PRIMARY PULMONARY HYPERTENSION

EXECUTIVE SUMMARY

FROM THE

World Symposium – Primary Pulmonary Hypertension 1998

Evian, France
September 6-10, 1998

go-sponored by

The World Health Organization

edited by Stuart Rich, MD
This document is a reprint of the "Primary Pulmonary Hypertension – Executive Summary" posted on the World Health Organization website. All or any part of this document may be reproduced. Proper citation is:


The designations employed and the presentation of the material in this publication do no imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization. Designated trademarks, logos, and brands are the property of the respective owners.

This document may be accessed in its entirety at:
http://www.who.int/ncd/cvd/pph.html
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>The Pathology of Pulmonary Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Pathobiology of Pulmonary Hypertension</td>
<td>6</td>
</tr>
<tr>
<td>Risk Factors and Associated Conditions for Pulmonary Hypertension</td>
<td>9</td>
</tr>
<tr>
<td>Genetics of Pulmonary Hypertension</td>
<td>11</td>
</tr>
<tr>
<td>Diagnosis and Assessment of Pulmonary Hypertension</td>
<td>13</td>
</tr>
<tr>
<td>Medical Therapy of Pulmonary Hypertension</td>
<td>18</td>
</tr>
<tr>
<td>Atrial Septostomy for Pulmonary Hypertension</td>
<td>22</td>
</tr>
<tr>
<td>Transplantation for Pulmonary Hypertension</td>
<td>24</td>
</tr>
<tr>
<td>Nomenclature and Classification of Pulmonary Hypertension</td>
<td>25</td>
</tr>
</tbody>
</table>
INTRODUCTION

Primary pulmonary hypertension is a rare condition, with an estimated prevalence of 1-2 per million people. Because the symptoms of PPH are nonspecific, and the physical findings can be subtle, the disease is often diagnosed in its later stages. The natural history of PPH is usually progressive and fatal.

In 1973, the World Health Organization sponsored an international meeting on primary pulmonary hypertension, spurred by the interest created by the sudden increase in patients with PPH who had used the anorexin, aminorex fumarate. At that vanguard meeting, international experts reviewed and discussed the pathology, pathophysiology, epidemiology, and clinical features of PPH. The meeting also focused on defining areas of future research with the goal of providing a better understanding of the cause and discovering effective treatments for PPH.

The past 25 years has witnessed remarkable progress in the field of pulmonary hypertension. The pathology is now better defined and intricate pathobiologic mechanisms are becoming unfolded that explain many of the enigmatic features of PPH. Risk factors have been identified, and the genetics are being characterized. Advances in technology allow a better diagnosis and assessment of the disease severity. Important therapies are now available that have been shown to improve quality of life and survival.

On the 25th anniversary of this first meeting, clinical scientists from around the world gathered again to review and discuss the features of PPH, as well as the field of pulmonary arterial hypertension. Ironically, a recent epidemic of PPH associated with a new class of anorexigen has again heightened world interest. Like before, the merging of a variety of disciplines provided an opportunity for discussion and debate, leading to a better understanding of the pathology, pathobiology, risk factors, genetics, diagnosis and treatment of the disease. New drugs, such as epoprostenol, and surgical therapies, such as heart-lung transplant that were unavailable 25 years ago, are having an important impact on the prognosis.

This executive summary highlights key features of PPH and represents a consensus of the participants who contributed to this working meeting. It provides insights into our current understanding of PPH, with specific recommendations for current practice and future directions for research.

SCIENTIFIC ORGANIZING COMMITTEE

Stuart Rich, MD - Chair ........................................Rush Medical College (Chicago, USA)
Lewis J. Rubin, MD – Co-Chair ................................University of Maryland (Baltimore, USA)
Lucien Abenhaim, MD ............................................McGill University (Montreal, Canada)
Robyn J. Barst, MD ..................................................Columbia University (New York, USA)
Bruce H. Brundage, MD ........................................UCLA School of Medicine (Los Angeles, USA)
Alfred P. Fishman, MD ...........................................University of Pennsylvania (Philadelphia, USA)
Prof. Sheila G. Hayworth .........................................University of London (London, UK)
Prof. Timothy Higenbottam ............................The University of Sheffield Medical School (Sheffield, UK)
David Langleben, MD ............................................McGill University (Montreal, Canada)
THE PATHOLOGY OF PULMONARY HYPERTENSION

VASCULAR ABNORMALITIES

The pathology of the pulmonary vascular bed in pulmonary hypertension remains central to our understanding of clinical observations and pathobiologic mechanisms. The cellular and molecular features of the pathology continue to influence the clinical appraisal of the disease.

ENDOTHELium

The endothelium presents a challenge to the pathologist because of the marked heterogeneity in the endothelium of the pulmonary vascular bed. In addition, the relationship between the phenotype and function of the endothelial cell is not fully understood. There may also be discordance between the patient age and the apparent cell age of the endothelium.

The characteristics of the disease and the vulnerability of different phenotypes to a variety of insults may determine the nature and severity of endothelial changes that are observed. This makes our understanding of how modulating the chemical and physical environment alters the endothelium quite important. Immunocytochemistry and in situ hybridization has shown that endothelial cells have increased levels of Factor VII antigen, the VEGF receptor, Kdr, endothelial nitric oxide synthase and endothelin-1. It is possible that these endothelial markers can be applied to diagnose early lesions.

It is not known at what stage during the evolution of PPH that endothelial cell proliferation occurs since it has not been consistently reported by all pathologists. Its presence, if confirmed, would suggest that a somatic mutation, rather than non-selective cell proliferation in response to injury, accounts for the growth advantage of endothelial cells in PPH.

SMOOTH MUSCLE CELLS

Heterogeneity exists in the smooth muscle cells and fibroblast populations. Like the endothelium, the relationships between phenotype and function need clarification. There needs to be emphasis on the synthesis of matrix components and the modulation of phenotype to degrade and synthesize specific components. Interconversion may occur between cell types (i.e., fibroblast to smooth muscle cell,
endothelium to smooth muscle cell), as well as the possibility of new vessel formation. With respect to the adventitial fibroblast, it manifests a peculiar response to physical stress in relation to matrix production. Finally, information from the study of normal vascular development and differentiation needs to be applied to the pathology of pulmonary hypertension.

In the large muscular and elastic arteries, smooth muscle cell hypertrophy and increased connective tissue and extracellular matrix is found. Dissolution of the elastic lamina is also a frequent finding. In the subendothelial or intimal layer, increased thickness may be the result of both recruitment and/or proliferation of smooth muscle-like cells. It is possible that precursor smooth muscle cells are in a continuous layer in the sub-endothelial layer along the entire pulmonary artery. These cells are similar to the pericytes that are responsible for the appearance of muscle in normally non-muscular arteries and that contribute to the intimal thickening in larger arteries.

