

## Lung Transplantation

### Report of the ATS Workshop on Lung Transplantation

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#### PURPOSE

In the last 20 years, transplantation of the kidney, liver, and heart has become an important therapeutic option for patients with irreversible failure of these organs. Clinical application of lung transplantation has evolved more recently and, on October 2 to 4, 1991, the American Thoracic Society convened a workshop to review the current state-of-the-art in this field. This report attempts to summarize current knowledge and practice, with special emphasis on those factors unique to lung transplantation and those program and patient-related factors that appear to be associated with successful outcome.

#### HISTORY

Although lung transplants were performed as early as 1963 (1), these pioneering efforts failed for a variety of reasons. The most important of these related to the lack of modern immunosuppressive drugs at that time. High-dose corticosteroids, which were the principal method of immunosuppression, severely impaired bronchial healing and increased the susceptibility of recipients to infection (reviewed in reference 2). Because of the high rate of failure, lung transplantation efforts were virtually abandoned from 1973 until the early 1980s, when the introduction of cyclosporine A as a powerful immunosuppressant and an alternative to corticosteroids resulted in renewed interest in this procedure.

Combined heart-lung transplantation was introduced at Stanford University (Stanford, CA) for primary pulmonary hypertension in 1981 (3), and for end-stage pulmonary vascular disease of any etiology at the University of Pittsburgh (Pittsburgh, PA) in 1982 (reviewed in reference 4). The Toronto Transplant Group reported successful single lung transplantation in 1986 for pulmonary fibrosis in two patients (5). In recent years, single lung transplantation has also been performed in patients with chronic obstructive pulmonary disease (6), some forms of Eisenmenger's syndrome (7), and primary pulmonary hypertension (7). Double lung transplantation has been performed in the same situations in which single lung transplantation has been performed and is particularly suited for cystic fibrosis and other types of bronchiectasis (8).

Expansion in this field is reflected in the following statistics. In the United States (9):

- 182 lung transplants and 56 heart-lung transplants were performed in 1990.
- As of October 1991, 600 patients were awaiting lung transplants; 169 were awaiting heart-lung transplants.

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- Of the 265 transplant centers, 77 centers perform lung transplants and 82 perform heart-lung transplants.

The St. Louis International Lung Transplant Registry has recorded 890 transplants occurring worldwide from November 1983 to October 1991, 481 of which were performed in the United States (JD Cooper, personal communication). Frequency of lung transplantation is currently limited by the scarcity of organ donors. However, as noted in the assessment report of the Agency for Health Care Policy and Research, "lung transplantation has evolved as a clinical procedure achieving a favorable risk-benefit ratio and acceptable 1- and 2-year survival rates" (10).

#### SUCCESSFUL LUNG TRANSPLANTATION: PROGRAM-RELATED FACTORS

Several program-related factors have been identified as being important in the outcome of lung transplants. These include donor and recipient selection, accurate diagnosis of rejection, transplant center characteristics, and choice of procedure.

#### Donor-related Issues

The most important donor-related issues are how donor acceptability is determined, how the acceptable cadaver donor is managed, and what methods are used to preserve the donated organ itself. Although donor selection criteria may vary, generally used guidelines are outlined in table 1. Other factors merit consideration. Although not absolutely necessary, ABO identity and matched cytomegalovirus (CMV) serology between donor and recipient are desirable. The use of ABO-compatible, but not identical, donors may result in the development of potentially life-threatening hemolytic anemia mediated by immunocompetent donor cells present in the donor organ. Although it is desirable to use CMV negative donors for CMV negative recipients (11), since CMV mismatching may be associated with CMV disease, it is usually not practical to select only matched donors due to extensive CMV exposure. Most transplant programs will use a CMV-positive donor for transplantation into a negative recipient. Ganciclovir has been shown to be effective in the prevention of infection in high-risk patients and the treatment of patients with CMV pneumonia (12).

