Cardiac transplantation, first introduced 30 years ago, has become a widely used and increasingly important procedure for treatment of truly end-stage heart disease. Current use is limited strictly by donor supply, making selection of appropriate recipients an important ethical and societal issue. Survival rates after transplantation rose in the 1980s with the use of cyclosporine and have remained relatively consistent since then, although recipients older than 65 years or younger than 1 year have lower survival rates than recipients of other ages. Although immunosuppressive drugs have helped establish cardiac transplantation as a successful procedure, risks of opportunistic infection and rejection, as well as coronary arteriopathy, have led to development of new immunosuppressive agents currently under study. Future alternatives to the current technology of cardiac allotransplantation may include xenotransplantation and/or nonbiological replacement of the heart with mechanical devices.

THE SURGERY

Technique

The technique for performing orthotopic heart transplantation has changed little since its original description in the laboratory by Lower and Shumway in 1960. It involves removal of both donor and recipient hearts by transection at the midatrial level (thus preserving the multiple pulmonary venous connections to the posterior wall of the left atrium in the recipient) and transection of the great vessels just above their respective semilunar valves.

In the early years of heart transplantation, the donor cardiectomy was required to be performed in an operating room adjacent to that in which the recipient was being prepared, necessitating transport of the brain-dead donor (on life support) to the recipient hospital. In 1962 it was demonstrated in the laboratory that cold ischemic times of up to 7 hours were safe and resulted in normal cardiac allograft function. In the mid 1970s, what is termed distant heart procurement became the norm; the donor heart is now usually “harvested” by a surgical procurement team at a distant hospital and transported expeditiously to the transplant center in iced cardioplegic solution while the transplant surgical team prepares the recipient and explants the recipient’s heart in a similar manner. The donor heart is then implanted in the orthotopic position with surgical anastomoses at the midatrial level and the aorta and pulmonary arteries. In recent years, a variation on this procedure, bicaval anastomosis, which preserves the anatomical integrity of the right atrium by using anastomoses at the level of the superior and inferior venae caves, has gained popularity. Although the surgery itself takes about 15 minutes longer with this technique, the preserved right atrial anatomy may lead to more normal tricuspid valve function and better preservation of sinoatrial node function.

It has not been possible to extend the safe cold ischemic time for donor hearts, a fact that clearly limits the possibility of applying the recently called-for national allocation policy for donor organs to the allocation of hearts.

Physiology

The heart reimplanted in the orthotopic position is surgically denervated and responds to physiologic stimuli with atypical adaptive mechanisms. For instance, it is unable to acutely increase heart rate in response to exercise or hypotension, but responds acutely instead with an increase in stroke volume, a reliance on the classic Frank-Starling mechanism. The transplanted heart remains sensitive to circulating catecholamines and does increase heart rate later in the course of exercise or hypotension in response to increases in levels of these hormones. Afferent denervation typically makes the patient incapable of experiencing the subjective sensation of angina pectoris in response to ischemia.

The overall maximum exercise capacity of heart transplant recipients is subnormal, most likely due to this denervated state, although most patients are
capable of resuming normal lifestyles and reasonably vigorous activity levels. The issue of whether reinervation ever occurs has been controversial. Although a number of studies have documented physiological evidence of reinervation following transplantation, including release of cardiac norepinephrine in response to tyramine infusion,14 physiological functional responses to tyramine infusions,15 and the occurrence of classic angina pectoris,16 evidence of late improvement in exercise capacity has not been found.17

