NHLBI Workshop Summary

Idiopathic Pneumonia Syndrome after Bone Marrow Transplantation

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Introduced in the early 1970s for treatment of aplastic anemia and leukemia, bone marrow transplantation offers potentially effective treatment for a growing number of patients. The procedure is now recognized as therapeutic for an increasing number of diseases. Furthermore, advances in transplant immunobiology, supportive care, and prevention of graft-versus-host disease, coupled with the availability of suitable donors, make the technique both effective and feasible. In 1990 more than 5,500 patients received allogeneic marrow transplants from matched or partially matched family members, and more than 5,000 autologous transplant procedures were performed. The recent creation of the National Marrow Donor Program (NMDP), which currently lists more than 600,000 potential donors, has made identification of unrelated phenotypically HLA-identical donors possible for patients who do not have suitable donors among family members. It is estimated that more than 500 unrelated transplants will be performed in 1992.

Despite these encouraging developments, transplantation-related complications, especially those involving the lung, have limited the success of bone marrow transplantation. Interstitial pneumonitis accounts for more than 40% of transplantation-related deaths in most large series. Of these pneumonias, approximately half are noninfectious idiopathic pneumonia, herein referred to as idiopathic pneumonia syndrome (IPS).

Although IPS is an important clinical entity, progress in understanding the pathogenesis of IPS has been limited. The lack of progress is partly due to different definitions of the disease, different diagnostic criteria, and the relatively small number of patients studied at most centers. However, our understanding of related areas that may be pertinent to the problem of IPS has progressed. For example, there have been major advances in basic immunobiology, radiation biology, the biology of inflammation, and the role of specific cytokines. More is known about cellular and molecular mechanisms of lung injury and repair. Improved diagnostic procedures to identify infectious causes of lung disease are now becoming available. The applicability of this emerging knowledge, including the therapeutic potential of anti-inflammatory and immunomodulating drugs to the problem of IPS, has not been fully explored.

A workshop sponsored by the Division of Lung Diseases and the Division of Blood Diseases and Resources, National Heart Lung, and Blood Institute, National Institutes of Health, was held in September 1991 to summarize the state of knowledge regarding IPS. Recent clinical observations and developments in cellular and molecular mechanisms of tissue injury that relate to the pathogenesis of IPS were discussed with the goal of identifying promising directions for future research.

CLINICAL-PATHOLOGIC FEATURES

The discussion of the clinical-pathologic features of IPS was directed at the following objectives: (1) to summarize the current knowledge about noninfectious lung injury after high dose chemotherapy or chemoradiotherapy and marrow transplantation, including risk factors for development, clinical and pathologic features, and outcome; (2) to identify limitations in the current knowledge base; (3) to develop an operational definition of IPS that could facilitate future clinical and laboratory investigations.

Idiopathic Pneumonia Syndrome after Allogeneic Marrow Transplantation

The incidence of IPS after allogeneic marrow transplant is approximately 12%. The classic presentation of "interstitial pneumonia" includes dyspnea, nonproductive cough, hypoxemia, and nonlobar radiographic infiltrates. However, the clinical spectrum is broad, ranging from acute respiratory distress to incidental radiographic infiltrates. The median time of onset is 42 to 49 days after marrow transplant, but there is an early peak in the first 14 days, followed by a lower but consistent incidence through 80 days. When presented as a proportion of all pneumonias, most pneumonias occurring during the first 28 days are idiopathic; subsequently, the rate of noninfectious pneumonias is constant at 20%. Studies of "late" pneumonias (i.e., > 100 days after marrow transplant) report highly variable incidence of pneumonias that are idiopathic (20 to 54%) (1, 2). The true proportion is unknown, but it likely depends on the specific population studied.

Drs. Crawford and Hackman reviewed 41 cases of pneumonia seen at the Fred Hutchinson Cancer Research Center in which
open lung biopsy revealed no infection (3). The total in-hospital mortality rate was 71%, but only 32% died of progressive respiratory failure directly associated with the initial episode. Unexpectedly, irradiation dose greater than 1,200 cGy and acute graft-versus-host disease of Grade 2 or higher were associated with resolution of pneumonia. These apparently paradoxical findings suggest that total body irradiation and graft-versus-host disease might be causes of treatable (i.e., steroid-responsive) risk factors. Despite the absence of infection in the original lung biopsy, infection complicating IPS was later documented during the clinical course in 13 of the 41 cases of IPS and 11 of 16 autopsies. Cytomegalovirus (CMV), herpes simplex virus (HSV), and Aspergillus and Candida infections predominated.