In October 1990, the first lung transplant using a living donor was performed at Stanford University (13). Despite the shortage of cadaveric organ donors, the use of living donors is not a generally accepted alternative due to the potential risk to the donor that may result from reduced pulmonary reserve (14). The use of a single lobe rather than a whole lung may reduce the risk to the donor. However, it is unknown if the lung will grow and, if not, single lobe transplantation may lead to insufficient pulmonary function in the growing pediatric patient, thereby reducing the benefit to the recipient. Long-term survival rates with lobar transplants from living donors are unknown at this time.

The general shortage of organ donors makes it imperative to use donor management strategies that will maintain all transplantable organs in the optimal functional state. Volume repletion nor-

TABLE 1  
GENERAL DONOR SELECTION GUIDELINES\*

Age: < 65 for lung; < 45 for heart-lung
No severe chest trauma or infection
Clear chest X-ray (exceptions may occur)
No prolonged cardiac arrest (heart-lung only)
Minimal pulmonary secretions
Negative HIV screen
ABO compatibility
Similar total lung capacities

*Definition of abbreviation:* HIV = human immunodeficiency virus.

\* Adapted from Lawrence EC, Holland VA, Berger MB, Noon GP, Short HD, Whisennand HH, De Bakey ME. Lung transplantation: an emerging technology. *Tex Med* 1988; 84:61-7.

mally utilized to maintain adequate urine output in renal donors is at odds with maintenance of adequate lung function by volume restriction. However, optimal management of both kidneys and lungs may be achieved by maintenance of a low central venous pressure and fluid replacement sufficient to maintain adequate blood pressure and adequate but not excessive urine output. After organ recovery, the lungs are usually flushed with donor blood or Eurocollins solution and then maintained in cold Eurocollins solution (reviewed in reference 15), permitting preservation of the organ for 6 to 8 hr. Additional research is needed to develop procedures to extend lung preservation time.

#### Recipient-related Issues

The overall goal of recipient selection is to identify individuals whose pulmonary function and prognosis justify transplantation and whose current health will not increase the risk of the operation unnecessarily or jeopardize its long-term success. Currently used general guidelines for the selection of potential recipients are provided in table 2. Although recipient selection criteria have remained stringent overall, a major change accepted by many institutions has been a relaxation in the criterion prohibiting pretransplant corticosteroid treatment. Low-dose pretransplant corticosteroid therapy has proved to be acceptable and would allow transplantation of patients who cannot be completely weaned from such therapy (16). Other contraindications to lung transplantation are listed in table 3.

Clinical indications for lung transplantation vary depending on the disease state. Currently, the major diseases for which lung transplantation is a therapeutic option include pulmonary vascular disease (e.g., primary pulmonary hypertension, Eisenmenger's syndrome); obstructive lung disease (e.g., idiopathic emphysema,  $\alpha_1$  antitrypsin deficiency emphysema, cystic fibrosis, and bronchiectasis); and restrictive lung disease (e.g., idiopathic pulmonary fibrosis, sarcoidosis, asbestosis, eosinophilic granulomatosis, desquamative interstitial pneumonitis).

It has been estimated that patients with primary pulmonary hypertension have a median survival of 2.8 yr, with the main causes of death being progressive right ventricular failure or sudden death

TABLE 2  
GENERAL RECIPIENT SELECTION GUIDELINES\*

Untreatable end-stage pulmonary vascular disease of any etiology
No other significant medical diseases
Substantial limitation of daily activities
Limited life expectancy
Ambulatory with rehabilitation potential
Acceptable nutritional status
Satisfactory psychosocial profile and emotional support system

\* Adapted from Egan and colleagues (19).