CURRENT STATUS

Indications for Heart Transplantation

The indications for heart transplantation have always generically included the presence of end-stage heart disease irre- mediable by any more conventional forms of therapy and the absence of contraindications such as concomitant diseases that would separately limit survival. The application or interpretations of these principles has varied among centers and, in recent years, there have been concentrated efforts to devise uniform criteria for listing patients for heart transplantation. The first such consensus conference was the American College of Cardiology Bethesda Conference in 1982.18 More recently, in 1986, the United Network for Organ Sharing (UNOS) Board of Directors approved a set of UNOS Guidelines for Cardiac Transplantation Listing that emphasizes the need for maximizing current state-of-the-art medical therapy as well as objective assessment of patients’ functional capacity (mainly through peak oxygen uptake measured during maximum exercise testing) in selecting patients with the lowest probability of survival and, thus, the highest probability of benefit from transplantation (G. William Dec, MD, written communication, January 1998). The decision regarding timing of listing a patient with severe heart disease for transplantation can be difficult. Although survival rates after transplantation could be best if less-sick patients were selected, these patients’ prognosis without the transplant could be just as good as their prognosis with it.19 On the other hand, truly moribund patients with severe secondary organ dysfunction despite maximum support may have such high complication rates after transplantation that the use of scarce donor organs for such patients is unethical. Determining when in the course of an individual patient’s disease the individual should be listed for transplantation (that is, the point at which transplantation will improve his/her individual prognosis and lead to survival probability as good as heart transplant patients overall) is something of an art. The appropriate timing changes to later in the course of the disease as more effective measures to treat heart failure are developed.

Number of Transplants

The International Society for Heart and Lung Transplantation (ISHLT) has maintained a registry of heart transplanta- tions and outcomes since 1980 and, in 1987, combined with UNOS. Reporting to the registry is mandatory in the United States and the vast majority of non-US heart transplant centers contribute their data as well. Figure 1 is a graph of the number of transplantations per calendar year reported to this registry20 and demonstrates a plateau of annual procedures worldwide at about 3500 per year since 1990. This plateau is widely agreed to be due to limitations of donor availability and there is no expectation that the numbers will increase substantially in the foreseeable future. In the United States, the number of transplantations has plateaued at an annual rate of approximately 2500 procedures.

Number of Transplant Centers

According to UNOS registry data, there are currently 135 heart transplant centers in the United States, many of which perform few procedures. A recent analysis of registry data noted that 53% of US heart transplant centers (n = 80) performed fewer than 9 transplantations per year and patients at these centers had a significantly higher risk of mortality at early and intermediate points.21 The only real control of the proliferation of programs has been the setting of criteria for qualifications and training experience for cardiac transplant physicians by UNOS and the requirement that personnel meet these requirements for a program to be enrolled in the donor procurement system. In 1986, the Health Care Financing Administration (HCFA), which oversees the US Medicare program, approved coverage and payment for heart transplantation for Medicare recipients and established a transplant facility approval process that centers are required to complete to receive Medicare payment for heart transplantation.22 Most heart transplant recipients are not eligible for Medicare, but the approval program allows analysis of medical-center results according to whether programs have met the extensive HCFA criteria. A recent analysis of more than 9000 heart transplantations performed in US centers between 1986 and 1992 compared outcomes among patients having their procedures at centers with and without Medicare approval and found significantly lower mortality rates for patients from the centers that satisfied Medicare criteria, suggesting that the Medicare criteria can indeed identify “centers of excellence.”23

Organ Procurement and Distribution

Since 1986, the federal government has contracted with UNOS to operate the Organ Procurement and Transplantation Network (OPTN) to develop an equitable, scientific, and medically sound organ allocation system. The policies of this organization receive broad input from numerous constituencies, including transplant recipients, patient and donor families, and the OPTN membership, as well as concerned individuals and organizations from throughout the United States. In the current heart allocation system, a central computerized registry of waiting cardiac recipients categorized according to ABO blood type and body size is maintained by UNOS. When potential organ donors are reported to the OPTN, the heart is offered to the appropriate (according to blood type and body size) recipient with the most time accrued on the waiting list in the local area. If no appropriate recipient is available locally, the donor network searches the list for the next appropriate

Figure 1.—Number of heart transplantations (gray bars) and mean donor age (black line) per calendar year. Reprinted with permission from Hosenpud et al.20

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recipient within an 800-km (500-mile) radius, then within a 1600-km (1000-mile) radius. The roughly 3-hour limit on cold ischemic preservation time generally precludes more than a 1600-km transport distance for donor hearts.

