S T A T U S O F
L U N G T R A N S P L A N T A T I O N
1 9 9 0

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"Reimplantation of a detached extremity is as impossible as making a philosopher out of a monkey or trying to fly in air".

Hieronymus Brunschwig 1497 (1)

Status of Lung Transplantation in 1990

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I. Historical

In the last century heart-lung, double and single lung transplants have evolved from experimental procedures to clinically relevant, life saving operations. Historic milestones in heart and lung transplantation are listed in Table 1 (2, 3).

TABLE 1

Historic Milestones in Heart-Lung Transplantation

1905	First experimental heart-lung transplant.
1946	Surgical techniques perfected for heart-lung transplants.
1957	Cardiopulmonary bypass introduced.
1963	First single lung transplant in humans.
1968	First heart-lung transplant in humans.
1976	Introduction of Cyclosporin A immunosuppression.
1981	First successful heart-lung transplantation in humans.

The origin of heart and lung transplantation dates back to the beginnings of vascular surgery by Carrel who performed the first heterotopic heart-lung transplant in 1905 (4-6). In the 1940's the prolific Russian Demikhov exhaustively described improved surgical techniques that could adequately sustain animal life (7). Unfortunately, his techniques were not immediately available to the Western world. Following Webb's introduction of cardiopulmonary bypass in 1957, Hardy is credited with performing the first human single lung transplant in 1963. This initial procedure was technically successful but able to sustain life for only 18 days due to infection (8, 9). It was not until five years later that Cooley attempted the first human heart-lung transplant which was also clinically unsuccessful. Thus, the technical feasibility of transplants was established in humans by 1968. Marcus had introduced immunosuppression with cortisone in 1952, but there was little impact on the viability of transplants in humans (10). However, it was not until 1976 when Borel used Cyclosporin A instead of cortisone for immunosuppression that transplantation became a clinically viable procedure (11, 12). Subsequent refinements of immunosuppressive regimens allowed the technique to come of age in 1981 when the Stanford Group reported the first successful long term results of heart-lung transplantation in patients with pulmonary vascular disease (13). During the last decade single and double lung transplants have also evolved into reasonable options for the therapy of several end stage pulmonary diseases.

II. Incidence

The rapid developments in the field make an estimate of the number of procedures or the Centers in which they were performed

somewhat imprecise. The two sources of this information are the United Network for Organ Sharing (UNOS), which is a compulsory register of all transplants performed in the United States, and the International Lung Transplant Registry at Barnes Hospital, which records voluntarily reported foreign procedures. The recent striking increase in lung transplants performed in the United States is reflected by the data from UNOS in Table 2.

TABLE 2

Incidence of Lung Transplantation
in the United States

	1988	1989
Single/Double Lung	31	90
Heart-Lung	74	66
Total	105	156

UNOS reported that 31 single (SLT) or double lung transplants (DLT) were performed in 1988. In 1989 there was a three-fold increase to 90 procedures. During the same interval heart-lung transplants decreased from 74 to 66. This decrease in heart-lung transplantation reflects both an effort to maximally utilize donor organs and the success of single and double lung transplants. Data from the International Registry, which also include procedures reported to UNOS, are given in Table 3. Reporting began in 1983 and is current through April, 1990 (14).

TABLE 3

Cumulative Incidence of SLT and DLT

	1983-88	1983-90
Single Lung	51	209
Double Lung	37	96
Total	88	305

A total of 88 single and double lung transplants were reported through the end of 1988. The data for 1983-90 indicate that since 1988 there has been a four-fold increase in single lung but only a two and a half-fold increase in double lung transplants. Precise combined heart-lung data are not available for this time period.

III. Indications and Contraindications

For a patient to be considered for a lung transplant, the referring physician must first contact one of the Transplantation Centers. The thirteen Centers listed in Table 4 currently report outcomes to either UNOS or The International Lung Transplant Registry (15).

TABLE 4

Referral Centers for Heart-Lung and Lung Transplantation

Johns Hopkins University	Baylor College of Medicine
University of Pittsburgh	Vanderbilt University
University of Minnesota	University of Arizona
Stanford University	University of Mississippi
Harefield Hospital, England	Toronto General Hospital
Papworth Hospital, England	Barnes Hospital
	University of Texas-San Antonio

Of these institutions Johns Hopkins University, University of Pittsburgh, University of Minnesota, Stanford University and Harefield and Papworth Hospitals in England presently perform heart-lung transplants almost exclusively. The preferences for Baylor College of Medicine in Houston, Vanderbilt, Arizona and Mississipppi are not clear. Toronto General and Barnes Hospitals accept candidates for single and double lung transplants. The University of Texas Medical Center at San Antonio has a program limited to single lung transplantation and is the most active Center in Texas. As of this writing 27 single lung procedures have been performed at San Antonio. Baylor Medical Center in Dallas has recently performed a single lung transplant. The University of Texas Southwestern Medical Center at Dallas has recently received UNOS approval and will soon begin single lung transplantation.

Increasing experience with single lung transplantation continues to broaden the indications for this procedure while restricting those for the double lung and heart-lung transplants. For this reason single lung transplantation will be emphasized in this presentation.

Referring physicians should be familiar with the indications for transplantation and criteria for acceptance into a program which vary somewhat among institutions. The indications listed in Table 5 are accepted by most Centers.

TABLE 5

Indications for Single Lung Transplantation

I	End Stage Fibrotic Lung Disease
	Idiopathic
	Occupational
	Drug/toxin induced
	Sarcoidosis
II	Pulmonary Hypertension
	Primary pulmonary hypertension
	Correctable Eisenmenger's Syndrome
III	Chronic Obstructive Pulmonary Disease
	Emphysema associated with Alpha 1 antiproteinase deficiency
	Emphysema associated with tobacco abuse
IV	Miscellaneous
	Lymphangioleiomyomatosus
	Eosinophilic granuloma

Initially, only patients with fibrotic lung diseases or irreversible pulmonary hypertension were considered candidates for single lung transplantation. However, early concerns about ventilation perfusion mismatch and native lung hyperinflation causing compression of the allograph in patients with chronic obstructive pulmonary disease have not been borne out (16). Therefore, in some Centers indications for single lung transplant have expanded to include patients with obstructive lung disease and pulmonary hypertension who are not infected (17). Rare entities such as lymphangioleiomyomatosus and eosinophilic granuloma are also candidates for single lung transplants.

Indications for double lung and heart-lung transplantation are listed in Table 6 (18).

TABLE 6

Indications for Double Lung and Heart-Lung Transplantation

Double Lung	
	Pulmonary Infection
	Cystic fibrosis
	Bronchiectasis
	Chronic bronchitis
Heart-Lung	
	Pulmonary hypertension with irreversible cor pulmonale
	Independent pulmonary and cardiac disease

Double lung and heart-lung transplants have been successfully accomplished in most patients meeting the current indications for single lung transplantation; however, there are also specific circumstances for the use of these modalities. Chronic pulmonary infection in patients with cystic fibrosis, bronchiectasis or chronic bronchitis, contraindicates single lung transplantation. The probability of superinfection of the donor lung limits the options for these patient to double lung or heart-lung transplants. Likewise when there is simultaneous pulmonary and cardiac disease a heart-lung transplant is required.

Referring physicians should also be aware of the relative contraindications for any type of transplant listed in Table 7. Although there is some variability among Centers, these contraindications are generally applicable and require personal communication if exceptions are to be considered.

TABLE 7

Contraindications to Lung Transplantation

Sleep Apnea Syndrome
Recurrent pulmonary emboli
Active systemic illness (e.g. RA, Lupus, Scleroderma)
Skeletal abnormalities
Pleural symphysis
Center specific
Steroid therapy
Abdominal surgery

The sleep apnea syndrome is caused by obesity, upper airway or central nervous system dysfunction and is not alleviated by lung transplantation (19). The chance of recurrent embolization to the donor lung contraindicates transplantation for patients with chronic embolization. Some Centers have reported successful embolectomy for this type of patient (20). Patients with active systemic diseases such as sarcoidosis, rheumatoid arthritis, lupus erythematous and scleroderma have the undocumented possibility of disease activity in the donor organ and are not considered an acceptable risk because of the limited donor pool. Skeletal abnormalities such as severe kyphoscoliosis which may cause respiratory failure are mechanical defects that are not helped by organ transplantation. Previous major thoracic surgery or pleural symphysis for any reason are relative contraindications due to potential excess bleeding if cardiopulmonary bypass is employed (21). Previous chest tube placement or lung biopsy are not contraindications to single lung transplant. Preoperative steroid therapy is felt by some to impair healing sufficiently to increase anastomotic problems (19). The Toronto group also considers patients with previous major abdominal surgery as unacceptable, since they use the technique of omentopexy to protect the bronchial anastomosis.

Other Centers using different surgical techniques are not concerned by preoperative steroids or previous abdominal surgery in selecting candidates for transplantation (17).

IV. Selection Criteria

A. Recipients

The criteria for selection of candidates for lung transplantation have generally evolved from the medical and psychosocial data developed by the Stanford group, although there is some variation among Centers (22). Medical criteria compiled from several institutions are listed in Table 8 (17, 19, 21).

TABLE 8

Selected Medical Criteria for Lung Transplantation

Life expectancy 12-18 months
Age ≤ 60 years - single lung ≤ 50 years - double lung ≤ 50 years - heart-lung
Absence of systemic disease with end organ damage other than the lung
Right ventricular ejection fraction ≥ 25%
Ambulatory and non-ventilator dependent

Patients who otherwise meet indications for transplantation are placed on an active waiting list when it is estimated that their life expectancy is between 12 and 18 months. A one year life expectancy implies severe pulmonary functional limitation, usually New York Heart Association Class III or IV. This estimate of survival attempts to balance the deterioration of a progressive, fatal disease against the probability of a higher success rate in those who are less ill. Prediction of survival time is difficult, and accuracy varies with disease entity. Turner-Warwick has shown that patients with pulmonary fibrosis have a poor prognosis when they have a progressive parallel decline in both vital capacity and diffusion capacity in spite of treatment with corticosteroids (23). Patients with primary pulmonary hypertension or Eisenmenger's Syndrome with pulmonary hypertension also follow a predictable course. A consistently poor prognosis of 6-12 months of life has been demonstrated after the development of recurrent syncopal episodes, hemoptysis or both (22).

Patients with chronic obstructive lung disease and cystic fibrosis may also have a gradual decline in function with a

predictable mortality rate (24). However, obstructive diseases may have unpredictable acute exacerbations, usually related to infections, that may be fatal (25).

The difficulty in accurately predicting survival is shown by the mortality experience of one Center listed in Table 9 (21).

TABLE 9

Lung Transplantation Waiting List
Mortality

Diagnosis	Candidates Alive	Dead	Time on List (months)
Pulmonary fibrosis	29	8	1-20
Cystic fibrosis	14	6	3-13
COPD	17	1	7
Pulmonary hypertension	6	1	6

The average survival of candidates after list placement, regardless of diagnosis, was 6 to 7 months. Only two of the 66 patients awaiting transplantation at this Center survived for greater than one year.

Most Centers tend to be somewhat flexible about age limitations. The usual guidelines require an age of $\leq$ 60 years for single lung transplantation, while double lung or heart-lung transplantation candidates must be less than 45 to 50 years of age (2, 17, 25, 26). The younger age limit for multiple organ transplantation is an attempt to best utilize scarce donor organs.

Restricting transplantation to patients without other major organ damage or systemic disease promotes optimal utilization of organs. Additionally, Cyclosporin A causes renal and hepatic toxicity, and previously damaged organs would limit the drug's usefulness.