TABLE 3  
CONTRAINDICATIONS FOR LUNG TRANSPLANTATION\*

Active extrapulmonary infection
Significant disease of other organ systems
Current cigarette smoking
Poor nutritional status
Poor rehabilitation potential
Significant psychosocial problems, substance abuse, or history of medical noncompliance

\* Adapted from Marshall and colleagues (21).

syndrome (17). Factors correlated with mortality include cardiac disease resulting in marked limitation of physical activity, Raynaud's phenomenon, and hemodynamic variables. These factors are currently used for selecting patients for transplantation. Cystic fibrosis is a disease with a highly variable course; however, improvements in symptomatic therapy have increased survival rates (reviewed in reference 18). Although a variety of factors have been found to determine survival, clinical indicators such as frequency of hospitalization and antibiotic use and weight loss are more useful in predicting survival than are empiric measurements of respiratory function (reviewed in reference 19). Patients with idiopathic pulmonary fibrosis inevitably experience declines in functional status, most frequently due to disease progression (20). It is often difficult to distinguish clinical deterioration from disease-associated complications or adverse effects of therapy; however, mortality is most frequently due to respiratory failure (reviewed in reference 19). Factors considered in selecting patients for transplantation include severe dyspnea, honeycombing/pulmonary hypertension on chest X-ray or computerized tomographic scan, and severe physiologic derangement. Older patients with chronic obstructive pulmonary disease have a worse prognosis, as do patients with poor exercise tolerance, hypoxemia, hypercapnia, and cor pulmonale (reviewed in reference 12).

The extended waiting time for lung transplants is a direct result of the shortage of organ donors, as evidenced by the following December 1990 data from the United Network for Organ Sharing. Of the 226 patients awaiting heart-lung transplants, 47% had been waiting for more than 1 yr. Of the 309 patients awaiting lung transplants, approximately 12% had been waiting for more than 1 yr (9). Because of the long waiting time for donor organs, patients are often referred for transplant evaluation when a major decline in their condition is observed. Because of the rapid course of both pulmonary hypertension and pulmonary fibrosis, some clinicians favor referral at the time of diagnosis. However, at present, there is a lack of adequate data to determine the optimal referral time. The term "transplant window" has been used to refer to the period of time when the patient is sick enough to require transplantation and healthy enough to have a reasonable probability of success (21). Recent trends in the number of lung and heart-lung transplants by disease group are shown in table 4.

#### Choice of Procedure

The successful extension of single lung transplantation to obstructive lung diseases and pulmonary vascular disease, and the development of the bilateral sequential approach to "double" lung transplantation have diversified the choice of procedure for end-stage lung disease. A dogmatic approach cannot be justified in such a rapidly evolving area; however, some elements to be considered in choosing the procedure include shortage of organ donors, the nature of the original disease, and the likelihood for success based on our experience with graft function, graft survival, and patient survival.

TABLE 4  
NUMBER OF LUNG AND HEART-LUNG TRANSPLANTS\*

Year	COPD	$\alpha$ 1ATDef	CF	IPF	1PH	2PH
1987	5	4	1	20	1	0
1988	17	9	8	22	1	1
1989	33	21	14	35	14	3
1990	60	50	44	46	28	10

Definition of abbreviations: COPD = chronic obstructive pulmonary disease;  $\alpha$ 1ATDef = alpha-1 antitrypsin deficiency; CF = cystic fibrosis; IPF = idiopathic pulmonary fibrosis; 1PH = primary pulmonary hypertension; 2PH = secondary pulmonary hypertension.

\* Source: JD Cooper, personal communication.

Optimal use of the very limited pool of donor organs can best be achieved by using lung-only transplants when possible, thus reserving hearts for those patients needing heart or heart-lung transplants. A general framework for selection of procedure based on the nature of the original disease is provided in table 5. In addition to the diseases noted in table 5, bilateral lung transplantation may be considered for patients with significant chronic bronchitis and may be preferable in patients with extensive bullae in both lungs. The best procedure (single versus bilateral) for severe obstructive lung disease has not been determined. Single lung as well as bilateral single lung transplantation for pulmonary hypertension has produced good results in patients with primary pulmonary hypertension and Eisenmenger's syndrome associated with reparable cardiac defect, but these procedures are perhaps the most difficult in lung transplantation at the present time (reviewed in reference 19). Although right ventricular function generally improves quickly after lung transplantation, intraoperative and postoperative patient management is complex because of the imbalance between ventilation, which is evenly distributed between the native and transplanted lung, and cardiac output which is directed almost exclusively to the allograft (12). Therefore, the relative merits of single versus bilateral single lung transplantation in the pulmonary hypertension patient require further evaluation.