The only exception to the policy of patient priority according to time accrued on the waiting list is the listing of critically ill patients, defined as those confined to intensive care units and requiring intravenous inotropes and/or mechanical devices for circulatory support, as “status I,” with priority for donor hearts over others.

As noted earlier, the procurement of the donor heart usually involves one surgical team traveling to the donor hospital to explant the donor heart and transport it back to the transplant center while another surgical team prepares to operate on the recipient. Because most donors now provide multiple organs for transplantation, which may in turn go to multiple transplant centers, coordination of multiple surgical teams converging on the donor hospital can be a complicated problem.

**AFTER SURGERY**

**Survival Rates**

Survival was inferior (with 1-year survival rates of 70%) prior to 1985, when cyclosporine use became widespread. However, since 1985 survival rate has not increased, with current overall 1-year survival rates of approximately 80% (Figure 2). Survival significantly declines for each increase in decade of age, with a clinically significant decrease for patients older than 65 years (Figure 3). For the pediatric age group, the older group (aged 6-15 years) has survival virtually identical to that of the adult population, whereas the youngest patients (aged <1 year) have the worst survival probability and those aged 1 to 5 years have intermediate survival rates (Figure 4).

**Recovery and Quality of Life**

The majority of heart transplant recipients are able to return to New York Heart Association (NYHA) functional class I and physical and occupational activities of their choice.

**Immunosuppression**

Since the introduction of cyclosporine, which acts mainly by inhibiting lymphokine production and release, into clinical heart transplantation in the early 1980s, most centers have used a 3-drug regimen for long-term immunosuppression consisting of cyclosporine, azathioprine, and corticosteroids. Probably no
centers have identical drug protocols but all follow the principle of administering the most intense immunosuppression early after surgery and tapering the intensity later (in many cases, discontinuing maintenance corticosteroids). Many centers additionally use early postoperative lympholytic, or “induction,” therapy for several days, with either polyclonal antithymocyte globulin or the monoclonal anti-CD3 preparation OKT3. The advantages of using induction therapy have been debated but probably include the ability to delay the introduction of cyclosporine in patients with initially marginal renal function and a delay of the first rejection episode, which occurs when the patient is in a physiologically more recovered state, with resolution of many of the changes of end-stage heart failure.

The 1990s have been an era of much activity in the field of new immunosuppressive drugs and modalities, and several have found their way into clinical practice in heart transplantation either as part of maintenance immunosuppression or as therapy for graft rejection. Tacrolimus was first shown to be an effective substitute for cyclosporine in liver transplantation (and is perhaps uniquely effective for liver grafts), but is effective for “rescue” therapy for intractable rejection in cardiac transplant recipients when substituted for cyclosporine in the maintenance regimen. However, in randomized trials comparing initial tacrolimus-based with cyclosporine-based immunosuppression in heart transplant recipients, there did not appear to be a major advantage to using tacrolimus. Both drugs are nephrotoxic and neurotoxic but have different adverse effect profiles otherwise. Cyclosporine is associated with a high incidence of arterial hypertension, hirsutism, and gingival hyperplasia, whereas tacrolimus is associated with development of glucose intolerance.

Mycophenolate mofetil is the second new immunosuppressive agent to be approved by the US Food and Drug Administration (FDA) in the 1990s and is widely accepted and used as a substitute for azathioprine in renal transplant regimens. A preliminary report of its superiority to azathioprine in cardiac transplant recipients is encouraging (Jon Kobashigawa, MD, oral communication, 1998), but longer-term follow-up will be required to know whether the drug fulfills the laboratory model promise of decreased incidence of graft coronary artery disease and makes the high cost of this drug worthwhile investment. A number of other drugs (rapamycin, deoxypergualin, lefunomide) are currently in preclinical and clinical trials, and the options for designing individual immunosuppressive regimens will multiply greatly in the coming years. It seems doubtful that we will ever again see a time when all patients are given basically the same drug regimen.