The complexity of the remodeling in the media and adventitia is in part due to the presence of different smooth muscle cell types in several layers of the wall. Alterations in phenotype of the different layers of smooth muscle cells may contribute to the maintenance of PPH. The finding of a distinct smooth muscle cell type in the pulmonary artery needs further exploration. The phenotypes of smooth muscle cells are likely to have different functions and metabolic activity in each layer.

EXTRACELLULAR MATRIX
Alterations in the extracellular matrix secondary to proteolytic enzymes appear to contribute to the pathology in an important way. Matrix degrading enzymes can release mitogenically active growth factors that stimulate smooth muscle cell proliferation. In addition, elastase and matrix metalloproteinases can contribute to the up-regulation of the proliferation as well as the glycoprotein tenascin through a β3 integrin-mediated transcriptional control mechanism. This could explain robust cellular proliferation in the presence of excess deposition of a tenascin rich matrix. The degradation of elastin has also been shown to stimulate up-regulation of the glycoprotein fibronectin which stimulates smooth muscle cell migration.

THE PLEXIFORM LESION
The plexiform lesion remains a mystery. It is possible that it represents endothelial cells that are involved prominently in angiogenesis, perhaps akin to a neoplastic process. Morphologically they represent a mass of disorganized vessels with proliferating endothelial cells, smooth muscle cells, myofibroblasts and macrophages and arise from preexisting, presumably parent pulmonary arteries. Several studies have shown the involvement of growth factors that have been implicated in angiogenesis. Whether the plexiform lesion represents impaired proliferation or angiogenesis remains unclear.

PATHOLOGIC INTERPRETATION AND CLASSIFICATION OF PULMONARY HYPERTENSION
It is recommend that the previous pathological classification of pulmonary vascular disease be abandoned. It has been found to be too restrictive and the classes and grades do not correlate with the clinical and hemodynamic findings in a consistent prognostic fashion outside of congenital heart disease. Nor does the
graded classification system aid in clarifying the pathogenesis of the many causes of pulmonary vascular disease.

Rather than classifying the pathological abnormalities, we recommend the use of a new protocol designed to improve our understanding of the clinical picture, which is descriptive rather than prescriptive. We also encourage the application and interpretation of new histochemical and molecular biologic techniques. The pathologist is expected to interpret pathological findings in the light of the clinical and hemodynamic information, and to give guidance to the clinician by commenting on whether the findings are consistent with, or help explain, the clinical findings in light of our present understanding. The protocol should help ensure that the description of the findings be comprehensive, reproducible and be easy to follow by all pathologists.

The following structures should be examined and noted:

I. Vasculature

A. Vessels
   Elastic, pre- and intra-acinar arteries, microvessels, post-acinar and intra-acinar veins, capillaries, lymphatics, and bronchial vessels. The vessel lumen should be commented on with respect to thrombi (recent or old) and abnormal cellular and matrix components.

B. Components
   1. Endothelium/Intima
      (a) Cellular components (endothelial cells and smooth muscle cells)
      (b) Matrix (elastin, collagen, mucopolysaccarides)
   2. Media
      (a) Pattern (eccentric or concentric)
      (b) Cellular components (smooth muscle and/or other cells)
      (c) Matrix
   3. Adventitia
      (a) Cellular components (fibroblasts)
      (b) Matrix
   5. Inflammatory Cells
      (a) Types (neutrophil cells and mononuclear cells)
      (b) Sites (perivascular or vascular wall)
C. Quantification
Identify arteries by type of accompanying airways. An assessment of the number of affected vessels in proportion to total vessels at a given airway level should be given. The number of vessels in relation to the alveoli should be determined.

II. Lung Tissue

A. Components
Pre- and intra-acinar airway, alveoli, interstitium, and pleura

The description should include:

- Source of tissue –
  (post-mortem, explant, or open lung biopsy) with a comment on size
- Sample site –
  lobe, central or peripheral (avoid the lingula)
- Preparation of tissue –
  (fixation in inflation either via airways or by needle injection of unclamped biopsy are preferred)
- Stains –
  H and E, pentachrome, α-actin, factor VIII and iron.

COMMENTS

- Description of state of inflation and adequacy of sample size, airway and parenchyma including evidence of associated parenchymal disease
- Any other abnormalities or hemorrhage

Interpretation of the pathologic findings should be made in relation to the biochemical, radiologic, clinical and hemodynamic findings, to help guide the clinician. Are the pathologic findings consistent with the clinical picture? A diagnosis should be made where possible.

PATHOLOGY SUBCOMMITTEE

Prof. Sheila G. Haworth, Chair ........................................ University of London (London, UK)
Marlene Rabinovitch, MD, Chair ............................ The Hospital for Sick Children (Toronto, Canada)
Barbara Meyrick, PhD ....................................... Vanderbilt University (Nashville, USA)
Rene Michel, MD ......................................................... McGill University (Montreal, Canada)
Giuseppe G. Pietra, MD ...................................... University of Pennsylvania (Philadelphia, USA)
Julia M. Polak, MD ........................................ Imperial College School of Medicine (London, UK)
Lynne M. Reid, MD ............................................... Harvard Medical School (Boston, USA)
Rubin Tudor, MD ................................................. University of Colorado Health Sciences Center (Denver, USA)
PATHOBIOLGY OF PULMONARY HYPERTENSION

OVERVIEW

The aim of research in pathobiology is to discover the molecular process(es) behind the complex vascular changes associated with pulmonary hypertension.

Progress already realized from research in pathobiological mechanisms include:

- A description of phenotypic changes in endothelial and smooth muscle cells in hypertensive pulmonary arteries
- Recognition that cell proliferation contributes to the structural changes associated with the initiation and progression of pulmonary hypertension
- Recognition that apoptosis contributes to hypertensive pulmonary vascular disease
- Recognition of the role of matrix proteins and matrix turnover in vascular remodeling
- Recognition of the importance of hemodynamic influences on the disease process
- The development of a rationale for effective treatments directed towards specific pathobiologic processes

It is clear that gene expression in pulmonary vascular cells responds to environmental factors, growth factors, receptors, signaling pathways and genetic influences, which interact with each other. Examples of effector systems controlled by gene expression include:

- Transmembrane transporters
- Ion channels
- Transcription factors
- Modulators of apoptosis
- Kinases
- Cell to cell interactive factors (e.g., integrins and membrane receptors)
- Mechano-transducers
- Extracellular matrix turnover
- Growth factors/cytokines and chemokine networks

RECENT FINDINGS

The levels of investigation in the pathobiology of pulmonary hypertension include biochemical, cellular, integrated system and experimental models, and measurements in humans. Potentially important pathophysiologic processes which have been identified from descriptive studies from patients are listed
below. In most cases, it remains unclear whether the observations made are a cause or consequence of the disease.