The severe cachexia which commonly occurs in patients with obstructive pulmonary disease and cystic fibrosis precludes transplantation in some but not all Centers (2, 17, 19, 26, 27). Cachexia is thought to increase susceptibility to infection, delay wound healing, result in skin breakdown and interfere with pre and postoperative rehabilitation. Additionally, most Centers will not accept morbidly obese patients.

A right ventricular ejection fraction of $\geq$ 25% is utilized in most Centers as a selection criteria for single lung transplantation, since it indicates sufficient cardiac function to sustain the candidate through surgery without cardiopulmonary bypass and is compatible with postoperative myocardial

improvement. However, successful transplantation has occurred in patients with fractions as low as 12% (21).

Although exceptions have been made, most Centers require candidates to be at least ambulatory with oxygen and to not be ventilator dependent.

Psychosocial criteria devised by the Stanford group for transplantation candidates are listed in Table 10 (22). These criteria are more consistently utilized than the medical criteria by all Centers.

TABLE 10

Psychosocial Criteria for Transplantation

Absence of psychiatric illness or drug abuse
Tobacco abstention for $\geq$ 2 years
Motivation and ability for rehabilitation
Social support
Financial resources

The entire transplant process from initial referral to postoperative rehabilitation requires a motivated and psychiatrically stable patient and family. Psychiatric illness or current or prior drug abuse are considered contraindications to transplantation in virtually all Centers. Patients must demonstrate tobacco abstinence for at least two years. Strong preoperative motivation for rehabilitation is considered necessary for the patient to comply with a rigorous postoperative medical and rehabilitative program. Social support and sufficient financial resources are mandatory. Estimated cost of the surgical procedure and immediate postoperative care is approximately $120,000. With any complications a $200,000 liability is not uncommon. Proof of ability to pay is usually required prior to list placement. Maintenance Cyclosporin in noncystic fibrosis patients is estimated to cost $800 - $1,000 per month. Patients with cystic fibrosis require a significantly higher dose to maintain adequate blood levels and may have double the monthly drug cost. Only a few very selected insurance carriers will cover the procedures and there is no Medicare or Medicaid coverage. The patient and a family member frequently must move to the Transplant Center adding significantly to the financial liability.

B. Donors

One of the major factors limiting the growth of pulmonary transplantation is the shortage of suitable lung donors. It is estimated that only 10 to 15% of heart donors have lungs acceptable for transplantation (28). The lack of suitable donors is in part due to the inability to prevent or alleviate the lung injury associated with brain death. Selection of suitable donors

not only predicts early function of the allograph but also decreases early transplantation morbidity and mortality and improves clinical outcome (28-30).

Donor as well as recipient selection criteria vary between Centers. However, the general requirements of the donor listed in Table 11 should be familiar to referring physicians (17, 26, 31, 32).

Table 11

Selected Donor Criteria for Transplantation

Age
$\leq$ 40 years heart-lung
< 55 years single lung
Normal chest x-ray
Absence of signs of infection
Pa_{O2} > 300 mm Hg F_{IO2} = 1.0
Normal bronchoscopy
Similar chest size
ABO compatibility, HIV-, Hep B-

Heart-lung donors generally are required to be less than 35 to 40 years old, whereas single organs will be accepted from otherwise normal donors up to age 55. A normal chest radiograph is a requirement of all programs, and in some Centers a radiograph must be available within two hours prior to explant (32). Signs of infection are usually evaluated by Gram stains of tracheal secretions or bronchoalveolar lavage fluid. Specimens with large numbers of granulocytes or mouth bacteria are taken as an index of unwitnessed aspirations. Adequate gas exchange is usually considered to be a Pa_{O2} of greater than 300 mm Hg with a F_{IO2} of 1.0, with or without 5-10 cm H_2O of positive end expiratory pressure. Several Centers require bronchoscopy prior to explant to exclude foreign body aspiration. Radiographic and skeletal measurements have been used to grossly match donor to recipient size. The successful single lung program in San Antonio uses lean chest circumference measured at the nipple. The donor must match the recipient within 3 inches. Using this index they have had no cases of either over or undersized transplants (17). Due to the scarcity of donor lungs HLA typing is not required. However ABO blood groups are now generally matched between donor and recipient, since significant hemolysis has occurred using blood group O as a universal donor. All prospective donors are also tested for Hepatitis B, syphilis, toxoplasma gondi, cytomegalovirus and human immunodeficiency virus. A positive test for hepatitis B surface antigen or human immunodeficiency virus is a contraindication to procurement (32).

V. Surgical Considerations

A. Donor Preparation

An initial complication of successful early heart-lung transplants was pulmonary edema of the donor lung for about the first three postoperative days (13). The phenomenon was thought to be due to interruption of lymphatics and to susceptibility of the lung to ischemia. Subsequently, the techniques to preserve the donor lung listed in Table 12 have been developed, or are under investigation, to prevent this injury.

TABLE 12

Techniques for Donor Lung Preservation

Hypothermic cardiopulmonary bypass
Autoperfusion
Vasodilation
Prostacycline
Ca^{++} channel blockade
Verapamil
Alteration in superoxide radicals
Allopurinol
Superoxide dismutase
Catalase
Glutathione

Following the early pulmonary edema experienced in 1982 with reperfusion, several institutions began to employ cardiopulmonary bypass with profound hypothermia. This technique significantly decreased reperfusion injury following heart-lung transplantation especially when harvesting multiple organs (33-35). However, it limits the institution to on site donors and thus has limited practicability. Autoperfusion of the coronary and pulmonary arteries with packed red blood cells and Ambu bag ventilation of the lungs was developed in 1984 and perfected in 1987 (36). This technique provided reliable preservation for up to 6 hours, but it proved cumbersome and resulted in the loss of some organs during retrieval. A simpler technique employing pretreatment with prostacycline followed by a cold Euro-Collins solution flush during transport under hypothermic conditions was next reported successful in preventing a reimplantation response (37). Prostacycline is a potent pulmonary artery vasodilator and was initially employed to ensure even distribution of the cold perfusate (38). Subsequently, prostacycline has also been demonstrated to prevent leukocyte margination and adherence to damaged endothelium (39-42). These properties have made its use routine in many Centers for off site organ procurement.

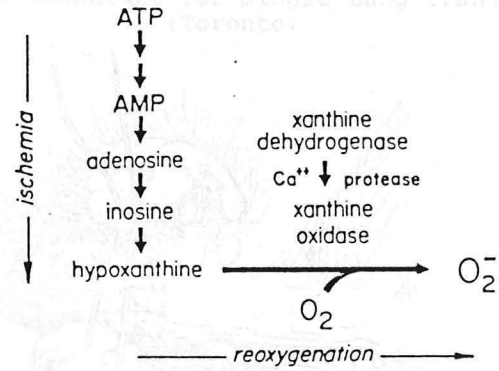
It has been noted that the structure of ribosomes is maintained in the explant during complete ischemia, but it rapidly degenerates after reperfusion causing severe disturbance

of protein synthesis (43). It has further been suggested that this reperfusion injury is based on Ca^{++} influx into cells caused by a change in permeability of the cell membranes. The Ca^{++} ion influx activates thomboxane and leukotrienes which induce platelet activation and release of vasoactive prostaglandins which then result in increase pulmonary vascular resistance and capillary permeability (44). Verapamil, a calcium channel blocker, has been used to interdict this series of events. When compared to the vasodilator hydralazine, Verapamil has been shown to increase oxygen tension and decrease pulmonary vascular resistance in the reperfused lungs of animals after three hours of ischemia (45).

Tissue reperfusion following ischemia also has been postulated to result in the production of superoxide radicals by the mechanism illustrated in Figure 1 (46).

FIGURE 1

Proposed Mechanism for Ischemia-Induced Production of Superoxide Radicals



Under conditions of ischemia ATP is converted to hypoxanthine. During reoxygenation the enzyme xanthine oxidase converts hypoxanthine to a superoxide radical. Superoxide radicals have been shown to induce lipid peroxidation resulting in an increased capillary permeability and massive tissue damage. These observations have led to the demonstration that pretreatment with allopurinol, a xanthine oxidase inhibitor, improves post-transplantation renal function and graft survival (47). Likewise, pretreatment with the free oxygen radical scavengers superoxide dismutase and catalase has resulted in significant improvement in posttransplant pulmonary function in animals (48).

Glutathione, which is also a free radical scavenger, acts through glutathione reductase to decrease oxidant injury and has been shown to extend ischemic protection time up to five hours when added to a flush solution (49).

Although each of these experimental techniques has been shown to be promising in prolonging ischemic preservation time, only the prostacycline flush has been adequately investigated in human lung transplantation to be recommended.

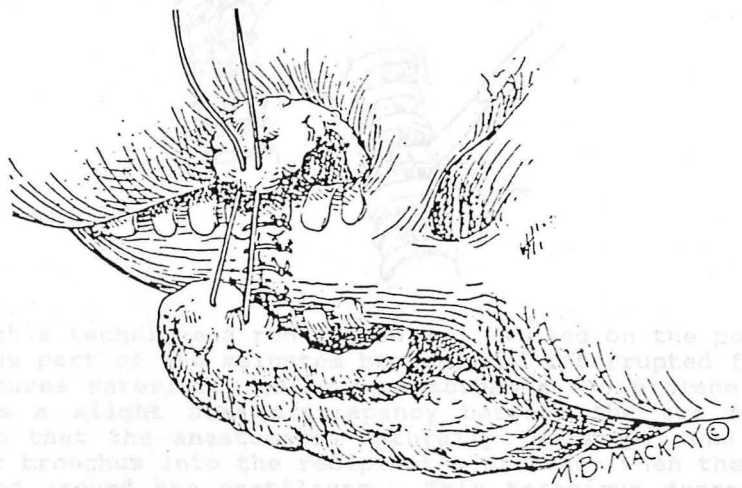
B. Transplant Techniques

Surgical technique is not generally within the scope of a Medical Grand Rounds. However, the referring physician should be aware of how differences in technique have correlated with morbidity and complications.

Both single and double lung transplants were pioneered by the Toronto group led by Dr. Joel D. Cooper who now heads the group at Barnes Hospital in St Louis. His unique technique for single lung transplantation is illustrated in Figure 2 (50).

FIGURE 2

Surgical Technique for Single Lung Transplant
(Toronto)



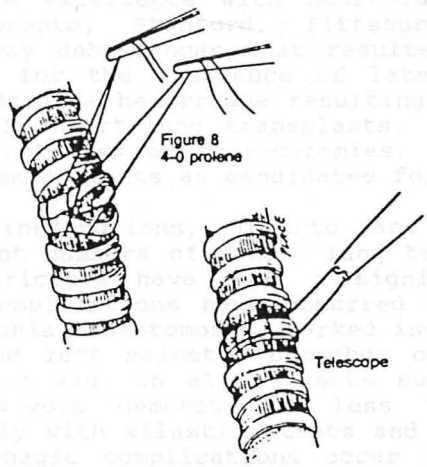
Following anastomosis of the recipient and transplant mainstem bronchi "the omentum is retrieved from its retrosternal position, brought inferior to the hilum of the lung and wrapped completely around the mainstem bronchus. The omentum is tacked to itself to avoid subsequent displacement. A free edge of the donor pericardium, left attached to the hilum of the lung, is tacked to the omentum to stimulate collateral circulation". These investigators had noted in animals that bronchial dehiscence secondary to poor healing was the single most limiting factor in successful lung transplantation. This omental flap technique was adopted for humans after extensive animal

experimentation revealed development of collateral circulation between omental and bronchial vessels which promoted better healing (51). For a double lung transplant the median sternotomy incision is extended into the upper abdomen, the omentum mobilized and then passed through the middle portion of the diaphragm and wrapped around the tracheal-bronchial anastomosis (50).