Augmented corticosteroid doses remain the basic form of therapy for cardiac graft rejection, but a number of other drugs and modalities have been investigated and are used for steroid-resistant rejection. They include the use of a course of daily lympholytic therapy with antithymocyte globulin or OKT3, the adjunctive use of methotrexate in doses similar to those used for rheumatologic diseases, the administration of total lymphoid irradiation, and the use of photopheresis.

LIMITATIONS OF TRANSPLANTATION

Early Limitations: Infection and Rejection

Given the current nonspecific means available to suppress the immune system, all organ allograft recipients can be viewed as existing on a fairly fine line between overimmunosuppression and underimmunosuppression. Underimmunosuppression can lead to graft rejection and even graft loss, whereas overimmunosuppression leaves a functioning graft but high susceptibility to opportunistic infections. With all organ allografts, the tendency toward rejection is most active early after transplantation and diminishes over time. The intensity of immunosuppression is usually adjusted accordingly.

Rejection of the cardiac allograft generally is not accompanied by clinical signs or symptoms in its early stages and may prove irreversible in the later stages, when clinical signs do supervene. Although a wide variety of electrocardiographic, echocardiographic, immunologic, and other modalities have been investigated as means to screen for early cardiac allograft rejection, none have been agreed on to have the high degree of sensitivity and specificity required to guide life-and-death decisions regarding immunosuppression. The endomyocardial biopsy was introduced at Stanford University, Stanford, Calif, in 1974 as means to diagnose rejection and assess the adequacy of rejection therapy, and it remains the “gold standard” of rejection diagnosis in 1998. The biopsy specimen is obtained by a transvascular approach with standard biopsie forceps, usually from a percutaneous right internal jugular approach, and processed for light microscopy. It is performed as an outpatient procedure and takes approximately 20 minutes to accomplish. An internationally accepted grading scale for reporting cardiac allograft rejection was adopted by the ISHLT in 1990 and consists of grades 0 to 4, with 4 being the most severe rejection. The recommended frequency for performing surveillance right ventricular biopsies varies from program to program, but most perform weekly biopsies for the first 4 postoperative weeks, then every other week for another month, monthly until 6 months following surgery, and every 3 months until the end of the first postoperative year. After the first year biopsy surveillance is highly individualized. Therapy for rejection generally consists of increasing immunosuppression; the intensity of the increase is determined by the histological and, occasionally, clinical severity of the rejection episode.

The most common, basic way to augment immunosuppression is by increasing corticosteroid dose, either as a “pulse” with intravenous methylprednisolone or with an increase in and subsequent taper of the oral maintenance dose. More intensive therapy, necessitated by the development of hemodynamic compromise or histologically high grades of rejection, usually includes lympholytic therapy (with polyclonal antithymocyte globulin or monoclonal anti-CD3 globulin) added to the augmented corticosteroid dose.

Infectious complications after heart transplantation, often associated with a necessarily high level of immunosuppression, run the gamut of opportunistic viral, protozoal, fungal, and bacterial organisms. The lung is the most frequent site of infection but clinical infections can occur in virtually any organ. A high level of surveillance is most important to detect such infections early in their course, especially with screening chest x-rays, and an aggressive approach to prompt specific diagnosis and therapy of the infection is essential for patient survival.

Only a few regimens for infection prophylaxis have been shown to be effective in transplant recipients, but these are important to pursue. They include prophylaxis against Pneumocystis carinii with sulfamethoxazole and trimethoprim, and prophylaxis against cytomegalovirus with ganciclovir and probably with cyto-megalovirus hyperimmune globulin in cytomegalovirus-seronegative recipients of a seropositive donor’s organ.