**POTASSIUM CHANNELS**

Inhibition of the voltage-regulated (Kv) potassium channel by hypoxia or drugs can produce vasoconstriction and has been described in pulmonary artery smooth muscle cells harvested from patients with PPH. It is therefore possible that defects in the potassium channel of pulmonary resistance smooth muscle cells are involved in the initiation and/or progression of pulmonary hypertension. It is possible that a genetic defect related to potassium channels in the lung vessels of PPH patients leading to vasoconstriction is central to the development of PPH in some patients.

**VASOCONSTRICTOR/VASODILATOR IMBALANCE**

An imbalance may exist in the vasoconstricting and vasodilating mediators or substances involved in control of pulmonary vascular tone. These include the prostacyclin versus thromboxane ratio, an increase in endothelin, a decrease in nitric oxide production or release of other vasorelaxant substances yet to be described. In addition, other factors might be involved such as serotonin, platelet-derived growth factor, angiotensin, or the loss of pulmonary vascular prostacyclin synthase gene expression. Vasoconstrictors may also serve as factors or co-factors which stimulate smooth muscle growth or matrix elaboration.

**PROSTACYCLIN SYNTHASE EXPRESSION**

The loss of the expression of the prostacyclin synthase enzyme and gene in lungs of patients with severe pulmonary hypertension is consistent with a decrease in pulmonary prostacyclin production. The loss of prostacyclin synthase expression is likely one manifestation of an altered pulmonary hypertensive endothelial cell phenotype.

**NITRIC OXIDE PRODUCTION AND CHEMISTRY**

Reduced expression of nitric oxide synthase in the endothelium of patients with pulmonary hypertension has been demonstrated and correlates inversely with the extent and severity of morphologic lesions. Although it is unsettled as to whether or not this a cause or result of the disease, it is consistent with endothelial dysfunction underlying PPH as part of the disease process. Nitric oxide is important in the signal transduction of angiogenesis, as VEGF receptor activation results in increased nitric oxide production. Similarly, the expression of endothelin 1 is inversely related to that of nitric oxide synthase. These findings suggest that whether or not abnormal endothelial function is the underlying cause of PPH, the progression of the disease is invariably accompanied by a worsening of endothelial function that itself can promote disease progression.

**INFLAMMATION**

Mediators of inflammation can cause vasoconstriction and cell growth in animal models where inflammation is associated with pulmonary hypertension. The presence of mast cells in the pulmonary vasculature of patients with PPH, and increased levels of TGF-β, interleukin 1 and 6, and the chemokine MIP 1α has been described in patients with PPH. 5-lipoxygenase (5-LO), and 5-lipoxygenase activating protein (FLAP) over-expression have also been described in PPH.
SEROTONIN
Serotonin is a pulmonary vasoconstrictor and growth factor for vascular smooth muscle cells. It has not been established whether serotonin is essential to PPH, but elevations of plasma serotonin levels and impaired platelet storage of serotonin in patients with PPH have been described, and these have persisted in patients with PPH following lung transplantation.

ANGIOGENESIS
Misguided angiogenesis has been suggested as one mechanism for the development of plexiform lesions. One study has suggested that monoclonal expansion of endothelial cells occurs in PPH and is the basis for the plexiform lesion, whereas plexiform lesions in secondary pulmonary hypertension are polyclonal, suggesting that they occur via pathogenetically different routes. It is possible that medial hypertrophy and hyperplasia are early changes that result from misguided angiogenesis, as a consequence of a phenotypically altered endothelial cell.

THROMBOSIS
Thrombosis in situ of the pulmonary vascular bed has been proposed as a causative or contributing feature of pulmonary hypertension. Abnormalities in platelet activation and function, and biochemical features of a procoagulant environment within the pulmonary vasculature support a potential role of thrombosis in disease initiation in some patients. The interaction between growth factors, platelets, and the vessel wall suggest that thrombosis may play a fundamental role between many of the described pathobiologic processes in PPH and disease progression.

HEMODYNAMICS AND SHEAR STRESS
Several studies suggest that local hemodynamics can influence pulmonary vascular remodeling. A classic example is the pulmonary hypertension that occurs in congenital systemic to pulmonary shunts. It is believed that endothelial cells release mediators that induce vascular smooth muscle cell growth. Experimental data suggests that medial hypertrophy can be converted into a neointimal pattern when pulmonary vascular injury is coupled with increased blood flow. These neointimal lesions are composed of smooth muscle cells since they are immunoreactive to anti-α smooth muscle actin antibody. It is now accepted that hemodynamic shear stress acts through the endothelium to regulate vessel tone and in the chronic restructuring of blood vessels. Thus, the endothelium serves as a complex mechanical signal transduction interface between blood flow and the vessel wall.

EXTRACELLULAR MATRIX
Several studies demonstrate persistent matrix protein synthesis in pulmonary arteries obtained from patients with severe PPH. The observation that these pulmonary arteries are actively remodeling provides the rationale for developing pharmacologic inhibitors of remodeling that may halt, or even reverse, progression of disease.
FUTURE GOALS OF PATHOBIOLoGIC RESEARCH

- To discover the final common pathways for pulmonary hypertensive diseases
- To identify candidate genes for sporadic and familial PPH
- To identify the causative molecular process that are linked to epidemiologic risk factors
- To develop molecular biochemical and physiologic tests to monitor and diagnose the disease
- To develop new treatments based on established pathobiologic mechanisms

PATHOBIOLoGy SUBCOMMITTEE

Prof. Timothy Higenbottam, Chair ...... The University of Sheffield Medical School (Sheffield, UK)
Prof. Robert Naeije, Chair .................. Erasme Hospital (Brussels, Belgium)
Norbert F. Voelkel, MD, Chair .... University of Colorado Health Sciences Center (Denver, USA)
Mitchell D. Botney, MD .................. Washington University-St. Louis, USA)
Brian Christman, MD .................. Vanderbilt University (Nashville, USA)
Adel Giaid, MD ............................... McGill University (Montreal, Canada)
Charles A. Hales, MD .................. Harvard Medical School (Boston, USA)
Philippe Herve, MD .......................... Marie Lannelongue Centre Chirurgica (LePlessis Robinson, France)
Joseph Loscalzo, MD, PhD .................. Boston University (Boston, USA)
E. Kenneth Weir, MD .................. University of Minnesota (Minneapolis, USA)

RISK FACTORS AND ASSOCIATED CONDITIONS FOR PULMONARY HYPERTENSION

A risk factor for pulmonary hypertension is any factor or condition that is suspected to play a causal or facilitating role in the development of the disease. Because risk factors relate to the probability of occurrence of the disease, they must be present prior to the onset of the disease. Risk factors may include drugs, chemical products, diseases or a clinical state (age, gender). When it is not possible to determine whether a factor was present before the onset of the PPH, and thus it is unclear whether it played a causal role, the term “associated condition” is used. Associated conditions can be diseases that occur together with primary pulmonary hypertension, and thus are the result of a common risk factor. When associated conditions appear after the onset of PPH, it may be possible that PPH is a risk factor for that condition.

