Evidence suggests that obliterative bronchiolitis (OB) following human heart-lung transplantation is a form of allograft rejection related to augmented expression of class II major histocompatibility complex antigens (MHCII) on airway epithelium and mediated by activated T cells. Other forms of OB, including those related to viral infection and autoimmune disease, may reflect a similar mechanism.

Airway disease associated with pathologic evidence of obliterative bronchiolitis (OB) has emerged as the most important long-term complication of heart-lung transplantation, occurring in 50 percent of the patients who left the hospital with normal cardiopulmonary function. Early observations showed the development of obstructive physiology demonstrated by lung function studies, and the disorder most accurately could be described as unexplained, unclassified obstructive lung disease (UUOLD). As histologic material was reviewed, it became apparent that the major cause of the obstructive physiologic defect was obliterative bronchiolitis. All ten patients showing obstructive physiologic features from whom lung tissue was available demonstrated obliterative bronchiolitis on pathologic analysis. To date, the pathophysiology of post-transplant airway disease is poorly understood.

The pathologic features of pulmonary rejection have been investigated extensively in animal models and consist of perivascular and peribronchial cellular infiltration, alveolar exudation, and terminal necrosis. However, interpretation of these studies is complicated by the presence of infection and a lack of uniformity in donor-recipient matching, immunosuppressant regimens, and experimental protocols. A recent animal study overcame many of these problems and described four stages of acute pulmonary rejection in inbred rats which were not immunosuppressed. The initial latent phase was sequentially followed by the vascular phase (infiltration of recipient lymphocytes around graft blood vessels, airways, and bronchus-associated lymphoid tissue), the alveolar phase (lymphocyte accumulation in alveolar walls and spaces), and the destruction phase (cellular necrosis and alveolar exudation). However, extrapolation of these findings to the clinical arena is complicated by the impracticality of donor-recipient HLA matching in humans because the paucity of donors, the use of immunosuppressant regimens to modify the rejection process, and immunologic differences between subprimates and humans. Furthermore, the prevalence and severity of OB in human heart-lung transplant recipients is clearly disproportionate to the relatively minor airway changes described in animal models of acute rejection.

LUNG IMMUNOGENICITY

It is generally accepted that the immunogenicity of allografts depends on their expression of class II major histocompatibility complex antigens (MHCII). Recognition of donor (foreign) class II antigens by recipient lymphocytes results in the generation of allospecific activated helper T lymphocytes, which then mediate graft rejection. Allograft rejection is therefore stimulated by the expression of MHCII antigens and effected by activated T cells. In general, these considerations suggest that rejection could theoretically be modified not only by attenuation of the effector response, but also by manipulation of the immunologic stimulus. Specifically, downregulation of allograft MHCII antigenic expression could reasonably be expected to modify rejection by reducing or preventing the activation of recipient lymphocytes. To date, clinical management of transplant recipients emphasizes suppression of the effector response, but limited data are available to evaluate the diagnostic and thera-
HypothESIS

These considerations may be relevant to the development of OB in the transplanted lung. Unlike other transplanted organs, the lung is subjected to a continuous bombardment of antigenic stimuli (both infective and noninfective) from the ambient air, and current evidence suggests that microaspiration of pharyngeal flora occurs commonly in normal subjects. The prevalence of viruses suggests that viral inhalation or aspiration with γ-interferon generation must be a common event. It may be speculated that antigen deposition results in airway inflammation with upregulation of bronchial epithelium MHCII expression, activation of recipient T lymphocytes, and a rejection reaction centered on the airways (Fig 1). Some clinical support for these observations is provided by our recent report of a heart-lung transplant recipient who developed bronchitis in three separate occasions following culture-proven viral respiratory tract infection.

Inhaled factors may be especially critical in the transplanted lung devoid of autonomic innervation.

Bronchial hyperreactivity has been universally present in all of our transplant recipients studied to date (perhaps related to parasympathetic muscarinic denervation hypersensitivity), and the precise effects of denervation on other aspects of airway function including cough reflexes and mucociliary clearance is unknown. Impaired clearance of inhaled antigens may increase their immunogenicity and provide another reason for targeting of the immune response onto the airway.