Late Limitations: Graft Coronary Artery Disease and Malignancy

A diffuse obliterative form of coronary arteriopathy affects increasing numbers of cardiac transplant recipients over time and its ischemic sequelae are currently the main complications limiting truly long-term survival in cardiac transplant recipients. The disease is angiographically apparent in up to 10% of patients 1 year after transplantation and affects approximately 50% by 5 years following the procedure. The vascular disease is lim-
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The diffuse nature of their disease and cutaneous cancers. Organ transplantation has proved to be no exception, and a registry based at the University of Cincinnati, Cincinnati, Ohio, has documented the incidence of posttransplant malignancies since 1968. According to the most recent ISHLT registry report, malignancy accounts for 11.8% of deaths after heart transplantation.20 Most of these have been posttransplantation lymphoproliferative disease.

There is convincing evidence that most posttransplantation lymphoproliferative disease is related to infection (either primary or reactivation) with the Epstein-Barr virus.67-69 The tumors frequently occur in unusual extranodal locations and may respond to reduction in immunosuppression,70 although such reduction is clearly a “double-edged sword” in the field of heart transplantation because it may result in graft rejection.

THE FUTURE

Improved Immunosuppression

Newer drugs that are moving into clinical trials so far seem to have fewer toxic effects than those they may replace, and, in animal models, several have shown promise of being associated with a lesser incidence of cardiac allograft vasculopathy. Even if this were the only advantage of a new drug it would be a major advance in the field. Ultimately, it is hoped that advances in immunology will lead to the ability to induce a state of specific donor tolerance in which long-term or maintenance
immunosuppression is unnecessary. Recent reports of the use of CTLA4-Ig and anti-CD40 ligand in animal models have been encouraging in this regard. 19

Permanent Mechanical Support
Even the development of the most optimum ways of suppressing the immune system will not address the disparity of the increasing demand for donor hearts and the plateau of supply at a level that provides perhaps 1 in 10 potential recipients with a needed donor heart. For this reason, alternatives to cardiac allografting continue to be actively pursued, and none is more vigorous than the work on nonbiological or mechanical heart replacement. First introduced as temporary support devices or bridges to transplantation in the 1980s, both the total artificial heart 27,28 and the left ventricular assist device were intended ultimately to provide alternatives to biological replacement of the heart. The left ventricular assist device has proved quite effective as a bridge to transplantation, extending life and restoring moribund patients to a much more normal physiological state and much better candidacy for transplantation. 27,28 A first clinical trial of a left ventricular assist device as an alternative to medical therapy for patients who are not transplant candidates (for reasons of age or comorbid conditions) is currently underway (Eric A. Rosse, MD, written communication, January 1998) and will likely be followed by other clinical trials directly comparing left ventricular assist device support with transplantation. The advantages of a mechanical device for cardiac replacement include the lack of need to suppress the immune system and all of the consequences attendant on such suppression, as well as potentially unlimited supply of devices, in contrast with the limited supply of donor hearts. The disadvantages of mechanical devices (at least of the current generation of them) include the human immunodefiency virus 1 and 2 epidemics resulting from simian retroviruses introduced across species lines into humans. 27 There is a general presumption that the greater phylogenetic distance between humans and swine makes swine safer donors, but no data exist to substantiate this assumption. This potential risk to public health has led some prominent leaders in the field to call for a moratorium on human xenotransplantation until the risks are better defined and national and international policy addresses the issue at a societal level. 27 Thus, whether xenotransplantation will become a common part of clinical practice remains unclear, but if and when it does, the field of organ replacement will have taken its most major step forward.

Conclusion
Thus, cardiac transplantation has become a mature field during the past 30 years. Slow progress is being made in conquering the complications that limit truly long-term survival, but the limited donor supply will always mean that transplantation can only save a fraction of those who could benefit from it. How to distribute these scarce organs is a difficult societal and ethical issue and one that is currently being addressed at the highest levels. In the larger picture, alternatives to allografting for cardiac replacement are the most pressing need.

References