The second major surgical technique shown in Figure 3 was developed in an animal model in San Antonio by Dr. Kent Trinkle and colleagues (17).

FIGURE 3

Surgical Technique for Single Lung Transplant
(San Antonio)



In this technique a running suture is used on the posterior, membranous part of the mainstem bronchi and interrupted figure of eight sutures anteriorly using nonabsorbable 4-0 prolene. There is always a slight size discrepancy between the two bronchial stumps so that the anastomosis naturally telescopes one ring of the donor bronchus into the recipient's bronchus when the sutures are placed around the cartilages. This technique decreases the operating time and also eliminates the pain and ilius associated with the laparotomy which is necessary to mobilize the omentum (17).

C. Technical Complications

Early airway complications and postoperative deaths have been attributed to surgical technical difficulties. The most serious problems encountered are listed in Table 13.

TABLE 13

Complications Related to Surgical Techniques of Lung Transplantation

Procedure	No.	Airway Dehiscence or Stricture	Hemorrhage
HLT	111	4 (3.6%)	17 (15 %)
DLT	27	7 (25 %)	2 (7.4%)
SLT			
Toronto	15	4	0
Houston	5	2 (13.9%)	1 (2.3%)
San Antonio	23	0	0

The cumulative experience with heart-lung transplantation reported from Toronto, Stanford, Pittsburgh and Harefield indicate four airway dehiscences that resulted in death. Data are not available for the incidence of late stricture of the airway (51-53). Massive hemorrhage resulting in death occurred in 15% of the early heart-lung transplants, always in patients with previous sternotomies or thoracotomies. This complication has eliminated these patients as candidates for transplantation.

Only two institutions, Toronto and Pittsburgh, have reported significant numbers of double lung transplants. Airway dehiscence and stricture have been a significant problem in Toronto. These complications have occurred with both tracheal and bilateral bronchial anastomoses. Marked ischemia of the donor trachea, carina and left mainstem bronchus occurred within the first post-operative week in all patients succumbing to airway dehiscence. Survivors demonstrated less ischemia and were treated successfully with silastic stents and bronchial dilation (53, 54). Hemorrhagic complications occur less commonly with double lung than heart-lung transplants, most likely due to the recent more rigorous selection process.

Airway complications of single lung transplants are quite variable between institutions. The groups from Toronto and Houston have reported that up to 30% of patients have sufficiently serious problems that a second operation is necessary (26, 55), whereas, no airway problem has occurred in the 23 transplants using the telescopic technique in San Antonio (17). Hemorrhagic complications have been virtually non-existent with the latter.

VI. Medical Management

A. Immediately Postoperative

Immediate postoperative medical management is empiric and varies among Centers. The general categories of therapy used for single lung transplantation listed in Table 14 are addressed in all institutions.

TABLE 14

Postoperative Medical
Management of Lung Transplants

Ventilatory support
Fluid management
Hemodynamic management
Antimicrobial therapy

1. Ventilatory Support

Ventilatory support is maintained routinely for 3-5 days postoperatively. The goal of ventilatory support is to achieve the lowest fraction of inspired oxygen and the lowest peak airway pressure compatible with sufficient tissue oxygenation. Although undocumented, the level of peak airway pressure has been postulated to correlate with anastomotic healing. Nevertheless, almost all patients are immediately placed on either 5 or 10 cm of positive end-expiratory pressure (56). PEEP is used by some surgeons in the operating room immediately upon implantation of the donor lung (17). Ventilation is then maintained with a low tidal volume or with reverse inspiratory/expiratory ratio ventilation to maintain peak airway pressure at <50 cm H_2O (17). Depending on the adequacy of donor preservation, the native or transplanted lung may initially participate more effectively in arterial oxygenation. Thus, positioning the patient so that the best lung is dependent may improve ventilation-perfusion mismatch. Similarly, the selective reduction of pulmonary artery flow to areas of low ventilation can be achieved by pulmonary artery balloon catheter occlusion, particularly when the native lung is causing the mismatch (56). Essentially, the patient receives ventilatory support in any manner that achieves adequate arterial oxygenation at the lowest possible fraction of inspired oxygen.

Weaning and extubation times vary greatly but are attempted between the third and seventh days. Minimal weaning parameters usually include a vital capacity of 10 ml/kg of lean body weight and the ability of the patient to initiate a negative inspiratory pressure of -20 to -30 cm of water. In single lung transplants the combination of a denervated transplant and innervated native

lung is postulated to produce a sense of dyspnea in some patients despite adequate gas exchange. The patient should be warned of potential dyspnea preoperatively to relieve anxiety during weaning. Prior to weaning, a period of complete paralysis and sedation have also been employed to decrease metabolic requirements and prevent insomnia and agitation (17). Methods of weaning have included T-bar trials with adequate rest, intermittent mandatory ventilation, continuous positive airway pressure and pressure support ventilation. All have been used successfully and are most likely interchangeable. No matter which method is used, mild to moderate hypercarbia is common in the first 24 to 48 hours and should not curtail the weaning attempt. During weaning trials the patient frequently has a metabolic alkalosis secondary to a forced diuresis, and the hypercarbia may be merely a compensatory mechanism (56).

2. Fluid Management

Cardiopulmonary bypass with anticoagulation is necessary for double lung transplants and may be associated with significant hemorrhage. Therapy with blood products and fluids is required frequently resulting in pulmonary edema. Reopening of the sternum may be necessary in up to 28% to allow right ventricular filling and an adequate cardiac output. During this interval a diuresis is undertaken.

Single lung transplant almost never requires cardiopulmonary bypass; however, unique features of the procedure do complicate fluid management in the perioperative period. First, the entire cardiac output is forced to pass through the remaining native lung during the operation. Pulmonary artery pressure is usually elevated prior to the procedure and rises even further during it. The pulmonary hypertension may result in increased fluid movement into the interstitium and alveolae. The excess lung water would be of little consequence if the donor lung immediately participated in normal gas exchange. However, there is always some ischemic damage to the donor lung preventing it from functioning well at the outset (57, 58). Further, these patients usually have a positive fluid balance for at least 24 hours postoperatively. All of these factors combine to ensure pulmonary edema in both the native and transplanted lung. All Centers strive to achieve a negative fluid balance as soon as possible after surgery. Diuretics are aggressively administered until the patients preoperative weight is achieved. Should renal function be impaired due to hypotension, cyclosporin toxicity or sepsis, continuous ultrafiltration is employed to effect the fluid removal.

3. Hemodynamic Support

Hemodynamics are monitored in all patients by the placement of a Swan-Ganz catheter either pre or postoperatively. Double lungs transplants are usually unstable for 24 hours, frequently developing a high cardiac output and a low peripheral vascular

resistance. Consequently, they may need not only fluid administration but also alpha adrenergic stimulation. If there is no response to this therapy, reoperation with sternal opening usually results in decompression and hemodynamic stability.

Single lung transplants are relatively stable postoperatively, but Dopamine at a dose of <6 μg/kg/min is routinely administered to maintain renal perfusion at the lowest possible preload. The Dopamine is weaned following forced diuresis to preoperative weight.

4. Antimicrobials

Antimicrobial therapy is empiricly given to the donor and recipient. In some Centers the choice of agents is based on a gram stain of the secretions obtained by bronchoscopy at the time of transplant. A third or fourth generation Cephalosporin is usually employed to avoid the nephrotoxic effects of aminoglycosides. In an attempt to prevent CMV pneumonia some Centers administer Gancyclovir at a dose of 5 mg/kg for one week prior to transplant and then give 2 doses of CMV hyperimmune globulin at a dose of 500 mg/kg on the first and eighth postoperative day (17).

5. Immunosuppression

Immunosuppressive regimens are unique to each institution but involve some combinations of the drugs listed in Table 15.

TABLE 15

Immunosuppression for Heart-Lung Transplantation

Cyclosporin A
Azathioprine
Methylprednisolone
Antilymphocyte globulin
OKT_3

Since Borel showed in 1976 that Cyclosporin A reversibly inhibits T cell mediated alloimmune and autoimmune responses, it has become the major agent used in transplanted patients (11). The usual loading dose of Cyclosporin is 10 mg/kg given pre, intra or postoperatively depending on Center preference. The patients are then maintained, usually indefinitely, on a dose of drug that is regulated by repeated measurments of Cyclosporin blood levels, performed if possible by a radioimmunoassay employing a fluorescenated tracer. The therapeutic window is 120-275 mg/ml. Adverse clinic reactions of either rejection or toxicity tend to correlate best with trough levels. It is not known if blood or serum concentrations reflect levels at receptor

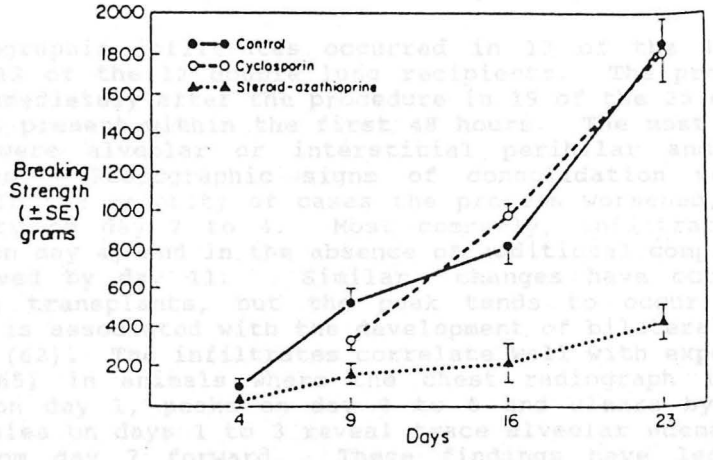
sites or with delayed cumulative biologic effects of the drug (58).

Azathioprine is also given in most Centers at a loading dose of 1.5-2.0 mg/kg with a maintenance dose of 2 mg/per day. There is no evidence that the addition of Azathioprine reduces drug induced renal injury or is synergistic with Cyclosporin. Nevertheless, this combination is the most widely used regimen. There is some evidence that the combination of Cyclosporin, Azathioprine and Prednisone increases the frequency of post transplant lymphoma (59).

A controversy over the potentially detrimental effects of steroids on bronchial wound healing has not been resolved. The data obtained in animals presented in Figure 4 is used by some Centers to avoid the use of steroids pre and immediately postoperatively (60).

FIGURE 4

Strength of the Bronchial Anastomosis
of Animals Treated with Two
Immunosuppressive Regimens



Breaking strength of a bronchial anastomosis was clearly lowered in animals treated with a Prednisone and Azathioprine regimen compared to a Cyclosporin regimen and to untreated controls. A Cyclosporin plus Azathioprine regimen has not been studied. Other Centers not only accept patients taking Prednisone but also administer 500 mgm of Methylprednisolone intraoperatively and 125 mgm every twelve hours postoperatively; no difficulty with anastomotic healing has been reported by these groups (17, 26).

Antilymphocyte globulin and OKT_3 antilymphocytic serum have also been used in the perioperative period; however, most Centers

have experienced the complication of sepsis with their use. These agents are therefore most often reserved for treatment of resistant rejection phenomena (17, 26, 56).

6. Radiology

Despite improvement in organ preservation, postoperative radiologic changes occur in the majority of patients. Table 16 lists these findings in 26 patients with single or double lung transplants (61).

