Taking Heart — Cardiac Transplantation
Past, Present, and Future
Sharon A. Hunt, M.D.

Heart transplantation hit the international news with a splash in December 1967, when the first human-to-human transplantation was performed in South Africa by Christiaan Barnard, and the first transplantation in the United States, performed by Norman Shumway at Stanford University, followed a month later. Initial enthusiasm for the procedure was quickly curbed, however, when it became evident that survival rates were usually measured in days or weeks. This poor survival was due not to poor surgical technique, but to an inadequate understanding of the type of postoperative complications one should anticipate and a lack of tools for addressing these complications when they were recognized.

A 1971 cover story in Life magazine, entitled “A New and Disquieting Look at Transplants,” reflected the public perception of

Dr. Flores is director of the Center for the Advancement of Underserved Children and a professor of pediatrics, epidemiology, and health policy at the Medical College of Wisconsin and the Children’s Research Institute of the Children’s Hospital of Wisconsin, Milwaukee.

the field, though the article focused specifically on the psychosis the patients experienced in the intensive care unit as a result of sleep deprivation caused by intense, round-the-clock surveillance by anxious clinicians. Problems that were less easily solved included the occurrence of allograft rejection and opportunistic infections.

After the early enthusiasm for the procedure subsided, a decade of slow, steady clinical research ultimately led to some viable solutions for these clinical obstacles, as well as to the recognition of an unanticipated hurdle that today remains the most important factor limiting long-term survival after heart transplantation: premature development of transplant coronary vasculopathy. Little has changed in surgical technique since the 1960s except for the introduction of the bicaval anastomosis (see figure), which better preserves the integrity of the sinus node and the architecture of the right atrium. In the 1970s, a number of developments helped to make the field ripe for resurgence. First, the use of endomyocardial biopsy to confirm a clinical diagnosis of acute allograft rejection and to document the adequacy of therapy was validated. After the introduction of cyclosporine-based immunosuppression in 1980, the clinical diagnosis of rejection became much more problematic, so routine surveillance biopsies of the heart were introduced; this approach remains the mainstay of diagnosis of rejection for the first one to three years after transplantation.

A second major advance during the 1970s was the development of safe methods for the cold preservation of donor hearts, with cold-ischemia times of up to three hours. This development opened the way to the procurement of hearts from distant donors, a system that is universally used today. In the early days, the donor had to be transferred to the transplantation center so that the heart could be harvested in an operating room adjoining that of the recipient — a cumbersome and expensive requirement to which many families of potential donors objected.

Subsequent legal recognition of the concept of brain death led to the founding of local and then national organ-procurement systems with uniformly applied criteria for the allocation of donated organs. For the past two decades, the national organ-allocation system has been run by the private United Network for Organ Sharing under contract to the federal government.

During the same period, recognition of which opportunistic infections were to be expected and their most common presentations in transplant recipients led to a highly aggressive approach to infectious complications and the institution of effective prophylaxis against some of the more prevalent ones — for example, the use of trimethoprim–sulfamethoxazole against Pneumocystis carinii infection.

The undisputed leader of the field during the 1970s was Stanford’s Shumway. Dr. Shumway died in February of this year, but not before seeing his vision of the wider application of heart transplantation become a reality.

It had initially been anticipated that young, healthy donor hearts would live out their biologic destiny in a new location and not develop coronary artery disease for many decades. This supposition was proved invalid in the early 1970s, when a number of early recipients of heart transplants died from ischemic heart disease. Pathologically, this disease was a form of intimal thickening that was characteristically diffuse, concentric, and longitudinal. Since it was entirely limited to vessels of the allograft, the intuitive conclusion was that it was immunologically mediated. Subsequent research has suggested that the process involves an initial immunologic insult to the coronary vasculature that can be exacerbated by nonimmunologic factors, such as dyslipidemia, diabetes, and viral infection. The model of graft vasculopathy has contributed greatly to an understanding of the biology of vascular injury and its sequela.