Conclusions regarding the causal relationship between risk factors and the development of PPH relate to the magnitude of the association, the temporality of the association, and consistency of the observations. The clinical features of PPH in patients with known risk factors are generally determined by the severity of the
PPH, and whatever influences the risk factor has on the overall medical condition. For example, the association of PPH and cirrhosis would have the combined clinical features of PPH and liver disease.

The exact mechanism by which the risk factors produce PPH has not been established. Given the fact that the absolute risk is generally low, factors of individual susceptibility are likely to play an important role.

The following risk factors have been categorized based on the strength of the association with PPH and their probable causal role. “Definite” indicates an association based on several concordant observations, including a major controlled study or a clear epidemic. Definite risk factors are considered to play a causal role in the development of the disease. “Very likely” indicates several concordant observations (including large case series and studies) that are not attributable to considered biases, or a general consensus among experts. “Possible” indicates an association based on case series, registries, or expert opinions. “Unlikely” indicates risk factors that have been proposed but have not been found to have any association from controlled studies.

A. Drugs and Toxins

1. Definite
   - Aminorex
   - Fenfluramine
   - Dexfenfluramine
   - Toxic Rapeseed Oil

2. Very Likely
   - Amphetamines
   - L-tryptophan

3. Possible
   - Meta-amphetamines
   - Cocaine
   - Chemotherapeutic Agents

4. Unlikely
   - Antidepressants
   - Oral Contraceptives
   - Estrogen Therapy
   - Cigarette Smoking

B. Demographic and Medical Conditions

1. Definite
   - Gender
2. Possible
   - Pregnancy
   - Systemic Hypertension
3. Unlikely
   - Obesity

C. Diseases
1. Definite
   - HIV Infection
2. Very likely
   - Portal Hypertension / Liver Disease
   - Collagen Vascular Diseases
   - Congenital Systemic-Pulmonary Cardiac Shunts
3. Possible
   - Thyroid disorders

RISK FACTORS AND ASSOCIATED CONDITIONS SUBCOMMITTEE
Lucien Abenhaim, MD, Chair ..................................................McGill University (Montreal, Canada)
Prof. Gerald Simonneau, Chair ........................................ Hospital Antoine-Bedelle (Clamart, France)
Miguel A. Gomez-Sanchez, MD .................. Hospital Universitario Doce de Octubre (Madrid, Spain)
Didier Lebrec, MD ...............................................................Hospital Beaufond (Clichy, France)
Rudolf Speich, MD ............................................................ University Hospitals (Zurich, Switzerland)

GENETICS OF PULMONARY HYPERTENSION

FAMILIAL PPH
PPH has been diagnosed in families worldwide. Currently there are 72 known families in the U.S., 10 in
Australia, 8 in England, 3 in Canada and 1 in Germany. The prevalence of genetic or familial PPH is
uncertain but is at least 6% of all PPH cases and may be considerably higher.

The transmission and development of PPH in families has many unique features. The age of onset is
variable and the penetrance is incomplete. Many individuals in families with PPH inherit the gene and have
progeny with PPH yet never develop PPH. The observation that there are fewer males born in PPH
families than in the population at large suggests that the PPH gene might influence fertilization or cause male fetal wastage.

Patients with familial PPH have a similar female to male gender ratio, age of onset and natural history of the disease as those with “sporadic” PPH. The documentation of familial PPH can be difficult since remote common ancestry occurs in patients with apparently sporadic PPH, and skipped generations due either to incomplete penetrance or variable expression can mimic sporadic disease. Because the clinical and pathologic features of familial and sporadic PPH are virtually identical, it seems likely that the same gene(s) may be involved in both forms of the disease. It also seems likely that the disease will not be due to an abnormal gene product resulting from a mutation, but will be due to abnormal production or regulation of a normal gene product.

Vertical transmission has been demonstrated in as many as five generations in one family and is highly indicative of a single dominant gene which is believed to be autosomal for PPH. Genetic anticipation has been evident in familial PPH since early reports. Trinucleotide repeat expansion, originally described in several neurologic disorders, remains the only known biologic explanation for genetic anticipation in PPH and raises the possibility that the pathogenesis of familial PPH might have a neurologic basis. The entire spectrum of pathologic features associated with sporadic PPH, including plexogenic arteriopathy, thromboembolic arteriopathy, veno-occlusive disease and pulmonary capillary hemangiomatosclerosis have been reported in different families with PPH.

The locus of a gene linked to familial PPH has been identified on chromosome 2q31-32, and analysis of the genome containing the gene has been reduced to less than 7 million base pairs. Investigators have reported positive results of microsatellite marker investigations which link familial PPH to the same 25-27 region on chromosome 2q31-32. PPH1 is the Human Genome Organization approved designation DGB:1381541. The clinical transmission of the gene is typical of other genetic diseases that are based on expanded trinucleotide repeats, but may involve abnormal promoter or modifier gene functions as well. The low penetrance of this gene confers only about a 10-20% likelihood of developing the disease.

**Counseling Patients with Familial PPH**

A complete family history should be obtained on every patient with PPH in order to explore the possibility of familial disease. Because lifetime penetrance is only 10-20% even if the gene is present, the likelihood of a first degree relative being affected when only one person in a family has PPH is estimated at 6-12%. If there is a second case known in the family, the risk rises to 5-10% lifetime. Based on current data, it is unlikely that screening the family members for the presence of disease will be of value when one member of the family has PPH. Children of an affected parent, with familial PPH, have only a 5-10% lifetime risk of developing the disease. Although clinical screening of asymptomatic family members will have a low yield, individual clinicians and families may opt to do so because of the severity of the disease.

Most experts currently advise against recommending genetic testing of family members in families with familial PPH because knowledge of the gene and its relationship to the disease is not advanced enough to provide true informed consent to anyone requesting the test. However, in large families where a sufficient
number of DNA samples can be collected, it is possible to provide information on carrier status by constructing genetic haplotypes.

IMMUNOGENETICS
Although PPH has been associated with autoimmune phenomena, the association remains unclear. The data suggest that a subset of patients with PPH may have a genetically programmed and immunologically mediated component to their pulmonary hypertension which may predispose them to developing a diagnosable connective tissue disease over time.

FUTURE RESEARCH
At the present time efforts are being focused towards the actual identity of the PPH 1 gene. This will allow studies of gene regulation and function, the use of transgenic and knockout animal models, as well as transfection with native missense plasmids to clarify the pulmonary vascular and embryological and systemic effects of the gene and its product. It is conceivable that the gene may be highly polymorphic. If it contains an unstable trinucleotide repeat expansion, then the number of repeats will likely determine the penetrance and probably the severity of the disease.