#### Transplant Center Characteristics

Although there is limited experience with lung transplantation, the extensive experience in transplantation of other organs suggests that certain features of the transplant center are associated with enhanced success. Those standard features which are generally accepted as well as those desirable to enhance the program are listed in table 6. Because of the limited experience in lung transplantation, the list of minimal and desirable features cannot be comprehensive. Certainly there are successful transplant programs which do not currently include all "desirable" features. However, experience in transplantation of other organs has shown that, on the average, the number of procedures performed does correlate with transplant success as measured by improved graft sur-

TABLE 6  
TRANSPLANT CENTER FEATURES

<b>Standard Features</b>
Well-qualified medical and surgical personnel
Local and readily available support in all necessary areas, particularly immunology, pulmonary medicine, infectious diseases, cardiology, and rehabilitation
Adequate experience in transplantation medicine
<b>Desirable features</b>
Qualified house staff available on a 24-h basis
Number of lung transplants performed is adequate to develop and maintain proficiency
Active programs in basic and clinical research related to transplantation

vival (22-24). Further, the availability of an active research program may facilitate development of new and improved protocols.

#### SUCCESSFUL LUNG TRANSPLANTATION: PATIENT-RELATED FACTORS

The International Lung Transplant Registry, which includes a total of 849 lung transplant procedures performed to date, reports a 1-yr survival rate of 61% overall, and a 2-yr survival rate for single lung transplants of 56% (10). Data from the registry of the United Network of Organ Sharing show a 1-yr graft survival rate of 52.3% for 132 lung transplants performed in the United States during the period October 1, 1987 to December 31, 1989 (25). Several of the patient-related factors affecting graft and patient survival (e.g., rejection, infection, and obliterative bronchiolitis), are discussed below.

#### Rejection

In the past, diagnosis of acute rejection has been made on the basis of increasing radiographic infiltrates, decreasing oxygenation, fever, and decreasing perfusion on perfusion scans in single lung recipients. All of these findings and studies, however, are not specific for lung rejection. Infection and adult respiratory distress syndrome can also cause these abnormalities (26). Large doses of corticosteroids will also temporarily suppress the inflammation associated with an infectious process, leading to the misguided belief that rejection has been successfully treated. A useful clinical measure for the diagnosis of rejection has been the response to a pulse dose of intravenously administered methylprednisolone, particularly in the first 2 to 3 wk after transplantation. Decreases in radiographic infiltrates, improvement in oxygenation, reduction in temperature, and improvement in exercise tolerance, sense of well-being, and improvement in perfusion scans occur over a 12 to 24-hr period. However, if the underlying process were infection due to bacteria or fungus, such an approach could lead to clinical deterioration. The use of bronchoscopy with

TABLE 5  
TRANSPLANTATION PROCEDURE BY DISEASE STATE\*

Transplantation Procedure	Disease State
Heart-lung	Eisenmenger's syndrome with irreparable cardiac defect; pulmonary hypertension with cor pulmonale; end-stage lung disease with concurrent severe cardiac disease
Double lung	Cystic fibrosis; generalized bronchiectasis; some patients with COPD
Single lung	Restrictive fibrotic lung disease; Eisenmenger's syndrome with reparable cardiac anomaly; some patients with COPD; primary pulmonary hypertension

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

\* Adapted from Egan and colleagues (19).

transbronchial biopsy is more often helpful than clinical criteria in diagnosing rejection. However, lung biopsy is invasive and accompanied by risks (27). Bronchoalveolar lavage is a less invasive procedure than transbronchial biopsy and has been used to try to distinguish between infection and acute rejection. While important differences are present in the types and functions of the cells recovered during the different clinical events, sufficient overlap exists that no single combination of parameters can, as yet, be used to distinguish reliably between infection and rejection (28). It has been suggested that the donor-specific primed lymphocyte response of bronchoalveolar lavage cells is useful in the diagnosis of lung allograft rejection (29), but additional research is needed to clarify this issue.