Investigations into therapies for graft vasculopathy have centered on palliation and prevention. Standard palliative percutaneous interventions, including angioplasty and coronary stenting, have been shown to be safe and to have some short-term effectiveness in the occasional patient with one or more focal coronary narrowings. However, the technology is not applicable in the majority of patients with diffuse, distal disease. Pharmacologic interventions have thus far been validated mainly for the prevention of this disease. Such interventions have included statins and the newer immunosuppressive agents mycophenolate mofetil and the mammalian target of rapamycin (mTOR) inhibitors everolimus.
A Standard (Biatrial) Heart Transplantation

B Orthotopic Cardiac Transplantation with Bicaval Technique

Standard (Panel A) and New Bicaval (Panel B) Surgical Anastamoses.
and sirolimus (formerly known as rapamycin). A single study involving 46 patients has suggested that sirolimus has the potential to reverse angiographic disease in some patients with established disease.5

Most postoperative medical regimens for cardiac-transplant recipients now consist of multidrug immunosuppression incorporating a calcineurin inhibitor (cyclosporine or tacrolimus), a cell-cycle agent (usually mycophenolate mofetil), and corticosteroids in the early postoperative period. Most programs also include a statin. With increasing frequency, the mTOR inhibitors are being introduced later after transplantation, to help spare renal function by permitting the use of lower doses of the calcineurin inhibitors and to prevent graft vasculopathy. The use of mTOR inhibitors in the very early postoperative period is limited because of concern regarding potential impairment of wound healing.

In the 21st century in the United States, the summation of all these advances has produced an annual cohort of approximately 2000 new transplant recipients, who have an 87 percent probability of surviving the first year after transplantation, a “half-life” in excess of 10 years, and a high probability of an excellent quality of life.3 The number of transplants is strictly limited by donor availability and has changed little over the past 15 years, despite a trend toward using older donors. These 2000 recipients represent a small dent in the overall population of patients who are dying of end-stage heart failure, but for younger patients without serious coexisting conditions who are willing to submit to the requirement of a lifetime of medication and medical care, this possibility is an outstanding alternative to early death.

The use of xenografts (organs...
from nonhuman species) has been viewed as an attractive alternative to human donors, potentially providing an unlimited supply of organs. Unfortunately, substantial immunologic barriers — as well as concerns regarding the transmission of infectious agents that are benign in one species but not in others (as the human immunodeficiency virus proved to be) — have thus far been insurmountable. As Dr. Shumway was fond of saying, “Xenografts are the future of transplantation . . . and always will be.”

However, the future is likely to hold improvements in the quality and length of life for heart-transplant recipients, as bench work in fields such as vascular biology and immunology translates into clinical reality. Circumventing the problem of relentless graft vasculopathy will clearly prolong many lives. And achievement of the holy grail of transplantation — immune tolerance or acceptance of the graft with maintenance of normal immune function in other respects — will eventually open the door to normal lives and life spans for all transplant recipients.

Dr. Hunt is a professor of cardiovascular medicine at the Stanford University School of Medicine, Stanford, Calif.

Thoughts from the Transition Zone

J. Terrance Davis, M.D.

I got the call earlier today. A teenager has been on life support at our hospital while awaiting a heart transplant. She was running out of time when we got the offer of a heart, and it was my job to recover the organ. Before I knew it, I was arriving at a suburban hospital 600 miles away, accompanied by my resident and a procurement technician. When we drove in, it seemed like any other emergency department at night.

But as we walked through the emergency room (ER), all grew quiet. There were eyes upon us, and as people stepped aside, I sensed their ambivalence at our arrival: “Something good will come of this. It’s almost over. What a shame.” In this small hospital, the tragedy of a young life lost in a motor-vehicle accident had permeated every department.

This is the donor zone. Teenagers stood in the hallways crying and comforting one another, medical teams had given their all but to no avail, and the family was trying to come to grips with the loss. It is a zone of intense sadness. Out of sight of all this, back in the operating room, a heart was beating in a body with no future.

The recovery was routine — and yet extraordinary. An army of coordinators had been on the telephone for hours to bring together people who could maximize the potential of orphaned organs in a body that was about to die. Working side by side, we and another team that was taking the liver and kidneys divided shared vessels in the middle. When we all were ready, I put the cold potassium solution into the heart, which immediately stopped beating and turned into a flaccid, pale, cold, apparently lifeless organ. I removed the heart from the body, realizing that this act completed the process of death and marked the beginning of a difficult time in the donor zone.

People here would go home grieving. But I had much to think about — no time to reflect. I thanked everyone, and we jumped into the waiting ambulance. The funeral procession for the donor was yet to come; this was a different sort of journey for a heart headed to a new home.

Soon, we will enter the recipient zone. It will be permeated by anticipation, excitement, and hope. As I walk through that ER, eyes will once again be on me, but the message they convey will be different: Good news! They’re waiting for you!