TABLE 16

Postoperative Radiologic Findings
in Single and Double Lung Transplants

Type of Infiltrate	SLT	DLT
Perihilar and basal	5	6
Perihilar only	3	1
Basal only	3	3
Consolidation	8	10

Radiographic infiltrates occurred in 13 of the 14 single lung and 12 of the 12 double lung recipients. The process was present immediately after the procedure in 19 of the 25 cases and was always present within the first 48 hours. The most frequent findings were alveolar or interstitial perihilar and basilar infiltrates. Radiographic signs of consolidation were also common. In the majority of cases the process worsened, peaking in severity on day 2 to 4. Most commonly, infiltrates began clearing on day 4, and in the absence of additional complications had resolved by day 11. Similar changes have occurred in heart-lung transplants, but the peak tends to occur somewhat later and is associated with the development of bilateral pleural effusions (62). The infiltrates correlate well with experimental data (63-65) in animals where the chest radiograph is always abnormal on day 1, peaks on day 3 to 5 and clears by day 11. Lung biopsies on days 1 to 3 reveal trace alveolar edema and are normal from day 7 forward. These findings have led to the conclusion that radiographic infiltrates beginning after day 5 should not be assumed to be due to the transplantation per se, and some other cause such as infection or rejection should be sought (61).

B. Subsequent

1. Infection

a. Prevalence

Shortly after heart-lung transplantation was begun it was recognized that infectious pneumonias were more frequent and severe than in heart transplantation alone. Table 17 compares the infectious complications experienced in Pittsburgh in the two groups (66).

TABLE 17

Pneumonias in Heart-Lung and Heart Transplant Recipients

Organism	Heart-Lung No. 31	Heart No. 119
Bacterial pneumonia	26 (84%)	35 (29%)
CMV pneumonia	10 (32%)	7 (6%)
Pneumocystis pneumonia	8 (20%)	9 (8%)

Bacterial pneumonia occurred in the majority of heart-lung but the minority of heart only recipients. The heart-lung patients also had a marked increase in cytomegalovirus and pneumocystis pneumonia relative to heart transplant patients. A similar experience has also been reported at Stanford (67).

Total infectious episodes in patients with single and double lung allografts performed by the Toronto Group are listed in Table 18 and are similar in frequency to the heart-lung experience (68).

TABLE 18

Total Infectious Episodes in 40 Patients with Single or Double Lung Transplants

Infection	Number	Percent
Bacterial	32	80
Viral	12	30
Fungal	5	13
Mycobacterial	1	3
Protozoal	1	3

Of the 51 infectious episodes, bacterial infections occurred in 80% with >75% of these pulmonary in origin. Viral and protozoal (pneumocystis) infections are somewhat under

represented in this series compared to reports from other Centers which experience an attack rate of up to 80% of patients (69). The difference may be caused by stricter criteria for donor and recipient selection. Infections are more common in double lung recipients (76%) than single lung recipients (56%).

b. Bacterial

Bacterial infections tend to occur from the first 2 postoperative weeks up to 3-6 months post transplant. Causative agents that have been documented are given in Table 19 (70).

TABLE 19

Bacterial Pathogens Isolated from 21 Infections in Lung Transplant Patients

Type of Infection	Number	Percent
Gram negative		43
Pseudomonas	4	
Escherichia coli	2	
Enterobacter	1	
Acinetobacter	1	
H. influenza	1	
Gram positive		29
Staphylococcus aureus	6	
Mixed flora	5	23
Mycoplasma	1	5

Lung transplantation has been shown to result in decreased bacterial clearance, perhaps due to disruption of lymphatics and denervation, which may lead to the increased susceptibility to nosocomial infections (73). Not unexpectedly, gram negative bacteria are the most frequent pathogens isolated with Pseudomonas predominating in most series (67). Gram negative bacterial pneumonias are even more striking in experimental animals. Canine lung allograft recipients intentionally inoculated with S. pneumoniae and untreated with antimicrobials develop pneumonia with E. coli, Pseudomonas and Enterobacter (72). Staphylococcus aureus is the organism most often cultured from the implanted lung trachea, but it accounts for only a third of pneumonias. Donor cultures have been shown to be poor predictors of the cause of early infections (71).

Confirmation of bacterial infection is most commonly attempted with bronchoalveolar lavage with semiquantitative culture of the fluid recovered (74, 75). Despite identification of an organism, treatment remains empiric, most commonly including a fourth generation cephalosporin. Aminoglycosides are avoided due to the renal toxicity of Cyclosporin treatment.

c. Cytomegalovirus

Cytomegalovirus is an increasingly common pathogen in lung transplanted patients. As illustrated in Table 20, knowledge of the CMV antibody status of donor and recipient may help predict infection with this agent (76).

TABLE 20

CMV Infection and Antibody Status in Lung Transplant Patients

	D-R-	D+R-	D+R+	D-R+
Number	50	10	17	15
Titer rise	--	10	12	11
CMV pneumonia	1	6	9	7
CMV death	--	4	1	2

When 50 recipients with negative CMV titers were matched pretransplant to 50 CMV negative donors (D-R-), only one patient developed CMV pneumonia. Ten donor positive and recipient negatives (D+R-) transplants occurred prior to the availability of CMV matching; all developed a rise in CMV titer, 6 became infected and 4 died. Thus, it is clear that CMV negative recipients must receive a CMV negative donor lung. If the recipient is CMV positive a majority will develop a rise in titer, evidence of infection or both whether the donor is positive or negative. Since these data have been available there is not only strict matching of donors and recipients, but also strict adherence to the use of only CMV - blood products in all recipients.

The clinical manifestations of post transplant cytomegalovirus infections are listed in Table 21 (77).

TABLE 21

Manifestations of Cytomegalovirus Infection in 32 Lung Transplant Patients

Manifestation	No. Infect.	Percent
Asymptomatic	9	28
Esophagitis	1	3
Viral syndrome	6	18
Pneumonia	16	50

About half of the patients with CMV infection are asymptomatic, have symptoms of esophagitis or develop a viral syndrome with systemic symptoms of fever chills, malaise,

abdominal discomfort and leukopenia without evidence of specific organ disease. CMV infection was diagnosed in these patients by a positive culture of bronchoalveolar lavage fluid, serum buffy coat or urine (78). Fifty percent develop CMV pneumonia despite allograft matching and use of CMV negative blood products. The lung allograft, like an allergenic bone marrow transplant, is uniquely predisposed to primary or recurrent infection with this agent (79). The time frame for CMV pneumonia and allograft rejection not only overlap but may produce identical clinical and radiographic features. All symptomatic patients with pulmonary infiltrates should be evaluated for CMV disease infection by bronchoalveolar lavage.

Techniques for the detection of cytomegaloviral diseases have been evaluated and shown in Table 22 (80).

TABLE 22

Sensitivity and Specificity of 23 Diagnostic Techniques in Patients with CMV Infection

Technique	No. Pts.	Positive	Sensitivity Percent	Specificity Percent
Cytologic exam	21	6	29	100
Immunofluorescent antibody	22	13	59	100
Routine viral culture	23	21	91	100
Cytospin culture	23	22	96	100

Cytologic exam and immunofluorescent antibody staining of BAL fluid are proven techniques and highly specific; however, they are relatively insensitive. Viral cultures of BAL fluid are both sensitive and specific but results are not available for 2 days to 4 weeks. The newest diagnostic technique involves centrifugation of the specimen at 700 g for 40 minutes followed by incubation with fibroblasts for 16 hours. This technique has a comparable specificity and sensitivity to routine culture and is available in less than a day. A negative cytospin for CMV is required by most Centers before patients are treated with steroids for rejection.

Prophylactic and therapeutic regimens currently available for prevention or treatment of CMV infections are listed in Table 23.

TABLE 23

Prophylactic and Treatment Regimens for CMV Infections

Acyclovir 800 - 3200 mg/d
CMV hyperimmune globulin
Ganciclovir
Ganciclovir + hyperimmune globulin

Oral acyclovir in a dose of 800 - 3200 mg/d given 6 hours prior to renal transplantation and daily for 12 weeks has been shown to not only reduce the prevalence of CMV infection but also to decrease morbidity (81). CMV hyperimmune globulin has been shown to reduce CMV infection by 40% in renal transplants when given both pre and postoperatively (82).

Ganciclovir given intravenously at a dose of 10 mg/kg/d for 2 weeks has had limited success in the treatment of CMV pneumonia with approximately 40% of patients responding for short periods of time (83, 84).

More recently Ganciclovir at a dose of 6 mg/kg/d for 2 weeks plus cytomegalovirus immune globulin at 400 mg/kg on days 1, 2, 7 and 14 was used in the treatment of CMV pneumonia in bone marrow transplant patients. Fifty two percent survived the initial episode of pneumonia with cessation of viral secretion in 74%. Recurrence occurred in 20% (85). The relative success of this regimen in bone marrow transplantation recommends its use in lung transplants with CMV pneumonia.

d. Pneumocystis carnii

Infections with the protozan Pneumocystis carini have been recognized since the beginning of successful immunosuppression and organ transplantation. Disease in lung allografts due to PCP has several characteristics listed in Table 24 that are unique to the organism (77, 86)

TABLE 24

Pneumocystis carini in Lung Transplants

Characteristic	Total Transplants %	Pts. with Pneumocystis %
Incidence of Pneumocystis	88	
Asymptomatic		70
Pneumonia		30
Onset of pneumonia >2 mos.		100
PCP with prophylaxis	0	

Pneumocystis carini organisms were recovered by bronchoalveolar lavage in 88% of heart-lung transplant recipients who had not received antibiotic prophylaxis. Among patients yielding organisms approximately 70% were asymptomatic and had a normal chest radiograph. Pneumonia with fever, radiographic infiltrates and hypoxemia occurred in about 30%. Conversely, 192 heart transplants with symptomatic pneumonia only 4% had Pneumocystis (86). All reports indicate that the onset of Pneumocystis pneumonia always occurs more than 2 months post transplant, and it has been reported as late as 17 months. These data have led to empiric prophylaxis with trimethoprim-sulfamethoxazole at a dose of 1 tablet of Bactrim DS twice daily for 7 days each month (86). This therapy is universally effective in patients who are able to tolerate the medication (77, 86). Diagnosis and treatment is similar to that of any immunosuppressed patient.

e. Other

The organisms listed in Table 25 have been the most common causes of systemic infections in patients with lung and heart-lung transplants (77).

TABLE 25

Systemic Infection in Lung Transplants

	No. Pts.	No. Infect.	Percent
Fungal			
C. albicans	75	8	10
Aspergillus	75	3	4
C. neoformans	75	1	1
Virus			
Herpes simplex virus	51	9	17
Epstein-Barr virus	60	7	12

Candida albicans is the most frequent fungal cause of systemic infection with a prelavence of 10 to 13% (77, 87). These infections have been documented from 9 to 90 days post transplant and are almost always related to colonization of the donor lung. There is a broad spectrum of clinical presentations including mycotic aneurysms with or without rupture, mediastinitis and tracheal dehiscence. Treatment with Amphotericin B has been unsuccessful, and the mortality has been 100%. Low dose Amphotericin prophylaxis of 0.3 mg/kg/d for 14 days has been successful in preventing disease in 15 recipients who received candida positive donor lungs (77).

Invasive pulmonary and disseminated aspergillosis has been reported in a small number of patients. Most of these patients

were also infected with C. albicans, and the diagnosis was not made until autopsy. Treatment experience is not available.

Only one infection with Cryptococcus neoformans has been reported. The infection was disseminated and occurred more than 6 months post transplant.

Of the 75 heart-lung transplants reported by The University of Pittsburgh there has not been a case of histoplasmosis, coccidiomycosis or blastomycosis. However, these organisms are not endemic to the Pittsburgh area.