These retrospective findings suggest that effective intervention aimed at modifying the acute lung injury may alter the outcome in the one third of patients with IPS who died as the direct result of their pneumonia. In addition, the appropriate diagnosis and treatment of infections complicating the course of IPS may favorably alter outcome.

Idiopathic Pneumonia Syndrome after Autologous Marrow Transplant

The occurrence of IPS after autologous marrow transplantation is of particular interest since the allograft reaction associated with graft-versus-host disease is presumably not applicable in this setting. Also, the identification of viral agents, particularly CMV, in autologous marrow transplant patients is considerably less common than after allogeneic marrow transplant. Therefore, IPS after autologous marrow transplantation more likely represents the result of pretransplant conditioning regimens consisting of high dose chemotherapy and radiation. To assess the risk factors and clinical characteristics of IPS occurring after autologous marrow transplantation the experience at the University of Nebraska Medical Center was reviewed (4). In a series of 141 consecutive patients, 29 were identified with acute lung injury. In these patients sequential aliquots of bronchoalveolar lavage fluid became progressively bloodier. Hence, the syndrome was termed diffuse alveolar hemorrhage (DAH). DAH was preceded by 3 to 7 days of nonproductive cough and dyspnea in the majority of patients. Interestingly, none had hemoptysis. The majority of patients developed respiratory failure followed by progressive respiratory insufficiency leading to death. DAH was associated with age greater than 40 yr, total body radiation, transplantation for solid tumors, high fevers, and renal failure or insufficiency. DAH was not associated with prolongation of the prothrombin time or the partial thromboplastin time, and although the majority of patients were thrombocytopenic, platelet transfusions did not correct the syndrome.

Clinical Epidemiology of Idiopathic Pneumonia Syndrome

Data from the international Bone Marrow Transplant Registry on patients transplanted between 1985 and 1990 were analyzed for the workshop by Dr. Mary Horowitz, updating a previous assessment of risk factors for IPS (5). Patients included recipients of HLA-identical sibling transplants for both leukemia and aplastic anemia as well as recipients of identical twin transplants for leukemia. Diffuse pneumonia of all causes occurred in 25% of patients after HLA-identical sibling marrow transplant for leukemia. Approximately one half of the pneumonias were of noninfectious etiology. Increased risk of developing noninfectious pneumonia was associated with a low Karnofsky performance score prior to transplantation, higher doses of total-body radiation, and the presence of graft-versus-host disease. Recipients of HLA-identical sibling transplants for aplastic anemia appear less likely to develop IPS than do those who receive transplants for leukemia. This may be due to the less intense pretransplant conditioning regimens given for aplastic anemia. Interestingly, recipients of identical twin transplants for leukemia also developed less IPS than did those who received HLA-identical sibling transplants for leukemia despite similar conditioning regimens. The risk for these twins was similar to the risk of developing IPS after HLA-identical sibling transplants without graft-versus-host disease and to the risk reported after autologous marrow transplants. These preliminary data lend strong support to the concept that immune factors related to graft-versus-host disease are significant risk factors for IPS.

Pathologic Features of Idiopathic Pneumonia Syndrome after Marrow Transplantation

Dr. Hackman discussed open lung biopsies from patients with IPS at the Fred Hutchinson Cancer Research Center. Two main histopathologic patterns were identified: interstitial pneumonitis and diffuse alveolar damage. Specific histologic abnormalities occasionally present were bronchiolitis, vascular alteration, and cellular atypia, but these findings were not clearly associated with any clinical features of the patients, including graft-versus-host disease. Although diagnosis of IPS implies the elimination of infectious etiologies, the extent to which possible infection can be excluded is not well defined. The increasing availability of sophisticated and sensitive technologies, i.e., immunohistochemistry, in situ hybridization, and polymerase chain reaction (PCR), to detect occult infection is likely to require ongoing assessment of the adequacy of evaluation of infections. For example, recent PCR analysis of HHV-6 in normal lung and IPS lung samples (from previously stored, frozen specimens) indicated significantly higher levels of the viral genes in IPS. Although the clinical significance of these findings is not yet clear, the study illustrates the possible role of occult infections in IPS and the potential diagnostic value of biopsy tissue.