GENETICS OF PULMONARY HYPERTENSION SUBCOMMITTEE

David Langleben, MD, Chair .......................................McGill University (Montreal, Canada)  
John H. Newman, MD, Chair .....................................Vanderbilt University (Nashville, USA)  
C. Gregory Elliott, MD ..............................................University of Utah (Salt Lake City, USA)  
James E. Loyd, MD ....................................................Vanderbilt University (Nashville, USA)  
Jane H. Morse, MD ....................................................Columbia University (New York, USA)  
John Phillips, MD .....................................................Vanderbilt University (Nashville, USA)  
Richard C. Trembath, MD .........................................University of Leicester (Leicester, UK)

DIAGNOSIS AND ASSESSMENT OF PULMONARY HYPERTENSION

The diagnostic strategy for evaluating patients with pulmonary hypertension is well accepted with a high degree of consensus among experienced clinicians. Utilizing current medical technology, the correct diagnosis and assessment of the severity of pulmonary hypertension in a given individual can be made with a high level of confidence. The consensus regarding the general diagnostic approach to pulmonary hypertension now permits focusing on specific problematic areas.
SCREENING FOR PULMONARY HYPERTENSION

Screening appropriate patient populations may lead to the early identification of pulmonary hypertension in asymptomatic or minimally symptomatic individuals, or in symptomatic patients in whom the diagnosis was not previously suspected. This could allow early initiation of treatments at a time when dynamic or reversible pathogenic mechanisms are present, increasing the likelihood of a successful treatment outcome. Screening tests should be noninvasive and low risk, if possible, and have a relatively high sensitivity and specificity for detecting pulmonary hypertension.

Screening may be appropriate in groups of patients at increased risk of developing pulmonary hypertension. In such instances, general screening should always begin with a thorough clinical interview to elicit symptoms consistent with pulmonary hypertension, and a thorough physical examination to elicit physical findings consistent with the diagnosis. When the history and physical examination are inconclusive, further diagnostic testing may be appropriate.

The following recommendations are made regarding specific subgroups of patients. A transthoracic echocardiogram is currently the preferred screening test for the presence of pulmonary hypertension.

CONNECTIVE TISSUE DISEASES

The Scleroderma Spectrum of Diseases
Because of the high prevalence of pulmonary hypertension in these patients, as well as the availability of effective treatments, a transthoracic echocardiogram is recommended to be performed annually in patients with or without symptoms of pulmonary hypertension.

Systemic Lupus, Rheumatoid Arthritis, and Other Connective Tissue Diseases
Because of the low prevalence of pulmonary hypertension, and the lack of established effective treatment, a transthoracic echocardiogram is recommended only if patients have symptoms suggestive of pulmonary hypertension.

FAMILIES OF DOCUMENTED PPH
A detailed family history should be taken at the time the diagnosis of PPH is made in the proband. It is reasonable to consider a transthoracic echocardiogram in the first degree relatives at the time of diagnosis, at any time symptoms consistent with pulmonary hypertension arise, or every three to five years in asymptomatic individuals. In addition, relatives should be made aware of symptoms consistent with pulmonary hypertension. The basis for these recommendations is the greater prevalence of familial PPH than previously reported, and the availability of effective treatments. In addition, screening asymptomatic family members will help gather additional information about the prevalence of familial PPH and the effectiveness of early intervention.

LIVER DISEASE/PORTAL HYPERTENSION
Because pulmonary hypertension in these patients renders them at very high risk for liver transplantation, and because there is effective treatment available, a transthoracic echocardiogram should be performed in all patients when they are evaluated for liver transplantation.
HIV INFECTION
Because of the low prevalence of pulmonary hypertension in this subgroup, a transthoracic echocardiogram is recommended only in subjects who are HIV positive if they have symptoms consistent with pulmonary hypertension.

PATIENTS WITH A HISTORY OF INTRAVENOUS DRUG USE
Because the prevalence of pulmonary hypertension is uncertain in this subgroup, a transthoracic echocardiogram is recommended only in those patients who have symptoms consistent with pulmonary hypertension.

PATIENTS WITH A HISTORY OF APPETITE-SUPPRESSANT DRUG USE
Because of the low prevalence of pulmonary hypertension in this subgroup, a transthoracic echocardiogram is recommended only in patients who have symptoms consistent with pulmonary hypertension.

THE EVALUATION OF MILD PULMONARY HYPERTENSION
The widespread use of Doppler echocardiography in the assessment of nonspecific cardiovascular symptoms or signs has led to occasional observations of mildly increased right ventricular systolic pressure. Mild pulmonary hypertension is defined as a systolic pulmonary artery pressure of 40-50 mmHg, which corresponds to a tricuspid regurgitant velocity on Doppler echocardiography of 3.0-3.5 m/sec. The following recommendations are made regarding the assessment of mild pulmonary hypertension.

ASYMPTOMATIC INDIVIDUALS (INCIDENTAL DISCOVERY)
It is recommended that a Doppler echocardiogram be repeated in six months along with a detailed history and physical examination.

SYMPTOMATIC INDIVIDUALS
It is recommended that signs of pulmonary hypertension warrant right heart catheterization for confirmation of the hemodynamic findings. If the right heart catheterization does not reveal pulmonary hypertension at rest, it is recommended that pulmonary hemodynamics be measured during exercise. Patients in whom mild pulmonary hypertension exists at rest, or develops with exercise, should be managed like other patients with pulmonary hypertension.

HIGH RISK INDIVIDUALS
Individuals who are asymptomatic but at high risk of developing pulmonary hypertension should have a Doppler echocardiographic exam repeated in six months. If the presence of mild pulmonary hypertension is confirmed, they should undergo the same evaluation as do patients with symptomatic pulmonary hypertension.
MEDICAL TESTING TO CHARACTERIZE PULMONARY HYPERTENSION

Recent advances in medical technology have greatly improved noninvasive measurements rendering them more precise, reproducible, and reflective of the underlying pathophysiology of the disease.

ECHOCARDIOGRAPHY WITH DOPPLER
The following parameters are suggested for measurement:

- tricuspid regurgitant velocity
- pulmonary artery systolic flow acceleration time
- right ventricular ejection time
- right ventricular dimensions
- right ventricular volumetric data
- right ventricular index of myocardial performance
- timing of mid-systolic deceleration of right ventricular ejection

Echocardiography with Doppler may be useful in the follow-up of patients with pulmonary hypertension to monitor progression of the disease and/or the response to therapy.

MAGNETIC RESONANCE IMAGING (MRI)
The following parameters may be useful in evaluating the patient:

- right ventricular morphology
- right atrial morphology
- pulmonary artery morphology
- right ventricular function

The value of serial MRI scans in following the course of patients is not established.