Herpes simplex virus (HSV) infection has occurred in 17% of heart-lung transplants reported from the Papworth Hospital in England (88). Seven had mucocutaneous symptoms, but there were also six episodes of HSV pneumonia. All episodes occurred within 2 months of transplant in HSV antibody positive recipients. Five of the six episodes of pneumonia developed within one week of beginning treatment with methylprednisolone or OKT_3 monoclonal antibody. The diagnosis of pneumonia was made by the typical histologic appearance on transbronchial biopsy associated with positive viral culture. Acyclovir was successful in treating the pneumonia in 5 of 6 patients and is now recommended as prophylaxis for all HSV positive recipients at a dose of 200 mg IV 4 times a day for 10-14 d followed by Acyclovir PO indefintely.

Twelve percent of patients have developed Epstein-Barr virus (EBV) infection from 1 to 3 months post transplant. The previous serologic status of these patients is not known. The clinical manifestations not only include a typical mononucleosis syndrome but also the development of significant lymphoproliferative disease. Acyclovir in conjunction with a reduction in Cyclosporin dosage has resulted in regression of disease, but most patients have then developed chronic rejection manifested by obliterative bronchiolitis (77).

2. Rejection

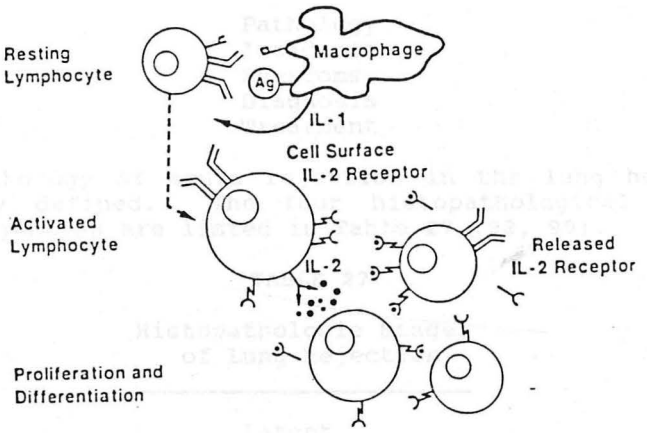
a. Immunology

Lung and heart-lung transplantation was abandoned two decades ago owing to a variety of problems the most important of which was an inability to control acute rejection of the transplant. Recent advances in defining the intricate network of cellular and humoral immune defense mechanisms and the characterization of the major histocompatibility complex have broaden an understanding of the rejection process and provided new avenues for therapeutic intervention.

The current concepts of the immunopathogenesis of allograft rejection are shown in Figure 5 (89).

FIGURE 5

Model of T Cell Activation
Resulting in Allograft Rejection



Transplant alloantigens, like other foreign antigens, are phagocytosed by macrophages which initiate the immune response. These macrophages release interleukin 1 (IL 1), process the foreign antigens and then present them to resting immune T lymphocytes of appropriate HLA Class II specificity (90, 91). In response to the combined stimulus provided by the processed alloantigen, HLA II antigen, and IL 1, resting T cells are activated to secrete interleukin 2 (IL 2) and to express newly synthesized receptors on their cell surfaces (92-94). Following binding of IL 2 to a receptor, a series of intracellular events occur, including RNA and DNA synthesis, which results in clonal expansion of the activated T cells and their differentiation into activated cells. Thus, the end result of this immunologic cascade is the generation of alloantigen-specific activated T cells, particularly those with suppressor/cytotoxic characteristics. These cells then infiltrate and attempt to destroy the allograft (95-97).

b. Acute Rejection

The management of lung transplantation patients requires the physician to have knowledge of the clinical parameters of acute lung rejection listed in Table 26.

TABLE 26

Clinical Considerations in Acute
Lung Transplants Rejection

Pathology
Incidence
Symptoms
Diagnosis
Treatment

The pathology of acute rejection in the lung has not yet been clearly defined. The four histopathological stages of pulmonary rejection are listed in Table 27 (98, 99).

TABLE 27

Histopathologic Stages
of Lung Rejection

Latent
Vascular
Alveolar
Necrosis

The earliest histopathologic finding is interstitial edema with little cellular infiltrate, termed the latent stage. As acute rejection progresses there is infiltration of mononuclear cells, predominantly lymphocytes and plasma cells into the perivascular and peribronchial epithelium. The alveolar stage is characterized by the presence of alveolar edema and fibrin with a paucity of mononuclear cells. Finally alveolar infiltration by mononuclear cells leads to frank alveolar wall necrosis and irreversible damage to the part of the transplanted lung involved. To diagnose and stage acute rejection by lung biopsy requires a generous sample size at an appropriate biopsy site.

The most extensive data on acute rejection in lung transplantation are from the Toronto Group and are shown in Table 28 (100).

TABLE 28

Acute Rejection of Single and Double Lung Transplants

	SLT	DLT
Acute Rejection		
mean onset (mos.)	1.7	4.9
range of onset (mos.)	0.25-7.0	0.25-13
Incidence (%)	68	75
Mortality (%)	6	0

Histologic changes of acute rejection occur on average 1.7 months following single lung transplants but have a range of 1 week to 7 months. Acute rejection in double lung transplants tends to occur later at a mean of 4.9 months but with a range of 1 week to 13 months. Thus, the time of onset is too broad to be of diagnostic help. Episodes of acute rejection are quite common, occurring in 68% of SLTs and 75% of DLTs. Mortality, however, is quite low with only 1 death among 15 patients (6%) with SLTs and none in DLTs.

A clinical diagnosis of acute lung allograft rejection is generally made from the constellation of findings in Table 29 (101, 102).

TABLE 29

Clinical Findings Suggesting the Diagnosis of Acute Lung Rejection

Fever
Worsening infiltrates
Worsening gas exchange
Exclusion of infection
Improvement with treatment

Fever, worsening infiltrates and worsening gas exchange all occur with both infections and episodes of rejection. In most Centers bronchoscopy and BAL are performed for the exclusion of infection. A negative CMV cytospin culture is mandatory in some institutions before institution of aggressive immunosuppression. If BAL results are considered negative for infection, presumed acute rejection is treated with 1 to 3 gm of intravenous methylprednisolone daily for at least 3 days (102). Rapid devescence of fever and improvement in gas exchange is considered to be diagnostic of an episode of acute rejection. If there is no gratifying response to steroid therapy, an attempt to make a more precise diagnosis is made. Various methods that have been employed are listed in Table 30.

TABLE 30

Methods Investigated for
Diagnosing Acute Rejection

Open lung biopsy
Needle biopsy
Transbronchial biopsy
Endobronchial biopsy
BAL
  Cell counts and differentials
  CD_4 or CD_8 cells
  DNA content
  Donor specific T cell reactivity
  IL 2R level

Open lung biopsy has been established as the 'gold standard' for the diagnosis of allograft rejection. When compared with autopsy data, open lung biopsy was 100% specific in the diagnosis of acute rejection in canine studies. Transthoracic needle biopsies correlated with open lung biopsy in only 59% of cases, and the complication rate was excessive (103). Conversely transbronchial biopsies for histologic examination has been reported to have a diagnostic sensitivity of greater than 80% (104, 105). Missed diagnoses have occurred due to sampling error, and at least one death secondary to hemorrhage has occurred. Endobronchial biopsies are less invasive and have been suggested as a possible source of diagnostic tissue. A subset of cytotoxic T lymphocytes, Leu-7 positive lymphocytes, have been shown to be a reliable marker of renal rejection. In a small series of patients these cells were demonstrated in the bronchial mucosa, submucosa and submucosal glands in association with severe lung rejection (106). Supportive data are needed to establish the sensitivity and specificity of this finding.

Bronchoalveolar lavage is essentially non-invasive but has yielded no cellular or immunologic markers that reliably predict rejection. Elements that have been investigated without success include total cell counts, differential cell counts, number of CD_4 or CD_8 cells and DNA content of BAL derived lymphocytes (107, 108). A potentially useful approach presently under investigation is to test BAL derived lymphocytes against donor cells. Data from Pittsburgh suggest that in some cases acute rejection is accompanied by donor specific reactivity of T lymphocytes and this reactivity decreases with treatment (109). When T cells are activated, Interleukin 2 is produced and Interleukin-2 receptors (IL-2R) are present in BAL supernatant or blood. Unfortunately, IL-2R are also elevated by infectious diseases (110).

Thus, open lung biopsy is the only reliable diagnostic procedure to diagnose acute rejection but is seldom employed due to the severity of illness of these patients. In patients not

responding to immunosuppression transbronchial biopsy may be useful. However, the most common therapy is to increase immunosuppressive therapy while administering broad spectrum antibiotic coverage.

c. Chronic Rejection

A syndrome of chronic rejection manifested by airway obstruction, hypoxemia and an increased mortality was first recognized in 1984 as a late complication of heart-lung transplantation and has been only rarely reported in single lung transplantation (111). Since that time the syndrome has been reported in up to 38% of long term survivors, and the well defined clinical manifestations are listed in Table 31 (112).

TABLE 31

Clinical Manifestations of Chronic Rejection
Due to Bronchiolitis Obliterans

Insidious onset
Bronchitis symptoms
Dyspnea
Lower respiratory tract infection
Rapid course

Most commonly the syndrome occurs 12 months post transplant with a range of 2 to 49 months. The symptoms are insidious in onset. The first symptoms suggest mild bronchitis with a cough that is usually minimally productive. Dyspnea occurs within months of onset of bronchitic symptoms and indicates extensive airways obstruction. Recurrent lower respiratory infections may be present but are not invariable. The untreated course is rapidly worsening airway obstruction.

Alteration in pulmonary functions are well described and are shown in Table 32 (112).

TABLE 32

Pulmonary Function Abnormalities
in Post Transplantation Bronchiolitis Obliterans

Decreased flow in small airways
Decreased flow in large airways
Hypoxemia
Hypocarbia

The first functional abnormality is a decrease in the FEF_{25-75} which indicates obstruction of small airways. This abnormality usually occurs while the patient is still asymptomatic. With the development of bronchitic symptoms a

rapidly progressing obstruction of large airways occurs manifested by a decreasing $FEV_{1.0}$. With the onset of dyspnea there is hypoxemia and an increase in the A-a gradient. Hypocarbia then ensues reflecting alveolar hyperventilation. Hypercarbia occurs only with terminal disease.

Management options are limited and are listed in Table 33.

TABLE 33

Management of Post Transplantation
Bronchiolitis Obliterans

Surveillance
Transbronchial biopsy
Treatment
Azathioprine
Methylprednisolone

Bronchoscopy has been positive for infection or rejection in 15% of asymptomatic patients and is relatively specific for this form of rejection (113). However, repeated bronchoscopies in asymptomatic patients are impractical. Thus, patients are followed routinely with spirometry, and a decrease in FEF_{25-75} is an indication for transbronchial biopsy. Immunosuppressive therapy has changed due to the recognition of this syndrome. Initially, maintenance immunosuppression did not include Azathioprine. Only patients who developed bronchiolitis were treated with 1.0-1.5 mg/kg/d of Azathioprine which slowed the rate of progression (114). Most patients now receive maintenance immunosuppression with Azathioprine. If bronchiolitis occurs while Azathioprine is being administered, augmentation of immunosuppression with pulse Methylprednisolone is the treatment of choice. No data on efficacy are currently available.

VII. Results

A. Survival

The collected experience through 1988 listed in Table 34 provides a reasonable estimate of expected survival posttransplant (15).