Bronchoalveolar lavage is increasingly the only source of pulmonary material obtained for the evaluation of post-transplant pneumonia, despite the inability of lavage to provide histopathologic information on structural alterations, possible interstitial fungus or neoplasm, vascular damage, or other abnormalities of potential therapeutic or prognostic importance. In contrast, open or thorascopic lung biopsy supplies this information as well as invaluable archival tissue for subsequent research.

Early diagnosis of lung injury could be useful in identifying patients at risk for developing IPS. Physiologic assessment of gas exchange and sensitive radiologic approaches such as high resolution computed tomography are likely to lack specificity. Surfactant proteins may be useful as markers of airway and alveolar injury and in assessing its severity.

Definition of Idiopathic Pneumonia Syndrome

The participants in the workshop suggested the term "idiopathic pneumonia syndrome" to describe diffuse lung injury occurring after marrow transplant for which an infectious etiology is not identified. It was agreed that use of histopathologic terms (such as "interstitial pneumonitis") in reference to the clinical disorder is inaccurate and should be avoided. It was also recognized that a clinical syndrome was being defined that has inherent heterogeneity. The heterogeneity includes varied clinical expression and severity from patient to patient, variable histopathologic correlates, and multiple potential etiologies. The participants endorsed the concept of a uniform operational definition to ensure that descriptive and interventional studies include comparable well-defined
patient populations. Features characterizing the desirable definition include the following: (1) the diagnosis of the syndrome should be feasible using readily available current technology; (2) the definition should be broad enough to include most cases of the syndrome but narrow enough so that few patients who do not have the syndrome (i.e., those with unrecognized infection) are included. The following definition was proposed.

I. Evidence of widespread alveolar injury. Criteria include:
   a. Multilobar infiltrates on routine chest radiographs or CT scans.
   b. Symptoms and signs of pneumonia, e.g., cough, dyspnea, rales.
   c. Evidence of abnormal pulmonary physiology.
      1. Increased alveolar to arterial oxygen gradient (compared
         with previous, if available).
      2. New or increased restrictive pulmonary function test abnormality.
   d. Ideally, a second confirmatory negative test for infection is done. This usually is performed 2 to 14 days after the initial negative bronchoalveolar lavage, and it may consist of a second bronchoalveolar lavage or an open lung biopsy.

II. Absence of active lower respiratory tract infection. Appropriate evaluation includes:
   a. Bronchoalveolar lavage negative for significant bacterial pathogens and/or lack of improvement with broad-spectrum antibiotics.
   b. Bronchoalveolar lavage negative for pathogenic nonbacterial microorganisms.
      1. Routine bacterial viral and fungal cultures.
      2. Shell-vial CMV culture.
      4. Detection methods for respiratory syncytial virus, parainfluenza virus, and other organisms (e.g., fluorescent antibodies or culture).
   c. Transbronchial biopsy if condition of the patient permits.
   d. Ideally, a second confirmatory negative test for infection is done. This usually is performed 2 to 14 days after the initial negative bronchoalveolar lavage, and it may consist of a second bronchoalveolar lavage or an open lung biopsy.

ROLE OF INFECTION

The possible role of infection in IPS remains an open question. CMV-associated interstitial pneumonia, a major consideration in the differential diagnosis of IPS, was reviewed as a paradigm for diffuse progressive lung disease. Recent developments in the treatment and prevention of CMV pneumonia were discussed, focusing on postulated immunopathologic mechanisms in both human and murine CMV pneumonia. Latent viral infections and mechanisms by which they might cause lung injury after marrow transplant were also considered.

The risk of developing CMV pneumonia is significantly higher in allogeneic recipients with acute graft-versus-host disease and less common in autologous and syngeneic recipients. Exposure to virus, including receipt of marrow from a seropositive donor, exposure to blood products from seropositive donors, and prolonged intensive immunosuppression have also been found to be important risk factors (6). Previous clinical trials for the treatment of CMV pneumonia using antiviral drugs alone or in combination with certain immunotherapeutic agents did not show changes in the high mortality rate of CMV pneumonia. However, combined therapy with ganciclovir and intravenously administered immune globulin recently has been shown to improve immediate survival in patients with CMV pneumonia, giving support to a postulated immune component in this disease (7–9). In addition, CMV pneumonia appears to be exceptionally prevalent in allogeneic marrow recipients; therefore, it may not be attributable to active virus replication alone but rather to an interaction between alloimmune responses and viral genes.