COMPUTED TOMOGRAPHY (CT) OF THE CHEST
The following parameters may be useful in evaluating the patient:

- right ventricular morphology
- right atrial morphology
- pulmonary artery morphology
- right ventricular function.

It is recommended that a high-resolution chest CT scan also be performed to evaluate the lung parenchyma and to detect the presence of pulmonary venocclusive disease.

The value of serial chest CT scans in following the course of patients is not established.
EXERCISE TESTING
A six-minute walk test or a cardiopulmonary exercise test is recommended in patients at the time of diagnosis and follow-up. Exercise tests best characterize the functional impairment of patients with PPH, and their response to therapy.

RIGHT HEART CATHETERIZATION
Right heart catheterization is recommended for all patients who are undergoing an evaluation of pulmonary hypertension. Measurements during catheterization should include the following:
- right atrial pressure
- right ventricular systolic and end-diastolic pressure
- pulmonary artery systolic, diastolic, and mean pressure
- pulmonary capillary wedge pressure
- systemic and pulmonary arterial oxygen saturation
- cardiac output

Vasodilator Testing
It is recommended that all patients undergo acute testing with a short-acting vasodilator to determine vasodilator responsiveness at the time of their initial right heart catheterization. The following vasodilators are recommended:
- intravenous epoprostenol sodium
- inhaled nitric oxide
- intravenous adenosine

Patients who appear responsive to acute vasodilator testing may have a favorable response to treatment with oral calcium channel blockers. Although there is no consensus about the definition of vasodilator responsiveness, a minimum acceptable response would be a reduction in mean pulmonary artery pressure of 10 mm/Hg associated with either no change or an increase in cardiac output. Patients who do not manifest responsiveness to acute vasodilator challenge are unlikely to have clinical benefit from oral calcium channel blocker therapy.

Assessment of Pulmonary Arterial Impedence
Measurements of the impedance of the pulmonary vascular bed, using the acceleration time interval measurements (AcT), may provide additional information about right ventricular performance. Impedence parameters may better reflect true right ventricular afterload and provide hemodynamic information beyond that derived from measurements of pressure and flow. Accurate assessment of impedance can be done at the time of cardiac catheterization using high-fidelity multisensor pressure and velocity transducers.

LUNG BIOPSY
Although pathologic assessment of the lung may provide insights into histopathologic characteristics of pulmonary hypertensive states, the procedure entails a risk and there is little evidence that it provides additional clinically useful information over careful noninvasive and hemodynamic assessment in most
patients. Lung biopsy cannot be recommended as a part of the routine evaluation of patients with suspected PPH. It should be considered when there appears to be a specific indication, such as a diagnosis of active vasculitis.

DIAGNOSIS AND ASSESSMENT SUBCOMMITTEE

Alfred P. Fishman, MD, Chair .................................. University of Pennsylvania (Philadelphia, USA)
Michael D. McGoon, MD, Chair .................................. Mayo Clinic (Rochester, MN USA)
Irina E. Chazova, MD ................................................. Ministry of Health of the Russian Federation (Moscow, Russia)
Peter F. Fedullo, MD ................................................... University of California (San Diego, USA)
Prof. Meinhard Kneussl .............................................. University of Vienna (Vienna, Austria)
Andrew J. Peacock, MD ............................................... Western Infirmary (Glasgow, Scotland)
Adam Torbicki, MD .................................................... National Institute of Tuberculosis and Lung Disease (Warsaw, Poland)

MEDICAL THERAPY OF PULMONARY HYPERTENSION

Over the past 25 years there has been considerable experience with a variety of medications for the treatment of primary pulmonary hypertension. The clinical experience with these medications are summarized.

CALCIUM CHANNEL BLOCKERS

RATIONALE
Calcium channel blockers are a chemically heterogeneous group of compounds that inhibit calcium influx through the slow channel into cardiac and smooth muscle cells. Their usefulness in PPH is believed to be based on the ability to cause vasodilatation of pulmonary vascular smooth muscle. They also produce electrophysiologic effects, possess negative inotropic properties and cause reflex increases in beta adrenergic tone.

EFFECTIVENESS
The data demonstrates that a minority (approximately 20%) of patients with PPH will respond to oral calcium channel blockers, documented by an improvement in symptoms and exercise tolerance, hemodynamics via a reduction in pulmonary artery pressure and an increase in cardiac output, and survival. Although most studies have used calcium channel blockers at relatively high doses, the optimal dosing of patients with PPH is uncertain. The direct effect of calcium channel blockers on pulmonary vessel wall biology is unknown.
Patients with no evidence of an acute hemodynamic response to these drugs are unlikely to benefit from chronic therapy. Because of the frequent reporting of significant adverse effects of calcium blocker in these patients, which include systemic hypotension, pulmonary edema, right ventricular failure, and death, it is not recommended that calcium channel blockers be used in patients in whom acute effectiveness has not been demonstrated.

FUTURE DIRECTIONS
Enhanced effects of calcium channel blockers when used in conjunction with intravenous vasodilators and oral thromboxane synthase inhibitors has been reported. It is recommended that the use of calcium channel blockers in combination with other treatments be pursued.

INOTROPIC AGENTS

RATIONALE
As the cause of death in patients with PPH is primarily right heart failure, the use of drugs that will improve right ventricular performance is warranted. Currently there are no data on the use of chronic inotropic therapy as a treatment of PPH. The experience of an increased mortality in patients with left heart failure treated with a chronic inotropic therapy is of concern.

EFFECTIVENESS
Class I Agents
These agents augment contractility by increasing intracellular cAMP and calcium. The short term use of parenteral inotropes may be of benefit in some circumstances.

Class II Agents
Digoxin has been shown to increase cardiac output and reduce circulating norepinephrine acutely in patients with PPH. Digoxin has also been shown to be chronically effective in patients with left ventricular failure. Digoxin is used by some experts in the management of PPH for these reasons.

FUTURE DIRECTIONS
A better understanding of the neurohumoral and hemodynamic effects of inotropic therapy in patients with PPH is necessary. Strategies should also be developed to attempt to restore normal gene expression of sarcomere proteins to improve the contractile performance of the cardiac myocytes.

ANTICOAGULANTS

RATIONALE
Histologic data demonstrating thrombotic lesions in small pulmonary arteries in a large percent of patients with PPH and biochemical data consistent with a hypercoagulable state in some patients with PPH provide a rationale for the use of anticoagulants in PPH.
EFFECTIVENESS
Clinical data supporting the chronic use of anticoagulation is limited but supportive. Warfarin has been shown to be associated with improved survival in one retrospective study of PPH, one retrospective study of patients with PPH associated with the use of aminorex, and one prospective study of PPH. The optimal dose of warfarin in these studies was not determined. The range of anticoagulation that is recommended is an INR of 1.5 to 2; however, different clinical circumstances may require adjustment of the range.