Immunosuppressive protocols for induction, maintenance, and/or treatment of rejection in lung and heart-lung transplantation are continuing to evolve. Current regimens use various combinations of cyclosporine, azathioprine, prednisone, and antilymphocyte or antithymocyte globulins. The approach currently used by most centers is a three-drug combination.

#### Infection

The primary determinant of early patient survival is infection. Bacterial pneumonia is common in the early postoperative period, but it is also a major infectious complication in the intermediate and late postoperative periods (30). Contributing factors in the development of bacterial pneumonia include immunosuppression and alterations in the natural lung defense mechanisms induced by transplantation. In the late postoperative period, the major predisposing factor appears to be the presence of chronic rejection. Parenteral antibiotics tailored to the etiologic agents and their sensitivities are the mainstay of treatment and are, fortunately, usually effective (31).

CMV is the most common cause of infection in the interval from 4 to 8 wk postoperatively. The rate of infection is affected by the serologic status of the recipient, the organ donor, and blood donors as discussed above. The use of oral acyclovir and intravenous ganciclovir for prophylaxis and treatment may provide some benefit (12). While bronchoalveolar lavage can reliably detect CMV infection in the allograft, accurate diagnosis of CMV pneumonitis may require a lung biopsy. Transbronchial biopsy has been a highly reliable technique for distinguishing between CMV infection and disease (32).

#### Obliterative Bronchiolitis

Obliterative bronchiolitis (reviewed in reference 33) in the post-transplant period is characterized by a progressive form of obstructive airway disease that can be fatal. Although the precise nature of obliterative bronchiolitis is yet to be defined, it is generally thought to represent chronic rejection of the allograft. It is characterized by an inflammatory process with a particular propensity for the smaller airways and bronchioles of the transplanted lung. These changes are similar to those found in obliterative bronchiolitis in other clinical settings. The incidence of obliterative bronchiolitis in long-term survivors of heart-lung transplants ranges from 10 to 54%; it has also been reported to occur in patients with single lung transplants, although the incidence is not yet known.

Earlier detection of obliterative bronchiolitis, via surveillance of pulmonary function and performance of transbronchial biopsies, has provided a clearer picture of airway involvement. Although current methods of diagnosis and treatment have somewhat altered the course of obliterative bronchiolitis, the key clinical features are an insidious onset of cough, which usually becomes in-

creasingly productive of purulent sputum, recurrent bacterial infections of the airway and parenchyma, and dyspnea.

Treatment of obliterative bronchiolitis has involved optimal maintenance immunosuppression and varies depending on the presence or absence of co-existing acute rejection. It is unclear at what point the increased risk of infection due to immunosuppressive therapy outweighs its benefits for the treatment of obliterative bronchiolitis. In addition, the role of adjunctive therapy, such as bronchodilators and aerosolized corticosteroids, is not clear at this time.

#### SUMMARY

This workshop has identified several factors associated with enhanced success, some major gaps in knowledge, and some unresolved issues in the field of lung transplantation. A summary of the most salient points is provided below.

##### What Are the Facts about Lung Transplantation?

- Improvements in donor and recipient selection, in immune suppression, and in surgical techniques have collectively led to enhanced survival.
- There has been an expansion in the number of diseases for which lung transplantation is a therapeutic option.
- There has been considerable expansion in the number of clinical programs performing lung transplants.
- There remains a very limited pool of donor organs and long waiting times for potential transplant recipients.