Several recent major trials investigated the role of ganciclovir prophylaxis in allogeneic marrow transplant recipients. At the City of Hope and Stanford, patients with asymptomatic pulmonary CMV infection (defined by positive CMV culture in bronchoalveolar lavage) were randomly assigned to prophylactic ganciclovir or to observation (10). A large treatment effect was found. The risk of developing CMV pneumonia in the ganciclovir-treated group was reduced to the level observed in a group of patients with a negative lavage on Day 35. Another randomized study from Seattle showed that early ganciclovir treatment in patients with positive surveillance cultures reduced the incidence of CMV pneumonia and improved survival (11). Because neither treatment protocol was completely successful in preventing disease, despite a presumed antiviral effect, ongoing studies are examining earlier treatment as well as immunotherapy (12).

Animal models of CMV lung infection and pneumonitis may provide insight into the pathogenesis of human CMV-associated pneumonia as well as other pneumonia that occurs in the setting of altered host immunity. In murine CMV, for example, it is known that virus can replicate in lung tissue without disease. Additional alterations in host immunity are required for pneumonitis, and the pattern of disease may vary with the type of immune alterations (13). The immunopathologic mechanisms involved in producing pneumonitis are poorly understood, but the possible role of cytokine-mediated lung injury (i.e., tumor necrosis factor) has been proposed in both human and murine CMV pneumonia. Also, products of latent CMV genes may act as antigens to trigger an immune response. Experimental evidence was presented that certain CMV genes have the ability to affect cytokine production by up-regulating the genes for interleukin-1, interleukin-1 receptor, and tumor necrosis factor (14).

Latent viral infections may play an important role in the pathogenesis of both the interstitial and bronchiolar forms of lung disease that are found in marrow transplant patients (15). Adenovirus, a common respiratory pathogen, is an example that could be relevant to the pathogenesis of IPS. These latent infections may produce disease in situations where there is a shift from latent to lytic infection or where proteins produced by latent viral infections either induce or amplify the inflammatory response. The early genes of the adenovirus, particularly the EIA region, produce proteins capable of causing cell division and growth, and they may amplify the inflammatory reaction by rendering cells susceptible to lysis by mediators such as tumor necrosis factor.

MECHANISMS OF LUNG INJURY

Cell-mediated Immunity

Lung injury that occurs in the context of allogeneic transplants is likely to be mediated in part by T-lymphocytes. Although nonspecific effector mechanisms (natural killer cells, cytokines) may play important roles, the activation of T-lymphocytes specific for alloantigens appears to be the initial immunologic event. During graft-versus-host disease, donor-derived T-lymphocytes with specificity for recipient histocompatibility antigens (Class I, Class II, or minor histocompatibility antigens, depending on the degree of donor-recipient HLA identity) develop. After lung or heart-lung transplantation, recipient T-lymphocytes also can become sensitized to donor histocompatibility antigens. If cytotoxic T-lymphocytes (CTL) are generated, direct cell-mediated damage can occur. Analyses of bronchoalveolar lavage cells have been used to
monitor lung transplant patients for acute rejection. Functional analysis of lavage cells, but not peripheral blood lymphocytes, to detect donor-specific alloreactivity appears to be a useful indicator of acute heart-lung transplant rejection (16) as well as a means of long-term monitoring of these patients for bronchiolitis obliterans. These functional analyses also may provide some insights into other pathogenetic mechanisms in immunologically mediated lung injury. For example, it has been noted clinically that CMV infection seems to augment lung allograft rejection. There is evidence that early immediate (IE) genes of human CMV can enhance monocyte IL-1β gene expression in response to lipopolysaccharide stimulation (17). The cellular immune response triggered by the CMV infection may also contribute to the augmentation of host-versus-graft response. Intragraft CMV-specific lymphocytes may be activated during infection. In lung recipients undergoing CMV infection, Zeevi and coworkers (18) have demonstrated accelerated CMV-specific proliferation of lavage cells but not of peripheral blood lymphocytes. The CMV-specific lymphocytes persisted in the allograft postinfection, and they were associated with elevated donor-specific alloreactive responses and increased IL-2 responsiveness of lavage cells (19).