FUTURE DIRECTIONS
New antithrombotic and anticoagulant drugs are being evaluated for several different clinical entities. Drugs that might be of promise in patients with PPH include monoclonal antibodies and other agents that block the glycoprotein IIb/IIIa platelet receptor, thromboxane synthase inhibitors and receptor blockers, and heparins and heparin-like compounds.

PROSTAGLANDINS

RATIONALE
The use of prostacyclin or an analogue as a treatment of PPH is supported by the demonstration of an imbalance of thromboxane to prostacyclin metabolites in patients with PPH, and the demonstration of a reduction in prostacyclin synthase in the pulmonary arteries of patients with PPH.

EFFECTIVENESS
Continuous intravenous prostacyclin has been evaluated in prospective, randomized clinical trials of PPH. The results confirm an improvement in exercise tolerance, hemodynamics, and survival in patients who are Functional Class III and Class IV. The mechanism of action of the chronic effects of prostacyclin is unknown in these patients, but it is likely multifactorial. Clinical data suggests that it lowers the pulmonary artery pressure, raises the cardiac output, improves systemic oxygen transport, and possibly reverses pulmonary vascular remodeling. Studies have also demonstrated that the lack of an acute response to prostacyclin does not preclude a chronic beneficial response. The development of tolerance to the effects of intravenous prostacyclin is common, and appears to respond to periodic dose escalation. However, the optimal dosing of intravenous prostacyclin for PPH remains uncertain.

FUTURE DIRECTIONS
Studies are necessary to clarify the mechanisms of action of prostacyclin on cardiac and vascular tissue. A better understanding of how to determine the optimum dosing of patients on intravenous prostacyclin is essential. Alternate delivery systems may enhance efficacy, improve safety, and reduce side effects. Trials looking at the effectiveness of prostacyclin analogues administered subcutaneously, by inhalation, and orally, are warranted. The use of these agents in less severely ill patients will be desirable as less complex delivery systems become available. Drugs that increase endogenous prostacyclin production should be pursued.
NITRIC OXIDE

RATIONALE
Nitric oxide activates guanylate cyclase in pulmonary vascular smooth muscle cells which increases cGMP and decreases intracellular calcium concentration, thereby leading to smooth muscle relaxation. When inhaled, the rapid combination of nitric oxide with hemoglobin inactivates any nitric oxide diffusing into the blood, preventing systemic vasodilation. Consequently nitric oxide is a potent and selective pulmonary vasodilator when administered by inhalation.

EFFECTIVENESS
Although there is a considerable experience in the use of nitric oxide as a short-term treatment of pulmonary hypertension in a variety of clinical situations, the role of nitric oxide as a chronic therapy for PPH remains investigational. The mechanism of beneficial effects of nitric oxide in PPH, both acutely and chronically are likely multifactorial.

FUTURE DIRECTIONS
More data is needed regarding the long-term efficacy and safety of chronic nitric oxide as inhalation therapy. Preliminary studies suggest the pursuit of nitric oxide potentiating compounds, such as phosphodiesterase inhibitors, is warranted. Histologic studies demonstrating reduced levels of nitric oxide synthase in the pulmonary vasculature of patients with PPH provides justification for the development of gene replacement therapy for this disease.

FUTURE DIRECTIONS FOR MEDICAL THERAPY
Considerable promise exists in the development of medical therapy for PPH following a wide variety of approaches. These include:

- studies of myocardial protein and genotypes
- development of vascular antiproliferative agents (including angiotensin converting enzyme inhibitors and endothelin receptor blockers)
- development of agents that affect ion channel function (such as potassium channel openers)
- studies of endothelial derived substance synthesis and metabolism
- studies of genotype and gene expression
- studies evaluating multimodal/combination therapies

Studies of the pathobiology of PPH have demonstrated abnormalities in cellular function of different cell types and sequential changes in vascular morphology and function leading to remodeling. These observations provide targets for the use of several agents in combination, and/or the staging of therapies. In addition to the reversal of remodeling, stimulation or enhancement of normal endothelial cell function may be possible.
MEDICAL THERAPY SUBCOMMITTEE

Robyn J. Barst, MD, Chair ........................................... Columbia University (New York, USA)
Bruce H. Brundage, MD, Chair ........................................... UCLA School of Medicine (Los Angeles, USA)
Stuart Rich, MD, Chair ........................................... Rush Medical College (Chicago, USA)
Lewis J. Rubin, MD, Chair ........................................... University of Maryland (Baltimore, USA)
Nazzareno Galie, MD ........................................... Universita degli Studi di Bologna (Bologna, Italy)
Stefan Janssens, MD, PhD ........................................... University of Leuven (Leuven, Belgium)
Jiri Widimsky, MD ........................................... Charles University (Prague, Czech Republic)
Warren Zapol, MD ........................................... Harvard Medical School (Boston, USA)

ATRIAL SEPTOSTOMY FOR PULMONARY HYPERTENSION

RATIONALE
The rationale for the creation of an atrial septostomy in PPH is based on experimental and clinical observations suggesting that an intra-atrial defect allowing right to left shunting in the setting of severe pulmonary hypertension might be of benefit. Although there exists a worldwide experience in over 60 patients, the procedure should still be considered investigational. Nonetheless, atrial septostomy may represent a real alternative for selected patients with severe PPH. Indications for the procedure include:

- recurrent syncope and/or right ventricular failure despite maximum medical therapy
- as a bridge to transplantation if deterioration occurs despite maximum medical therapy
- when no other option exists

As the disease process in PPH appears to be unaffected by the procedure, the long-term effects of an atrial septostomy must be considered to be palliative.

GUIDELINES
The procedure-related mortality with atrial septostomy in patients with PPH is high, and thus the following recommendations are made to minimize the risk:

- atrial septostomy should only be attempted in institutions with an established track record in the treatment of advanced pulmonary hypertension and an experience in performing atrial septostomy with low morbidity
- atrial septostomy should not be performed in the patient with impending death and severe right ventricular failure, on maximal cardiorespiratory support.
Predictors of procedure-related failure or death include:
- a mean right atrial pressure > 20 mmHg
- a PVR index > 55 U·M²
- a predicted one year survival less than 40%

Candidates for atrial septostomy should have a systemic arterial oxygen saturation on room air of greater than 90%. During the atrial septostomy procedure it is recommended that the patient have the following:
- mild and appropriate sedation to prevent anxiety
- supplemental oxygen
- careful monitoring of hemodynamics with particular monitoring of the systemic arterial oxygen saturation

The endpoint for the procedure should be considered a reduction in systemic arterial oxygen saturation of 5-10%. It is also recommended that the procedure be performed in a stepwise manner, to create the smallest possible septal defect that will produce hemodynamic changes.