Lung allografts, unique among transplanted organs in being continuously exposed to the atmosphere, are unusual in another respect in that bronchus-associated lymphoid tissue contains a large number of bone marrow-derived cells including lymphocytes, macrophages, and dendritic cells. Expression of MHCII antigens is documented to occur on the surface of these cells, so they could be expected to stimulate a rejection response after transplantation. The recent demonstration in animals that one of the earliest signs of lung rejection is infiltration of donor lymphocytes into recipient peribronchial lymphoid tissue is in accord with these observations.

We therefore suggest that the native immunogenicity of immunocytes concentrated in bronchus-associated lymphoid tissue, together with upregulation of bronchial epithelial immunogenicity, explains why airway disease has emerged as the most important clinical complication in heart-lung transplant recipients.

DIsCUSSION

Experimental evidence that MHCII expression is necessary for activation of allograft specific helper T lymphocytes, together with preliminary evidence in rats showing MHCII expression associated with rejection and a recent clinical study in renal transplant recipients, suggests that MHCII expression may prove to be a sensitive index of lung rejection. No data are currently available to evaluate the specificity of such a finding. While a wide variety of stimuli are now known to upregulate MHCII expression, the frequency of a consequent rejection reaction is unknown. Undoubtedly, other factors including the degree of donor-recipient mismatch, expression of different antigens, recipient immunologic responsiveness, and the nature of immunosuppressant therapy, all influence the response to upregulated MHCII. Nevertheless, increased expression of MHCII appears useful in the diagnosis of renal rejection, and a similar finding in lung allografts, even if not absolutely specific, might at least serve to identify patients at increased risk of rejection.

The diagnostic and therapeutic significance of lung immunogenicity should be amenable to in vivo investigation in both the animal laboratory and the
clinical arena. Using MHCII expression as an index of lung immunogenicity and given the availability of a suitable primate model, it should be possible to establish indices of immunogenicity at baseline (prior to transplantation) and sequentially after surgery. Comparison of MHCII expression with tissue histology and physiologic variables should determine both the sensitivity and specificity of MHCII expression in the diagnosis of rejection. Furthermore, in the light of recent data suggesting that downregulation of MHCII expression (in addition to suppression of the effector response) may be an important component of the antirejection action of both corticosteroids and cyclosporin, the value of titration of immunosuppressant regimens to optimize downregulation of MHCII expression could be explored.

If preliminary results in animals are encouraging, graft surveillance following clinical lung transplantation could be achieved by prospective endobronchial biopsies to monitor MHCII expression on bronchial epithelium. Survival following clinical heart transplantation was greatly improved when graft surveillance by endomyocardial biopsy became possible; a similar impact on survival following lung transplantation might be expected if the degree of MHCII expression on bronchial epithelium proved diagnostically useful. Unlike open lung biopsy, sequential endobronchial biopsies following transplantation are feasible and hardly more invasive than the current practice of obtaining sequential endomyocardial biopsies in heart transplant recipients. The risks vs benefits to transplanted patients would, however, require elucidation.

CONCLUSION

A reduction in allograft immunogenicity may be as effective as attenuation of the effector response in the treatment of rejection, and the recently documented effect of cyclosporin and corticosteroids in reducing MHCII expression may be an important component of their antirejection action. Specifically, airway disease following lung transplantation may be related to upregulation of MHCII on bronchial epithelium, and monitoring of MHCII expression may provide both a sensitive index of pulmonary rejection and a useful guide to its treatment. In general, increased awareness of the factors influencing immunogenicity should pay dividends not only in management of transplant recipients, but also in patients suffering from autoimmune disease and in the elucidation of precise mechanisms of action of immunosuppressant drugs. In conclusion, there is substantial evidence that induction of MHCII expression is an important mechanism in allograft rejection. This mechanism may be responsible for posttransplant OB and may also be important in other forms of OB, including those associated with viral infection and autoimmune disease.

REFERENCES