TABLE 34

Total Clinical Experience of
Thirteen Transplant Centers Through 1988

	Total	Alive	Percent
Single Lung	51	29	57
Double Lung	37	21	57
Heart-Lung	457	288	50

The results reflect overall mortality from the inception of the initial programs in 1982. Approximately 60 percent of single and double lung transplants can be expected to be alive after three years. The fifty percent survival for heart-lung transplants reflects more total patients and a significantly longer average follow-up than either the single or double lung experience. Collected data from Centers with the largest experience in single lung transplantation are listed in Table 35 (14, 17, 27).

TABLE 35

Survival of Patients with Single
Lung Transplants

	No.	% Overall Survival
Toronto	27	62
San Antonio	23	74
International Registry	185	67

Unadjusted overall survival rates are comparable; however, the San Antonio experience only began in March of 1988, and 74% represents the one year survival rate. For reference as of January, 1990, there had been 185 single lung transplants listed with the International Lung Transplant Registry. Thirty percent of these procedures had been performed either in Toronto or San Antonio and 124 (67%) are still alive (14).

The only significant experience reported for double lung procedures is listed in Table 36.

TABLE 36

Survival of Patients with Double Lung Transplants

	No.	% Overall Survival
Toronto	19	63
International Registry	96	55

The Toronto group has reported 19 operations with an overall survival rate of 63%. Total experience is best reflected by the procedures listed with the International Registry which show an unadjusted overall survival of 55% (14).

It has become clear that heart-lung transplantation will be used increasingly in patients with cystic fibrosis, bronchiectasis and concurrent heart and lung pathology. Adequate data to estimate survival in these groups are available only for patients with cystic fibrosis which are listed in Table 37.

TABLE 37

Expected Survival of Heart-Lung Transplanted Patients with Cystic Fibrosis

	No.	% Overall Survival
Papworth	27	74
Collected UK Experience	35	77

The majority of heart-lung transplants for cystic fibrosis have been performed in the United Kingdom at Papworth and Sick Children's Hospital. Their overall survival at 48 months is 74% compared to the collective experience in the UK of 77% (115, 116). The authors compared these results in cystic fibrosis patients to patients transplanted for primary pulmonary hypertension and for Eisenmenger's Syndrome and found no significant difference (116).

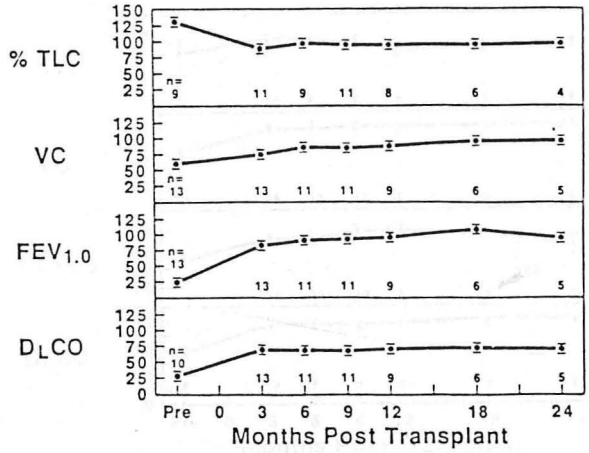
B. Functional Outcome

1. Pulmonary Function Tests

Success or failure of lung transplantation must be evaluated not only by survival but also by functional status. Extensive pulmonary function data are available and reveal similar physiologic changes in double lung and heart-lung transplants (117, 118). Pre and postoperative functions of double lung recipients are presented in Figure 6 (118).

FIGURE 6

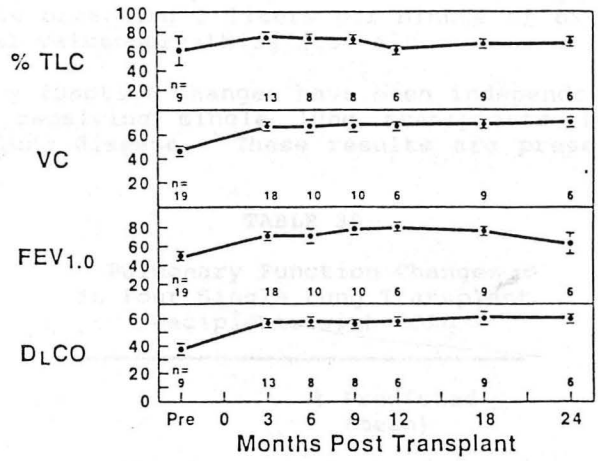
Pulmonary Function in 13 Double Lung Transplant Recipients



Total lung capacity (TLC), vital capacity (VC), forced expiratory volume in one second ($FEV_{1.0}$) and diffusion of the lung for carbon monoxide (D_{LCO}) values are improved at 3 months and show continued improvement up to 12 months posttransplant. Preoperative TLCs were increased in these predominantly emphysematous patients and became normal or slightly below normal postoperatively indicating mild restrictive defects in some. Preoperative vital capacities were secondarily restricted and returned to normal following operation. The severe degree of flow obstruction with $FEV_{1.0}$s averaging 25% of predicted also returned to normal. D_{LCO}s, an index of capillary volumes and surface area, were also severely reduced preoperatively, but this increased postoperatively to an average of 67% of predicted. This value represents only a mild reduction of gas transfer. Comparable functions in single lung recipients with fibrotic lung diseases are presented in Figure 7 (118).

FIGURE 7

Pulmonary Function in 19 Single Lung Transplant Recipients with Pulmonary Fibrosis



Preoperative TLC was decreased to 60% of predicted in these patients with primarily restrictive lung diseases and increased to 72% of predicted after transplantation. Vital capacity showed an even better increase from 40% to 79% of predicted. $FEV_{1.0}$ was reduced preoperatively in proportion to the reduction in vital capacity and increased to 77% of predicted postoperatively which indicated normal air flow. As would be expected, D_{LCO} did not increase as markedly as in patients with double lung transplantation.

Improvement in gas exchange in both SLT and DLT is presented in Table 38 (118).

TABLE 38

Gas Exchange in Single and Double Lung Transplant Recipients

Recipient	pH units	P_aCO_2 mm Hg	P_{ao2} mm Hg	Insp O_2 L/min
	mean			
Double lung				
Pre transplant	7.40	47	67	2
Post transplant	7.42	35	100	0
Single lung				
Pre transplant	7.42	43	65	2
Post transplant	7.44	37	79	0

Arterial blood gas measurements were made just prior to surgery and 3 months postoperatively in both groups. Double lung recipients (emphysematous group) showed a significant reduction in pCO_2 which correlated with the improvement in $FEV_{1.0}$. Both groups also had marked improvement of arterial oxygenation from a low P_{aO2} while breathing 2 liters per minute of oxygen to normal or near normal values breathing room air.

Pulmonary function changes have been independently evaluated in patients receiving single lung transplants for end stage obstructive lung disease. These results are presented in Table 39 (119).

TABLE 39

Pulmonary Function Changes
in Four Single Lung Transplant
Recipients with COLD

	% Predicted (mean)
VC	
Pre op	50
Post op	59
$FEV_{1.0}$	
Pre op	21
Post op	52

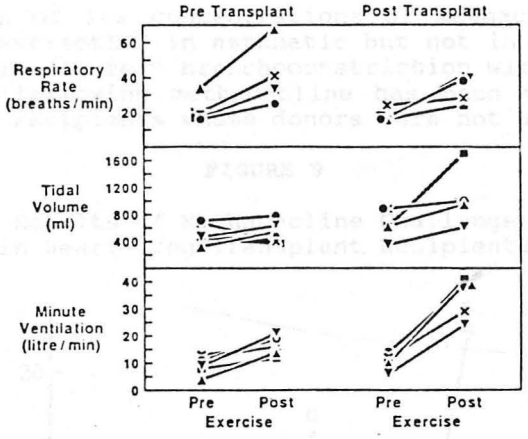
Single lung recipients achieve a smaller increment in vital capacity and $FEV_{1.0}$ than DLT, but all achieved normal postoperative blood gases while breathing room air. Since DLT patients have a higher operative mortality and greater morbidity, these results suggest that the single lung procedure may be preferable in patients with obstructive lung disease.

2. Exercise Capacity

Improvement in pulmonary function tests and gas exchange are associated with the increase in exercise capacity and change in ventilatory pattern shown in Figure 8 (118).

FIGURE 8

Ventilatory Changes During Exercise in
Single and Double Lung Transplant Recipients



Preoperatively only 5 patients could perform Stage I exercise studies. These patients could increase minute ventilation only modestly, and this was at the expense of a rapid respiratory rate without a change in tidal volume. Post transplantation there was a significant increase in minute ventilation by increasing tidal volume as well as rate. Exercise capacity was also increased. Prior to transplantation the maximum workload averaged 27 watts, while three months postoperatively the mean workload had increased to 73 watts.

However, as illustrated in Table 40, post transplant maximum exercise capacity remains abnormal (118, 120).

TABLE 40

Exercise Capacity of Single,
Double and Heart-Lung Transplant
Recipients at Twelve Months

	SLT	DLT	HLT
Maximum:			
Heart rate (beats/min)	133	129	149
Minute ventilation (L/min)	53	45	46
Oxygen consumption (ml/kg/min)	17	18	19
Oxygen consumption (% pred)	58	49	50

The maximum oxygen consumption at 12 months post transplant is approximately 50% of predicted for each type of lung transplant. Exercise was discontinued by transplant recipients

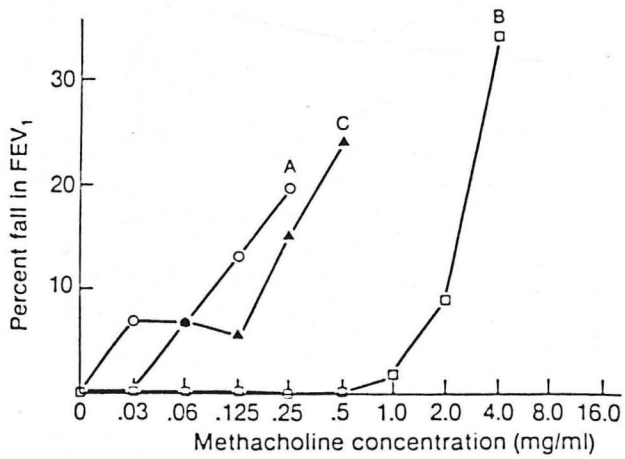
before maximum heart rate or ventilation was achieved. The limiting factor for exercise performance is not known.

3. Bronchial Hyperresponsiveness

Inhalations of low concentrations of methacholine aerosols cause bronchoconstriction in asthmatic but not in normal persons. As illustrated in Figure 9 bronchoconstriction with a significant fall in $FEV_{1.0}$ following methacholine has been noted in heart-lung transplant recipients whose donors were not asthmatic (121).

FIGURE 9

Results of Methacholine Challenge
in Heart-Lung Transplant Recipients



a, b, c = individual patients

All three patients had significant falls in $FEV_{1.0}$ at low concentrations of methacholine. The patients had bronchial mucosal biopsies at the time of challenge which revealed no inflammatory changes. Studies of double and single lung recipients have confirmed this hyperresponsiveness (122); however, the magnitude of change is much less in single lung recipients. Since HLT and DLT are bilaterally denervated investigators have suggested a role for tracheal innervation in maintenance of normal airway function.

VIII. Summary

Single lung transplantation is now a viable alternative to patients with terminal lung disease. Surgical technique is still evolving but it would appear that the simpler surgical procedure will be preferable. Survival rates can be expected to be at least 60 percent at three years and survival is associated with adequate exercise tolerance. Maintenance medical regimens result in considerable morbidity and a normal quality of life cannot be attained. Future investigation will likely alter this morbidity. The major problem of organ availability and expense will continue to limit the clinical usefulness of the procedure.