Before and after septostomy, transfusion of packed red blood cells or the use of erythropoietin may be necessary to increase oxygen delivery. Chronic anticoagulation is also recommended.

**FUTURE RESEARCH**
- The optimal timing of the intervention remains uncertain. Investigations should address whether or not the intervention should be performed earlier in the course of the disease.
- The mechanisms responsible for beneficial effects of atrial septostomy remain unclear. Possibilities that exist include:
  - Increased oxygen delivery at rest and/or with exercise
  - Reduced right ventricular end diastolic pressure or wall stress
  - Improvement of right ventricular dysfunction by Frank Starling mechanism or relief of ischemia
- Long-term effectiveness and possible undesirable effects need to be studied.

**ATRIAL SEPTOSTOMY SUBCOMMITTEE**
Julio Sandoval, MD, Chair .......................... Instituto Nacional de Cardiologia (Mexico City, Mexico)
Robyn J. Barst, MD ........................................ Columbia University (New York, USA)
Stuart Rich, MD ........................................... Rush Medical College (Chicago, USA)
Abraham Rothman, MD ................................. University of California (San Diego, USA)
TRANSPANTATION FOR PULMONARY HYPERTENSION

RATIONALE
Transplantation is an effective treatment for patients with advanced pulmonary hypertension. Since 1981, close to 1000 patients have undergone either a single lung, double lung or heart-lung transplant for pulmonary hypertension worldwide. Ages of recipients range from 2 months to 61 years. The operative mortality ranges between 16-29% and is affected by the primary diagnosis. PPH recipients of a single lung transplant appear to have a higher operative mortality than those undergoing transplantation for other conditions, whereas recipients of double lung or heart-lung transplant appear to have comparable results. The one year survival is between 70-75%, the three year survival between 55-60% and five year survival between 40-45%. The longest survival to date in a heart-lung transplant recipient has been more than 14 years.

GUIDELINES
Transplantation should be reserved for patients with pulmonary hypertension who have progressed in spite of optimal medical management. Advances in the medical therapy of PPH has improved the prognosis for many patients. As progress is made in the medical management of patients with PPH, the indications for transplant may evolve.

Patients should be referred for evaluation for transplantation at the appropriate time. The course of the disease and the waiting time must be taken into account. Timing the referral for transplantation depends on the patient’s prognosis with optimal medical management, the anticipated waiting time before transplantation in the region, and the expected survival after transplantation: Guidelines for timing the referral include:

- NYHA Functional Class III or IV in spite of medical therapy
- When treatment with prostacyclin is initiated, or is failing, or is causing intolerable side effects

There are several transplantation options. Acceptable results have been achieved with heart-lung transplantation, bilateral lung transplantation, and single lung transplantation. While there are advantages and disadvantages to each operation, there is currently no consensus regarding the best procedure. The availability of donor organs often influences the choice of procedure. It is possible that data on long-term survival in transplant recipients may demonstrate a survival advantage of one procedure over another.

While traditional measures such as survival and cardiopulmonary function have been emphasized, quality of life is equally important. Several studies have documented a significant improvement in both overall and health-related quality of life after heart/lung and lung transplantation for pulmonary hypertension. Only pilot studies have addressed the issue of cost effectiveness. When considering the cost effectiveness of transplantation, one needs to account for the anticipated medical care of the advanced PPH patient who often requires frequent hospitalization, and the expense of newer therapies, such as intravenous prostacyclin therapy at the present time.
FUTURE DIRECTIONS
Living related donor transplantation is controversial. Although related living donor lung transplantation has been successful, there is very limited experience in children and no known experience in adults with pulmonary hypertension. Extreme caution is advised when considering this approach at this time.

TRANSPLANTATION SUBCOMMITTEE
Stuart W. Jamieson, MB ......................................... University of California (San Diego, USA)
Elbert P. Trulock, MD ........................................... Washington University (St. Louis, USA)
Prof. Magdi Yacoub ............................................. British Heart Foundation (Middlesex, UK)

NOMENCLATURE AND CLASSIFICATION
OF PULMONARY HYPERTENSION

A diagnostic classification of the various forms of pulmonary hypertension can be helpful in communicating about individual patients and in standardizing diagnosis and treatment. Pulmonary hypertension can be classified in many ways. Several previous classifications have proved to be problematic.

The following is proposed to allow the categorization by common clinical features. This classification reflects recent advances in the understanding of pulmonary hypertensive diseases, and recognizes the similarity between primary pulmonary hypertension and pulmonary hypertension of certain known etiologies.

(In keeping with the new diagnostic classification, a new pathologic classification of pulmonary hypertension is proposed. The new recommendations for the pathologic characterization of pulmonary hypertensive states are included in the Pathology section.)

DIAGNOSTIC CLASSIFICATION

1. Pulmonary Arterial Hypertension
   1.1 Primary Pulmonary Hypertension
       (a) Sporadic
       (b) Familial
   1.2 Related to:
       (a) Collagen Vascular Disease
       (b) Congenital Systemic to Pulmonary Shunts
       (c) Portal Hypertension

25
2. Pulmonary Venous Hypertension
   2.1 Left-Sided Atrial or Ventricular Heart Disease
   2.2 Left-Sided Valvular Heart Disease
   2.3 Extrinsic Compression of Central Pulmonary Veins
      (a) Fibrosing Mediastinitis
      (b) Adenopathy / Tumors
   2.4 Pulmonary Veno-Occlusive Disease
   2.5 Other

3. Pulmonary Hypertension Associated with Disorders of the Respiratory System and/or Hypoxemia
   3.1 Chronic Obstructive Pulmonary Disease
   3.2 Interstitial Lung Disease
   3.3 Sleep Disordered Breathing
   3.4 Alveolar Hypoventilation Disorders
   3.5 Chronic Exposure to High Altitude
   3.6 Neonatal Lung Disease
   3.7 Alveolar-Capillary Dysplasia
   3.8 Other

4. Pulmonary Hypertension due to Chronic Thrombotic and/or Embolic Disease
   4.1 Thromboembolic Obstruction of Proximal Pulmonary Arteries
   4.2 Obstruction of Distal Pulmonary Arteries
      (a) Pulmonary Embolism (Thrombus, Tumor, OVA and/or parasites, Foreign Material)
      (b) In-situ Thrombosis
      (c) Sickle Cell Disease
5. Pulmonary Hypertension due to Disorders Directly Affecting the Pulmonary Vasculature
   5.1 Inflammatory
      (a) Schistosomiasis
      (b) Sarcoidosis
      (c) Other
   5.2 Pulmonary Capillary Hemangiomatosis

**FUNCTIONAL ASSESSMENT** *

A. Class I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.

B. Class II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

C. Class III – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.

D. Class IV – Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

* modified after the New York Heart Association Functional Classification