The activation of T-cells in lung is a pivotal event in immunologically mediated lung injury. Dendritic cells, strategically located beneath the airway epithelium, are powerful antigen-presenting cells (20). By themselves they do not appear to be significant immunostimulatory cells for allogeneic T-cells. However, in the presence of macrophages or cytokines (i.e., IL-1 and GM-CSF) they become potent immunostimulatory cells (in a mixed lymphocyte response assay). It is postulated that "maturation" of pulmonary dendritic cells into immunostimulatory cells may occur under the influence of cytokines produced in injured lung and contribute to T-cell-mediated lung injury. This hypothesis suggests that strategies to arrest the maturation of dendritic cells might be useful in overcoming cytotoxic immune responses in lung.

Cytokines as Mediators of Lung Injury
The discussion of cytokines focused on several specific cytokines with pleiotropic effects that are produced in the setting of lung injury. "Cascades" and "networks" involving multiple cytokines were discussed in the context of the pathogenesis of IPS, and the concept of resident alveolar cells (epithelial and endothelial cells and fibroblasts) capable of synthesizing and secreting cytokines and functioning as effector cells emerged as a recurring theme in the discussions.

Tumor necrosis factor (TNF), a mononuclear phagocyte-derived protein, is an important example of a cytokine with pleiotropic effects that influence the pathophysiology of the host. Although TNF may be important in homeostasis, excessive production of this cytokine has been implicated in a number of diseases, including septic shock, cachexia associated with cancer, AIDS, and parasitic infections. Elevated levels also occur with acute graft-versus-host disease and allograft rejection. In the context of the lung, the role of TNF in the elicitation of leukocytes and mediation of lung injury may be dependent upon a cascade of events that are associated with a network of cytokines represented by growth, differentiation, immunoenhancing, and chemotactic factors (21). These latter cytokines are fundamental to the recruitment of immune cells to the site(s) of inflammation. This recruitment of leukocytes is dependent upon the initial leukocyte-endothelial interaction, followed by diapedesis, and migration along an established chemotactic gradient. Recently, several investigators have led to the isolation, purification, cloning, and expression of chemotactic cytokines with specific leukocyte bioactivity.

Interleukin 8 (IL-8) and monocyte chemoattractant peptide-1 (MCP) are two chemotactic cytokines produced by both immune and nonimmune cells in response to TNF (22, 23). IL-8 is chemotactic for both lymphocytes and neutrophils in picomolar and nanomolar concentrations, respectively. In contrast, MCP has chemotactic and activating bioactivity for monocytes in nanomolar concentrations. The production of both IL-8 and MCP by the cellular constituents of the alveolar-capillary wall of the lung in response to TNF may provide an explanation for the subsequent recruitment of leukocytes into the lung. Mononuclear phagocytes and endothelial cells produce IL-8 in response to lipopolysaccharide, IL-1, or TNF. In contrast, pulmonary fibroblasts and epithelial cells express IL-8 only in response to a specific host-derived cytokine, IL-1 or TNF. In a similar fashion, MCP is produced by endothelial cells in response to lipopolysaccharide, IL-1, or TNF, whereas pulmonary fibroblasts and epithelial cells express MCP only in response to a specific host-derived cytokine, IL-1 or TNF. In distinction to IL-8, MCP does not appear to be expressed by mononuclear cells in response to lipopolysaccharide. These findings are relevant to an in vivo cytokine network that may contribute to the elicitation of leukocytes into the lung during the pathogenesis of inflammation. Potential strategies for intervening in the generation of this cascade may depend upon a "cocktail approach" using both pharmacologic and immunologic agents.

Recent research has indicated that cytokines, in addition to cytotoxic T-lymphocytes, have a major role in the pathogenesis of both acute and chronic graft-versus-host disease. T-lymphocytes with specificity for recipient-restricted histocompatibility antigens, have been identified in murine models of acute and chronic graft-versus-host disease. Both populations produce cytokines (TNF-α, TNF-β, IL-2, IL-4, γ-interferon) that may have a role in the pathogenesis of graft-versus-host disease.

