generally relate to implications for the pathogenesis and treatment of primary pulmonary hypertension.

One of the areas covered involved potassium and calcium channel function, as delineated by Steven L. Archer, MD. "Information from various studies suggests that an alteration in channel function may be involved with determining whether potassium or calcium can enter or exit cells and whether they will contract. This issue is especially important for smooth muscle cells in the vascular bed, because if they contract, they cause vasoconstriction and raise pulmonary vascular resistance, and can exacerbate pulmonary hypertension," said Dr Newman.

The second group of talks was concerned with signal transduction, which is related to the manner in which circulating molecules activate cells. Serotonin was a chief consideration in this discussion, because it is a mediator that enters cells through a transporter, and once in cells, it activates certain pathways that may lead to new growth of vascular cells and production of collagen. This process may promote occlusion of vessels as seen in pulmonary hypertension. This is important because it is known that blood vessels in the lung become occluded through a process in which fibrosis results in blockage of the central channel.

One of the exciting areas covered at the conference included work being done on transgenic models of pulmonary hypertension. Mutations in the BMPR-2 gene are a hereditary cause primary familial hypertension. William C. Nichols, PhD, and David Rodman, MD, have used transgenic mice with this gene altered so that we have an animal model that can mimic situations of primary pulmonary hypertension. They presented information on these models and what directions research will take with these animal models. "The hope is that over the next couple of years we will be able to further characterize animal models of pulmonary hypertension, which will lead to a better understanding of how to treat the disease. Currently the transgenic model is still too early in development to have produced any striking leads, but our expectations are high," said Dr Newman

The discussion of genetic factors involved in pulmonary hypertension continued with presentations on genetic modifiers by Jane Morse, MD, and James A. Knowles, MD, PhD, who focused on the concept of genetic susceptibility to primary pulmonary hypertension. "We know from patients who are in families where the disease is highly prevalent that there is a mutation in a receptor, called BMPR-2," said Dr Newman. "Even if a person has a mutation, there is only about a 20% risk of getting the disease in his or her lifetime, so there must be other factors that increase the risk—either other mutations or just other genetic characteristics. For virtually every characteristic there are multiple genetic modifications, sometimes called polymorphisms. Nationally and internationally, the effort to identify the genetic makeup that may predispose to pulmonary hypertension is growing stronger. It will turn into a big project over the next 5 to 10 years as we examine the genome to determine the kinds of differences that leave some patients at greater risk. For example, why did some people who took fenphen develop pulmonary hypertension? What are the underlying susceptibilities to that?"

Looking ahead to the most promising therapeutic strategies, presenters examined the relative merits of different approaches, particularly combinations of agents. "Everyone has been very excited about the advent of endothelin blockers and sildenafil," noted Dr Newman. "Now the question is, what kind of combinations should we use? Should we start oral drugs first and not use prostacyclin drugs until the oral therapy fails? Or will patients fare better if they undergo treatment with multiple drugs, such as we discovered with cancer therapy? In animal models, statins look very promising and they deserve clinical study because it is clear that they are useful in other vascular diseases. Sildenafil is also very exciting. In terms of feasible new approaches, the statins seem to be promising, but we are 2 to 3 years away from having specific drugs that may target other mechanisms such as serotonin or the mechanisms involving TGF-beta and potassium channels. These approaches are not quite ready but in the next 3 to 5 years we should have other new drugs with potential benefit."

Where does that leave prostacyclin, still considered the cornerstone of therapy? "Prostacylin remains the gold standard and is the agent we would all like to see another drug supercede. The goal is to get people off of prostacyclin as primary therapy, both for cost and for safety reasons. That's where we want to be headed."

One of the ultimate goals is to initiate treatment in patients predisposed to pulmonary hypertension as early as possible. "Familial pulmonary hypertension affords a unique opportunity to identify people who have a mutation and who could be candidates for preventive therapy," added Dr Newman. The problem in managing the "sporadic" patients is that preventive treatment cannot be used. This is because disease is already advanced when the diagnosis is made. This is why the identification of patients at risk for familial disease is so exciting. "The cases that we may be able to prevent are those persons who have a mutation but don't have any disease. They are clinically completely normal. If the statins seem to work, we could potentially design a study that might involve administering statins, plus several other drugs, to patients who have the mutation but are clinically normal to determine whether we could prevent pulmonary hypertension from developing."

Despite the promise of genetic testing suggested by the NIH conference, Dr Newman said it remains a long way from being routinely applied in clinical practice. "The problem is that in the general population, primary pulmonary hypertension is too rare to test the whole population. The cost is prohibitive. It would not be cost-effective if only one person in a million gets the disease. Genetic testing will be done in families where we know that mutations exist and potentially in patients who already have the disease but are the only affected person in a family. The current problem is that the gene is so large, with so many mutation sites, that no laboratory has been able to develop a feasible test. What will emerge from genetic testing and preventive therapy is a clearer understanding of what causes primary pulmonary hypertension and where we can successfully direct therapy. This will be a wonderful development." ■

A Who's Who from the NIH Conference on Primary Pulmonary Hypertension

A conference earlier this year sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health drew experts from around the country and Canada to discuss new directions in research. This conference, *Transactional Research in Primary Pulmonary Hypertension*, was chaired by John H. Newman, MD, Chief, Medical Service, VA Medical Center, and Professor at Vanderbilt University School of Mediine, Nashville, Tennessee.

The conference, held in Bethesda, Maryland, also included: Cochairman, Barry L. Fanburg, MD, Professor of Medicine, Department of Medicine, Pulmonary and Critical Care Division, New England Medical Center, Boston, Massachusetts.

Participants included:

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