REFERENCES

1. Danilevicius, Z.: SS. Cosmas and Damian. The patron saints of medicine in art. JAMA 201:1021-1025, 1967.

2. Tuna, I.C., S. W. Jamieson: Human heart and lung transplantation. Adv. Surg. 22:251-276, 1989.

3. Cooper, D.K.C.: Transplantation of the heart and both lungs. I. Historical review. Thorax 24:383-390, 1969.

4. Carrel, A: Anastomosis and transplantation of blood vessels. Am. Med. 10:284-1905.

5. Carrel, A., C. Guthrie: The transplantation of veins and organs. Am. Med. 10:1101, 1905.

6. Carrel, A: The surgery of blood vessels, etc. Johns Hopkins Hosp. Bull. 18:18, 1907.

7. Demikhov, V: Experimental Transplantation of Vital Organs, Haigh B (trans)., New York, Consultants Bureau, 1962.

8. Webb, W., H. Howard: Cardiopulmonary transplantation. Surg. Forum 8:313, 1957.

9. Hardy, J.D., W.R. Webb, M.L. Dalton, Jr., et al: Lung homotransplantation in man. JAMA 186:1065-1074, 1963.

10. Marcus, E., S. Wong, A. Luisada: Homologous heart grafts. Arch. Surg. 66:179-191, 1953.

11. Cooley, D., R. Bloodwell, G. Hallman, et al: Organ transplantation for advanced cardiopulmonary disease. Ann. Thorac. Surg. 8:30-46, 1969.

12. Reitz, B., N. Burton, S. Jamieson, et al: Heart and lung transplantation autotransplantation and allotransplantation in primates with extended survival. J. Thorac. Cardiovasc. Surg. 80:360-372, 1980.

13. Reitz, B.A., J.L. Wallwork, S.A. Hunt, et al: Heart-lung transplantation. Successful therapy for patients with pulmonary vascular disease. N. Engl. J. Med. 306:557-564, 1982.

14. Lung Disease Care and Education Briefing Paper: Lung Transplantation. Information for Lung Association Staff. Update Details 13:1-10, 1990.

15. Griffith, Bartley P.: Pulmonary Transplantation Status in 1989, In: Cardiac Transplantation, Chapter 17, pp. 249-259, M.E. Thompson, ed., F.A. Davis, Philadelphia, 1990.

16. Stevens, P.M., P.C. Johnson, R.L. Bell, et al: Regional ventilation and perfusion after lung transplantation in patients with emphysema. N. Engl. J. Med. 282:245-249, 1970.

17. Calhoon, J.H., F.L. Grover, W.J. Gibbons, et al: Single lung transplantation-alternative indications and techniques. Submitted to J. Thorac. Cardiovasc. Surg., May, 1990. In Press.

18. Dark, J., P.A. Corris: The current state of lung transplantation. Thorax 44:689-692, 1989.

19. Olivari, Maria-Teresa, R. L. Rosenblatt: Protocol for potential single lung transplant recipients. From the Cardiac Transplant Program, University of Texas Southwestern Medical Center/St. Paul Medical Center, June 5, 1990.

20. Moser, K.M., P.O. Daily, K. Peterson, et al: Thromboendarterectomy for chronic, major-vessel thromboembolic pulmonary hypertension. Ann. Int. Med. 107:560-565, 1987.

21. Morrison, D.L., J.R. Maurer, and R.F. Grossman: Preoperative assessment for lung transplantation. Clin. Chest Med. 11:207-215, 1990.

22. Jamieson, S.W., E.B. Stinson, P.E. Oyer: Heart-lung transplantation for irreversible pulmonary hypertension. Ann. Thorac. Surg. 38:554-562, 1984.

23. Turner-Warwick, M., B. Burrows, A. Johnson: Cryptogenic fibrosing alveolitis: response to corticosteroid treatment and its effect on survival. Thorax 35:593-599, 1980.

24. Traver, G.A., M.G. Cline, B. Burrows: Predictors of mortality in chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 119:895-902, 1979.

25. Gottlieb, L.S., O.J. Balchum: Course of chronic obstructive pulmonary disease following first onset of respiratory failure. Chest 63:5-8, 1973.

26. Lawrence E.C., V.A. Holland, M.B. Berger, et al: Lung transplantation: An emerging technology. Tx. Med. 84:61-67, 1988.

27. Morrison, D., T.J. Williams, G.A. Patterson, et al: Selection of patients for lung transplantation. Amer. Rev. Respir. Dis. 141:A682, 1990.

28. Hakim, M., T. Higenbottam, D. Bethune, et al: Selection and procurement of combined heart and lung grafts for

transplantation. J. Thorac. Cardiovasc. Surg. 95:474-479, 1988.

29. Haverich, A., W.C. Scott, S.W. Jamieson, et al: Twenty years of lung preservation--A review. Heart Transplant 2:234, 1985.

30. Wallwork, J., K. Jones, N. Cavarocchi, et al: Distant procurement of organs for clinical heart-lung transplantation using a single-flush technique. Transplantation 44:654-658, 1987.

31. Higenbottam, T., J. Wallwork: Transplantation of lungs. Postgrad. Med. J. 64(Suppl 4): 120-124, 1988.

32. Griffith, B.P., M. Zenati: The Pulmonary Donor. Clin. Chest Med. 11:217-226, 1990.

33. Hardesty, R.L., B.P. Griffith: Procurement for combined heart-lung transplantation. J. Thorac. Cardiovasc. Surg. 89:795-799, 1985.

34. Robicsek, F., P.W. Sanger, F.H. Taylor: Simple method of keeping the heart "alive" and functioning outside of the body for prolong periods. Surgery 53:525-530, 1963.

35. Baumgartner, W.A., G.M. Williams, C.D. Fraser, Jr., et al: Cardiopulmonary bypass with profound hypothermia: An optimal preservation method for multiorgan procurement. Transplantation 47:123-127, 1989.

36. Hardesty, R.L., B.P. Griffith: Autoperfusion of the heart and lungs for preservation during distant procurement. J. Thorac. Cardiovasc. Surg. 93:11-18, 1987.

37. Baldwin, J.C., W.H. Frist, T.D. Starkey, et al: Distant graft procurement for combined heart and lung transplantation using pulmonary artery flush and simple topical hypothermia for graft preservation. Ann. Thorac. Surg. 43:670-673, 1987.

38. Mundy, A.R., M. Bewick, S. Moncada, et al: Experimental assessment of prostacyclin in the harvesting of kidneys for transplantation. Transplantation 30:251-255, 1980.

39. Jones, D.K., D. Wheeldon, J. Kneeshaw, et al: Prostacyclin, cardiopulmonary bypass and the alveolar capillary membrane. Perfusion 1:165,1986.

40. Rubin, L.J., B.M. Groves, J.T. Reeves, et al: Prostacyclin induced acute pulmonary vasodilation in primary pulmonary hypertension. Circulation 66:334-338, 1982.

41. Higgs, E.A., S. Moncada, J.R. Vane: Prostacyclin (PGI_2) reduces the number of "slow moving" leucocytes in hamster cheek pouch venules. J. Physiol. 280:55P-56P, 1978.

42. Jones, G., J.V. Hurley: The effect of prostacyclin on the adhesion of leucocytes to injured vascular endothelium. J. Pathol. 142:51-59, 1984.

43. Cooper, H.K., T. Zalewski, K.A. Hossman: The effect of ischemia and recirculation on protein synthesis in the rat brain. J. Neurochem. 28:929-934, 1977.

44. Hoffner, J.E., I.F. McMurty, J.E. Repine: Platelet activating factor stimulates platelets to produce pulmonary hypertension and edematous lung injury in isolated perfused rabbit lungs. Clin. Res. 30:420A, 1982.

45. Hachida, M., D.L. Morton: The protection of ischemic lung with verapamil and hydralazine. J. Thorac. Cardiovasc. Surg. 95:178-183, 1988.

46. McCord, J.M.: Oxygen-derived free radicals in post ischemic tissue injury. N. Engl. J. Med. 312:159-163, 1985.

47. Owens, M.L., H.M. Lazarus, M.W. Wolcott, et al: Allopurinol and hypoxanthine pretreatment of canine kidney donors. Transplantation 17:427-427, 1974.

48. Cremer, J., M. Jurmann, L. Dammenhayn, et al: Oxygen free radical scavengers to prevent pulmonary reperfusion injury after heart-lung transplantation. J. Heart Transplant. 8:330-336, 1989.

49. Lewis, R.E., C.L. Bryan, D.J. Cohen, et al: Glutathione cryppreservation preserves pulmonary gas exchange after 5 hours ischemia in dog lung autotransplants. Am. Rev. Respir. Dis. 141:A406, 1990.

50. Cooper, Joel D.: Lung Transplantation. In: Heart and Lung Transplantation, Chapter 30, pp. 347-371, W. Baumgartner, B. Reitz, S. Achuff, eds., W.B. Saunders, Philadelphia, 1990.

51. Cooper, J.D.: Herbert Sloan Lecture. Lung transplantation. Ann. Thorac. Surg. 47:28-44, 1989.

52. Stevens, J.H., T.A. Raffin, J.C. Baldwin: The status of transplantation of the human lung. Surg. Gynecol. Obstet. 169:179-185, 1989.

53. Patterson, G.A., J.D. Cooper: Status of lung transplantation. Surg. Clin. North Am. 68:545-558, 1988.

54. Griffith, B.P., R.L. Hardesty, A. Trento, et al: Heart-lung transplantation: Lessons learned and future hopes. Ann. Thorac. Surg. 43:6-16, 1987.

55. Pearson, F.G.: Lung transplantation. Samuel Jason Mixter Lecture. Arch. Surg. 124:535-538, 1989.

56. Todd, T.R.J.: Early postoperative management following lung transplantation.. Clin. Chest Med. 11:259-267, 1990.

57. Parks, D.A., G.B. Bulkley, D.N. Granger: Role of oxygen free radicals in shock, ischemia and organ preservation. Surgery 94:428-432, 1983.

58. Todd, T.R., M. Goldberg, A. Koshal, et al: Separate extraction of cardiac and pulmonary grafts from a single organ donor. Ann. Thorac. Surg. 46:356-359, 1988.

59. Wilkinson, A.H., J.L. Smith, L.G. Hunsicker, et al: Increased frequency of posttransplant lymphomas in patients treated with cyclosporin, azathioprine, and prednisone. Transplantation 47:293-296, 1989.

60. Goldberg, M., O. Lima, E. Morgan, et al: A comparison between cyclosporin A and methylprednisolone plus asathioprine on bronchial healing following canine lung allotransplantation. J. Thorac. Cardiovasc. Surg. 85:821-826, 1983.

61. Herman, S.J.: Radiologic assessment after lung transplantation. Clin. Chest Med. 11:333-346, 1990.

62. Chiles, C., D.F. Guthaner, S.W. Jamieson, et al: Heart-lung transplantation: The postoperative chest radiograph. Radiology 154:299-304, 1985.

63. Siegelman, S.S., S.B.P. Sinha, F.J. Veith: Pulmonary reimplantation response. Ann. Surg. 177:30-36, 1971.

64. Prop, J., M.G. Ehrie, J.D. Crapo, et al: Reimplantation response in isografted rat lungs. J. Thorac. Cardiovasc. Surg. 87:702-711, 1984.

65. Tsai, S.H., O. Arnar, J. Haglin: Roentgenographic appearance of the transplanted primate lung: Autotransplanted lung. Am. J. Roentgen. 106:563-566, 1969.