##### What Additional Knowledge Is Needed?

- Better definition of the role of histocompatibility antigens in successful engraftment
- Development of optimal methods of preserving cadaveric donor lungs
- Better definition of the optimal window for transplantation for various diseases
- Definition of the long-term outcome of single lobe transplants in pediatric patients
- Improved methods to prevent, differentiate, diagnose, and treat rejection, infection, and obliterative bronchiolitis
- Determination of the full range of diseases for which lung transplantation can be considered an appropriate therapeutic option
- Long-term outcome in single versus double lung transplantation.

##### What Issues Remain Unresolved?

- At present, lung transplantation is not considered part of the usual and customary repertoire of procedures uniformly covered by public and private health insurance. As a result, the recipient population is restricted largely to those with private insurance and cases considered as special exceptions under federal financing programs.
- The potential for increasing the limited pool of donor organs through expanded use of living donor lobes poses ethical and clinical concerns.
- A series of issues is brought into play when any procedure evolves from the research to the clinical setting. Lung transplantation is no exception and the same dilemmas apply, including: For whom will this procedure be available? What are the ethical criteria in the procurement of tissue? How do transplantation needs relate to donor availability? When is it cost-effective? What social burden will this place on public and private financing of care?

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#### References

- Hardy JD, Webb WR, Dalton ML, Walker GR. Lung homotransplantation in man: the initial case. *JAMA* 1963; 186:1064-84.
- Montefusco CM, Veith FJ. Lung transplantation. *Surg Clin North Am* 1986; 66:503-15.
- Reitz BA, Wallwork JL, Hunt SA, Pennock JL, Billingham ME, Oyer PE, Stinson EB, Shumway NE. Heart-lung transplantation. Successful therapy for patients with pulmonary vascular disease. *N Engl J Med* 1982; 306:557-64.
- Griffith BP, Hardesty RL, Trento A, Paradis IL, Duquesnoy RJ, Zeevi A, Dauber JH, Dummer JS, Thompson ME, Gryzan S. Heart-lung transplantation: lessons learned and future hopes. *Ann Thorac Surg* 1987; 43:6-17.
- Toronto Lung Transplant Group. Unilateral lung transplantation for pulmonary fibrosis. *N Engl J Med* 1986; 314:1140-5.
- Trulock EP, Egan TM, Kouchoukos N, Kaiser LR, kPasque MK, Ettinger N, Cooper JD. Single lung transplantation for severe chronic obstructive pulmonary disease. *Chest* 1989; 96:738-42.
- Trulock EP, Cooper JD, Kaiser LR, Pasque MK, Ettinger NA. Washington University Lung Transplantation Group. Unilateral lung transplantation for pulmonary hypertension (abstract). *Am Rev Respir Dis* 1991; 143:A467.
- Pasque MK, Cooper JD, Kaiser LR, Haydock DA, Triantafillou A, Trulock EP. Improved technique for bilateral lung transplantation. *Ann Thorac Surg* 1990; 49:785-91.
- United Network for Organ Sharing. Annual Report for January 1, 1990-June 30, 1991. Richmond, VA: UNOS, 1991; 19-26.
- U.S. Public Health Service. Single and double lung transplantation. Health Technology Assessment Reports. Washington, DC: Agency for Health Care Policy and Research Publications Clearinghouse, 1991. DHHS Publication No. PB92-156793.
- Smyth RL, Higenbottam TW, Scott JP, Wallwork J. Transplantation of the lungs. *Respir Med* 1989; 83:459-66.
- Cremona G, Higenbottam TW, Wallwork JL. Transplantation for end-stage lung disease. *Respiration* 1991; 58:22-9.