At least three phases are involved in the development of acute graft-versus-host disease in a murine model (24). The initial afferent phase that occurs during the lymphoproliferative response to alloantigen involves the excessive production of cytokines, including interferon-γ production by CD4+ CD8+ T-lymphocytes, and/or natural killer (NK) cells. These cytokines activate NK or NK-like cells and prime macrophages. The second phase involves an initial injury to epithelial tissues, including the epithelium of the gastrointestinal tract, which appears to be mediated by activated NK or NK-like cells. In the third phase, as a result of injury to the gut epithelium, increasing amounts of gram-negative bacteria enter the portal circulation and are rapidly taken up and killed by Kupffer cells in the liver and by splenic macrophages. Bacterial-derived lipopolysaccharide then triggers the release of large amounts of TNF-α from primed macrophages, resulting in cachexia, further tissue injury, shock, and death of the transplant recipient. The three phases therefore include an afferent phase that leads to the activation of two different effector cells, NK or NK-like cells and macrophages, which in turn mediate the two efferent phases of tissue damage. Although such mechanisms are unproved in lung, the interaction of cellular immune mechanisms and infection, facilitated by cytokines, is a concept of potential importance since therapeutic opportunities exist for intervening in the generation of this cascade at multiple sites with both pharmacologic and immunologic reagents.

Idiopathic pneumonia in its advanced stages is characterized by a fibroproliferative reaction. The mechanisms controlling both cellular proliferation and matrix accumulation likely involve an interaction between fibroblasts and effector molecules (25). Potent stimulators of fibroblast proliferation, e.g., platelet-derived growth factor (PDGF), and fibroblast collagen synthesis, e.g., transform-
2. Promote clinical investigations relevant to the diagnosis, pathogenesis, and treatment of IPS. Unsettled issues related to occult and latent infection and mechanisms involved in the pathogenesis of IPS require ongoing investigation. Current approaches and new, innovative approaches to the clinical assessment of IPS should be encouraged. Few studies have investigated risk factors, prevention, and treatment in IPS. Specific areas where more research is needed include (1) assessment of methods for detection of active and latent viral infection in lavage fluid and cells as well as lung tissue samples; (2) identification of markers or detection methods to diagnose early or mild alveolar injury; (3) assessment of lavage constituents (including cells and bioactive molecules) for indications of alveolar injury or disease activity, and development of strategies for intervention in the development of IPS.

Investigators involved in clinical studies should be encouraged to form a working group, task force, or consortium with a commitment to continue to refine current diagnostic criteria and techniques, assess new methods to aid in diagnosis, and set standards for the collection and preservation of lavage fluid, cells, and lung biopsy material for further study. Participants should consider establishing reference laboratories for specialized studies such as PCR amplification of genetic material for evaluation of latent viruses. The group of participants should also encourage and facilitate interdisciplinary and interinstitutional collaboration in research directed at increasing the knowledge base relevant to the pathogenesis of IPS and planning intervention trials.

3. Promote research into cellular and biochemical mechanisms involved in tissue injury in the transplant setting with specific reference to the lung and IPS. The workshop identified many promising lines of research related to tissue injury in the setting of allogeneic transplantation and generated a number of hypotheses regarding mechanisms relevant to lung injury after marrow transplant. Specific examples of areas where more research is needed include (1) cellular and biochemical mechanisms involved in the afferent phase of the cell-mediated immune response, including the maturation of immunostimulatory cells and mechanisms of amplifying the immune response; (2) characterization and regulation of the inflammatory cell population in IPS such as by cell surface antigens, functional capacity, and cytokine generation; (3) assessment of the capacity of resident lung cells (e.g., epithelial cells and endothelial cells) to produce cytokines and their role in generating the inflammatory and immune response and the pathogenesis of lung injury in IPS; (4) the immunopathologic role of infectious agents, including latent gene expression (e.g., dysregulation of cytokine gene expression and alteration of immune recognition) and gram-negative bacterial products (e.g., lipopolysaccharide and other cell wall constituents); (5) mechanisms involved in radiation and chemotherapeutic drug-induced lung injury as well as strategies to protect the lung without sacrificing therapeutic effects. It is important to encourage the development of these and other research objectives and to stimulate the investigation of mechanisms of injury with specific reference to the lung.

Research in IPS will need to involve scientists from a variety of disciplines and clinical investigators from several specialties. Efforts to stimulate scientific dialogues should continue. Because investigators interested in studying IPS may have limited access to relevant clinical material at a single institution, research initiatives should encourage collaboration between transplant centers.

RECOMMENDATIONS AND FUTURE DIRECTIONS

1. Adopt an operational definition of IPS for use by multicenter registries as well as individual centers. This objective was viewed as central to the success of future clinical, epidemiologic, and laboratory investigations relevant to IPS. The criteria outlined in this summary were felt to be feasible using available technology and to represent a reasonable, but not final, definition.

2. Promote clinical investigations relevant to the diagnosis, patho-
References