66. Dummer, J.S.: Infectious Complications of Transplantation. In: Cardiac Transplantation, Chapter 10, pp. 163-178, M.E. Thompson, ed., F. A. Davis, Philadelphia, 1990.

67. Brooks, R.G., J.M. Hofflin, S.W. Jamieson, et al: Infectious complications in heart-lung transplant recipients. Am. J. Med. 79:412-422, 1985.

68. IV Toronto Lung Transplant Seminar: Presented by Toronto General Hospital, May 10-11, 1990.

69. Bennett, S., N.A. Ettinger, E.P. Trulock, et al: Cytomegalovirus infection in lung transplant recipients. Am. Rev. Respir. Dis. 141:A684, 1990.

70. Dummer, J.S., C.G. Montero, B.P. Griffith, et al: Infections in heart-lung transplant recipients. Transplantation 41:725-729, 1986.

71. Zenati, M., R.D. Dowling, J.S. Dummer, et al: Influence of the donor lung on the development of early infections in lung transplant recipients. J. Heart Transplant. 8:95, 1989.

72. Dowling, R.D., M. Zenati, A.W. Pasculle, et al: Antibiotic treatment of donors prevents experimental pneumonia in recipients of canine lung allotransplantation. Surg. Forum 40:372-374, 1989.

73. Mancini, M.C., W.N. Tauxe: Assessment of pulmonary clearance in heart lung transplant recipients using Technetium99 minimicronized albumin colloid. Am. Rev. Respir. Dis 133:A111, 1987.

74. Johanson, Jr., W.G., J.J. Seidenfeld, P. Gomez, et al: Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. Am. Rev. Respir. Dis. 137:259-264, 1988.

75. Corris, P.A., C.R. Swinburn, F. Freeman, et al: Value of bronchoalveolar lavage (BAL) in the diagnosis of pulmonary infections following cardiac and pulmonary transplantation. Am. Rev. Respir. Dis. 141:A407, 1990.

76. Smyth, R.L., T.W. Higenbottam, J.P. Scott, et al: Experience of cytomegalovirus infection in heart-lung transplant recipients. Am. Rev. Respir. Dis. 141:A410, 1990.

77. Dauber, J.H., I.L. Paradis, J.S. Dummer: Infectious complications in pulmonary allograft recipients. Clin. Chest Med. 11:291-308, 1990.

78. Bavoux, E., J. Cerrina, F. L.R. Ladurie, et al: Normal chest x-ray in cytomegalovirus (CMV) pneumonia after heart-lung and double lung transplantation. Am. Rev. Respir. Dis. 141:A409, 1990.

79. Meyers, J.D., N. Flournoy, E.D. Thomas: Risk factors for cytomegalovirus infection after human marrow transplantation. J. Infect. Dis. 158:478-488, 1986.

80. Crawford, S.W., R.A. Bowden, R.C. Hackman, et al: Rapid detection of cytomegalovirus pulmonary infection by bronchoalveolar lavage and centrifugation culture. Ann. Intern. Med. 108:180-185, 1988.

81. Balfour, Jr., H.H., B.A. Chace, J.T. Stapleton, et al: Randomized, placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. N. Engl. J. Med. 320:1381-1387, 1989.

82. Snydman, D.R., B.G. Werner, B. Heinze-Lacey, et al: Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal transplant recipients. N. Engl. J. Med. 317:1049-1054, 1987.

83. Keay, S., E. Petersen, T. Icenogle, et al: Ganciclovir treatment of serious cytomegalovirus infection in heart and heart-lung transplant recipients. Rev. Infect. Dis. 10:(Suppl 3):S563-S572, 1988.

84. Icenogle, T.B., E. Peterson, G. Ray, et al: DHPG effectively treats CMV infection in heart and heart-lung transplant patients: A preliminary report. J. Heart Transplant. 6:199-203, 1987.

85. Reed, E.C., R.A. Bowden, P.S. Dandliker, et al: Treatment of Cytomegalovirus pneumonia with ganciclovir and intravenous cytomegalovirus immunoglobulin in patients with bone marrow transplants. Ann. Intern. Med. 109:783-788, 1988.

86. Gryzan, S., I.L. Paradis, A. Zeevi, et al: Unexpectedly high incidence of Pneumocystis carinii infection after lung-heart transplantation. Am. Rev. Respir. Dis. 137:1268-1274, 1988.

87. Dowling, R.D., M. Zenati, J.S. Dummer, et al: Invasive candidiasis after heart-lung transplantation. Circulation 80 (suppl. II):640, 1989.

88. Smyth, R.L., T.W. Higenbottam, J.P. Scott, et al: Herpes simplex virus infection in heart-lung transplant recipients. Transplantation 49:735-739, 1990.

89. Lawrence, E.C.: Diagnosis and management of lung allograft rejection. Clin. Chest Med. 11:269-278, 1990.

90. Mizel, S.B., A. Ben-Zvi: Studies on the role of lymphocyte activating factor (interleukin 1) in antigen-induced lymph node lymphocyte proliferation. Cell. Immunol. 54:382-389, 1980.

91. Rosenwasser, L.J., C.A. Dinarello, A.S. Rosenthal: Adherent cell function in murine T-lympocyte antigen recognition. IV. Enhancement of murine T-cell antigen. Recognition by human leukocytic pyrogen. J. Exp. Med. 150:709-714, 1979.

92. Leonard, W.J., J.M. Depper, R.J. Robb, et al: Characterization of the human receptor for T-cell growth factor. Proc. Natl. Acad. Sci. USA 80:6957-6961, 1983.

93. Uchiyama, T., S. Broder, T.A. Waldmann: A monoclonal antibody (anti-Tac) reactive with activated and functionally mature human T-cells. J. Immunol. 126:1393-1397, 1981.

94. Smith, K.A.: T-cell growth factor. Immunol. Rev. 52:337-357, 1980.

95. Depper, J.M., W.J. Leonard, C. Grogula, et al: Interleukin-2 (IL-2) augments transcription of the IL-2 receptor gene. Proc. Natl. Acad. Sci. USA 82:4230-4234, 1985.

96. Robb, R.J., A. Munck, K.A. Smith: T-cell growth factor receptors: Quantitations, specificity, and biological relevance. J. Exp. Med. 154:1455-1474, 1981.

97. Smith, K.A. D.A. Cantress: Interleukin-2 regulates its own receptors. Proc. Natl. Acad. Sci. USA 82:864-868, 1985.

98. Veith, F.J., J.W.C Hagstrom, W.R. Anderson, et al: Alveolar manifestations of rejection: An important cause of the poor results with human lung transplantation. Ann. Surg. 175:336-348, 1972.

99. Prop, J., H.D. Tazelaar, M.E. Billingham: Rejection of combined heart-lung transplants in rats: Function and pathology. Am. J. Pathol. 127:97-105, 1987.

100. Chamberlain, D.: Lung transplantation - Pathology of rejection. Toronto Lung Transplant Program. Presented at Toronto Lung Transplant Seminar, Toronto General Hospital, May 10-11, 1990.

101. The Toronto Lung Transplant Group: Unilateral lung transplantation for pulmonary fibrosis. N. Engl. J. Med. 314:1140-1145, 1986.

102. Reitz, B.A., V.A. Gaudiani, S.A. Hunt, et al: Diagnosis and treatment of allograft rejection in heart-lung transplant recipients. J. Thorac. Cardiovasc. Surg. 85:354-361, 1983.

103. Koerner, S.K., J.W.C. Hagstrom, F.J. Veith: Transbronchial biopsy for the diagnosis of lung transplant rejection. Comparison with needle and open lung biopsy techniques in

canine lung allografts. Am. Rev. Respir. Dis. 114:575-579, 1976.

104. Starnes, V.A., J. Theodore, P.E. Oyer, et al: Evaluation of heart-lung transplant recipients with prospective, serial transbronchial biopsies and pulmonary function studies. J. Thorac. Cardiovasc. Surg. 98:683-690, 1989.

105. Higenbottam, T., S. Stewart, A. Penketh, et al: Transbronchial lung biopsy for the diagnosis of rejection in heart-lung transplant patients. Transplantation 46:532-539, 1988.

106. Hruban, R.H., W.E. Beschorner, W. Baumgartner, et al: Diagnosis of lung allograft rejection by bronchial intraepithelial Leu-7 positive T lymphocytes. J. Thorac. Cardiovasc. Surg. 96:939-946, 1988.

107. Maurer, J.R., E. Gough, D.W. Chamberlain, et al: Sequential bronchoalveolar lavage studies from patients undergoing double lung and heart-lung transplant. Transplant. Proc. 21:2585-1587, 1989.

108. Williams, T.J., D.M.G. Cochrane, G.A. Patterson, et al: Lymphocyte DNA content does not predict acute rejection in lung transplant recipients. Am. Rev. Respir. Dis. 141:A683, 1990.

109. Zeevi, A., H. Rabinowich, I. Paradis, et al: Lymphocyte activation in bronchoalveolar lavages from heart-lung transplant recipients. Transplant. Proc. 20:189-192, 1988.

110. Lawrence, E.C., V.A. Holland, J.B. Young, et al: Dynamic changes in soluble interleukin-2 receptor levels following lung or heart-lung transplantation. Am. Rev. Respir. Dis. 140:789-796, 1989.

111. Burke, C.M., J. Theodore, K.D. Dawkins, et al: Posttransplant obliterative bronchiolitis and other late lung sequelae in human heart-lung transplantation. Chest 86:824-829, 1984.

112. Theodore, J., V.A. Starnes, N.J. Lewiston: Obliterative bronchiolitis. Clin. Chest Med. 11:309-321, 1990.

113. Starnes, V., J. Theodore, P. Oyer, et al: Evaluation of heart-lung transplant recipients with prospective serial transmural biopsies and pulmonary function studies. J. Thorac. Cardiovasc. Surg. 98:683-690, 1989.

114. Glanville, A.R., J.C. Baldwin, C.M. Burke, et al: Obliterative bronchiolitis after heart-lung transplantation: Apparent arrest by augmented immunosuppression. Ann. Int. Med. 107:300-304, 1987.

115. Smyth, R.L., T.W. Higenbottam, J.P. Scott, et al: Mortality and morbidity following heart-lung transplantation for cystic fibrosis. Am. Rev. Respir. Dis. 141:A685, 1990.

116. Geddes, D.M., M.E. Hodson: The role of heart and lung transplantation in the treatment of cystic fibrosis. J. Royal Soc. Med. 82(Suppl 16):49-53, 1989.

117. Theodore, James: Physiology of the Lung in Human Heart-Lung Transplantation. In: Cardiac Transplantation, Chapter 3, pp. 57-69, M.E. Thompson, ed., F. A. Davis, Philadelphia, 1990.

118. Williams, T.J., R.F. Grossman, J.R. Maurer: Long-term functional follow-up of lung transplant recipients. Clin. Chest Med. 11:347-358, 1990.

119. Maurer, J.: Comparison of outcomes of double and single lung transplant for obstructive lung disease. Presented at Toronto Lung Transplant Seminar, Toronto General Hospital, May 10-11, 1990.

120. Williams, T.J., G.A. Patterson, P.A. McClean, et al: Stage 1 exercise testing early and late following single and double lung transplantation. Am. Rev. Respir. Dis. 141:A763, 1990.

121. Glanville, A.R., C.M. Burke, J. Theodore, et al: Bronchial hyper-responsiveness after human cardiopulmonary transplantation. Clin. Sci. 73:299-303, 1987.

122. Maurer, J.R., P.A. McLean, J.D. Cooper, et al: Airway hyperreactivity in patients undergoing lung and heart/lung transplantation. Am. Rev. Respir. Dis. 139:1038-1041, 1989.