- Goldsmith MF. Mother to child: first living donor lung transplant. *JAMA* 1990; 264:2724.
- Shaw LR, Miller JD, Slutsky AS, Maurer JR, Puskas JD, Patterson GA, Singer PA. Ethics of lung transplantation with live donors. *Lancet* 1991; 338:678-81.
- Reitz BA. Heart and lung transplantation. In: Baumgartner WA, Reitz BA, Achuff SC, eds. Heart and heart-lung transplantation. Philadelphia: WB Saunders, 1990; 319-46.
- Bryan CL, Anzueto A, Levine SM, Zamora CA, Calhoon JH, Grover FL, Trinkle JK. Corticosteroid therapy does not potentiate bronchial anastomotic complications in single lung transplantation (SLT) (abstract). *Am Rev Respir Dis* 1991; 143:A461.
- D'Alonzo GE. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115:343-9.
- Boat TF. Cystic fibrosis. In: Murray JS, Nadel JA, eds. Textbook of respiratory medicine. Philadelphia: WB Saunders, 1988; 1126-52.
- Egan TM, Kaiser LR, Cooper JD. Lung transplantation. *Curr Prob Surg* 1989; 26:673-751.
- Panos RJ, Mortenson R, Niccoli SA, King TE. Clinical deterioration in patients with idiopathic pulmonary fibrosis: Causes and assessment. *Am J Med* 1990; 88:396-404.
- Marshall SE, Kramer MR, Lewiston NJ, Starnes VA, Theodore J. Selection and evaluation of recipients for heart-lung transplantation. *Chest* 1990; 98:1488-1494.
- Evans RW, Manninen DL, Dong FB. The National Cooperative Transplant Study: Final report. The center effect in kidney transplantation: I. Preliminary results. Seattle, WA: Batelle-Seattle Research Center, June 1991. Publication No. BHARC-100-91-020; 38-i-38-10.
- Evans RW, Manninen DL, Dong FB. The National Cooperative Transplant Study: Final report. The center effect in kidney transplantation: II. Final results. Seattle, WA: Batelle-Seattle Research Center, June 1991; 39-i-39-42.
- Evans RW, Manninen DL, Dong FB. The National Cooperative Transplant Study: Final report. The center effect in heart transplantation. Seattle, WA: Batelle-Seattle Research Center, June 1991; 40-i-40-34.
- Annual Report of the U.S. Scientific Registry for Organ Transplantation and the Organ Procurement and Transplantation Network 1990. UNOS, Richmond, VA: UNOS and Bethesda, MD: the Division of Organ Transplantation, Health Resources and Services Administration.
- Paradis IL, Duncan SR, Dauber JH, Yousem S, Hardesty R, Griffith B. Distinguishing between infection, rejection, and the adult respiratory distress syndrome after human lung transplantation. *J Heart Lung Transplant* 1992; 11:5232-8.
- Higenbottam T, Stewart S, Penketh A, Wallwork J. Transbronchial lung biopsy for the diagnosis of rejection in heart-lung transplant recipients. *Transplant* 1988; 46:532-9.
- Rabinowich H, Zeevi A, Yousem SA, Paradis IL, Dauber JH, Kormos R, Hardesty RL, Griffith BP, Duquesnoy RJ. Alloreactivity of lung biopsy and bronchoalveolar lavage-derived lymphocytes from pulmonary transplant patients: correlation with acute rejection and bronchiolitis obliterans. *Clin Transplant* 1990; 4:376-84.
- Rabinowich H, Zeevi A, Paradis IL, Yousem SA, Dauber JH, Kormos R, Hardesty RL, Griffith BP, Duquesnoy RJ. Proliferative responses of bronchoalveolar lavage lymphocytes from heart-lung transplant patients. *Transplantation* 1990; 49:115-21.
- Dauber JH, Paradis IL, Dummer JS. Infectious complications in pulmonary allograft recipients. *Clin Chest Med* 1990; 11:291-308.
- Tuna IC, Jamieson SW. Human heart and lung transplantation. *Adv Surg* 1989; 22:251-76.
- Paradis IL, Grgurich WF, Dummer JS, Dekker A, Dauber JH. Rapid detection of cytomegalovirus pneumonia from lung lavage cells. *Am Rev Respir Dis* 1988; 138:697-702.
- Theodore J, Starnes VA, Lewiston NJ. Obliterative bronchiolitis. *Clin Chest Med* 1990; 11:309-21.