The Cutting Edge

A Look to the Future in Transplantation

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The American Society of Transplant Surgeons has seen remarkable evolution and progress during its brief 15 years of existence. It has served as a scientific bond for a group of pioneers and their followers who have developed and applied the most exciting and dramatic new method of therapy ever achieved—restoration of life by replacement of a diseased vital organ. Remarkably, almost all these pioneers are still actively practicing and continue to make meaningful contributions both scientifically and at a societal level.

The phenomenal success of solid organ transplantation has led directly to, or served as a catalyst for, major advances in numerous other fields, such as basic immunology, infection, nephrology, hepatology, cardiology, and pharmacology. The field of transplantation and the society are truly at the cutting edge of scientific advances in medicine—hence the title of this talk. But what about the future and the problems this rapid progress has already created? A cutting edge can be jagged and rough when greatly magnified and dangerous to those not skilled in its use.

The doomsday call is often heard reverberating from within our ranks, reinforced by the suffocating specter of malpractice, the depressing restriction of funds for research, the increasingly oppressive effects of bureaucratic controls and interventions, and a waning of interest from the public that has already seen the miracles of our handiwork and is ready to move on to bigger and more exciting miracles. Undoubtedly, there are some of us who will succumb to these pressures and retreat, as others have, to a more comfortable and less hectic life at one of the many hernia clinics of America. What about the rest of us and the future of transplantation and this sentinel society during the next 15 years, a period when nearly all of the pioneers will have retired?

I would like to begin with a review of where we have been during the last 15 years for four specific organs—the heart, liver, pancreas, and kidney—in order to address some of the current problems and to project what I think will come in the next 15

years so that we, as a society, can begin to plan for the inevitable and sometimes dramatic changes.

Cardiac transplantation had a dramatic but dismal start in the U.S. in 1968, dismal because most of the procedures at that time were done by technically adept cardiac surgeons who were ill prepared to deal with the immunosuppressive problems encountered in these difficult patients. As a result, only 15 heart transplants were performed in 1974 with a success rate, judged by one-year graft survival, of less than 50%. However, pioneering work with regard to patient management, largely at Stanford, and the commercial introduction of cyclosporine in 1983 made a difference in both the number performed and the success rate. More than 100 times as many heart transplants were done in 1988 as in 1974, and the success rate almost doubled, to 81% one-year graft survival, for those transplants being performed in 1987.

Liver transplantation has developed in this country primarily because of the efforts of a single individual, Dr. Tom Starzl, to whom the society is greatly indebted also for being its first president. With fewer than 20 transplants per year before 1980, the number performed lagged behind the number of heart transplants until 1988 when 1680 were performed like the heart transplants, the biological acceptance of the technically successful liver transplant which increased appreciably with the introduction and routine use of cyclosporine, which was available to Starzl before commercialization.

Transplantation of the pancreas has considerably lagged behind the transplantation of the heart, liver, and kidney, at least in numbers, because of the relatively poor technical success rate, limited ability to detect early rejection, and lack of convincing evidence that it prevented the ongoing progression of secondary complications associated with diabetes mellitus. Although first performed in the late 1960s, pancreas transplant activity was virtually nonexistent during the first few years of the society, but it reached nearly 200 in 1988 with a projected success rate of greater than 60% for the country as a whole.

ASTS was formed only a year after the initiation of the ESRD program that provided federal funding for kidney transplantation. A total of 3190 renal transplants were performed in 1974. There was a progressively rapid increase in the number of transplants until 1986, but thereafter both the number and success rate stabilized. It is noteworthy that the one-year graft survival did not improve between 1985 and 1987. Also of interest is the fact that the growth in kidney transplants has come largely from increased numbers of cadaver transplants. There have always been fewer than 2000 living donor renal transplants performed in the U.S. each year. This is of importance because the one-year graft failure rate has consistently been more than twice as high in recipients of cadaver organs, with approximately 1 in 4 organs of primary cadaver grafts currently being lost by the end of the first year. Since the survival trend has actually decreased during the last three years, it is unlikely that improvements in survival will occur without major changes in immunosuppression.

The ESRD program has seen an almost linear increase in the number of enrollees since its inception. Currently, there are more than 1,200,000 patients on dialysis in the U.S. with an annual increase of 9% per year. The cost of the ESRD program has risen

proportionately, although there has been little increase in cost during the 1980s when adjusted for inflation. The real dollar amounts per patient have been continuously eroded, by more than 50% since 1974, because of the insidious effects of inflation. It is appropriate to ask how this influences patient care.

The number of patients entering the waiting list for cadaver renal transplant has risen more sharply than the entry of dialysis patients, by approximately 14% per year. Currently, more than 16,000 patients are on the UNOS list for cadaver organs.

With all solid vital organs, there is an ever-growing discrepancy between the number of organs transplanted and the number of patients who could benefit from transplantation. It should be clear that the number of transplants that are being performed today is strictly limited by the availability of donor organs. Last year, there were only 4,083 donors of solid organs in the U.S., and the first quarter of this year appears to be down by approximately 10%. There may be several reasons for the lack of increase in suitable cadaver organ donors in the last three years: (1) improved care of the trauma patient, especially patients with neurosurgical trauma, because of advances in the field and the development of trauma centers; (2) a reduction in the incidence of deaths from motor vehicle accidents because of the increased use of passive restraint devices and tougher laws for driving under the influence of alcohol or drugs; (3) exclusion of many potential donors because of routine testing for hepatitis and HIV (this exclusion will become worse with testing for hepatitis C—it is noteworthy that the leveling off of cadaver donors in this country coincided roughly with the introduction of routine testing of donors for HIV); (4) exclusion of donors who might be in a high-risk category for the development of HIV infection; (5) possible resistance to organ donation because of required request legislation. I do not believe this to be an important factor, but there are insufficient data to make a meaningful conclusion.

It is probable, although not certain, that the number of potential donors in the U.S. who are suitable for organ donation is actually decreasing. If so, the percentage of suitable donors actually used for transplantation may be increasing. At the same time, it is clear that the organ procurement effort could be greatly improved and that ASTS should expend a major effort in this direction. In my opinion, a substantial increase in cadaver organ donation will not come from public education alone. Difficult ethical issues must be addressed and new ideas thoughtfully explored such as variants of implied consent, required referral, the use of living nonrelated donors, and the use of higher primates. Most of all, the public's trust and support must he rigorously maintained.

Renal transplants from living related donors clearly give the best results, but less than 2,000 are performed each year. This number could be increased significantly with better family counseling and by removing the disincentives for donation. As a cost-effective measure, a living donor should be guaranteed that he or she would not lose income because of donation, and full disability insurance should be provided for the extremely unlikely possibility that the donor would be unable to return to gainful employment. Both the pressure for the need for organs and the clearly superior results

of living related donor transplants will result in a reassessment of the use of living donors for transplantation including nonrelated donors.

Another way to improve organ availability is, in simple terms, to improve the results. A 15% increase in one-year graft survival would mean that 15% more organs would be available for transplantation during that year and perhaps even more during the ensuing years. Some ethical questions will arise in addressing this issue; as an example, with the current failure rates, should we be transplanting the highly sensitized patient who has had prior loss of a kidney from rejection in the first six months knowing that the failure rate will be l0% to 15% worse than for a nonsensitized patient? However, continued incisive and productive research is obviously the key to achieving better graft acceptance. It is here that this organization can make one of its greatest impacts. I believe that near-perfect graft survival will be a reality in the very near future, but achievement of this goal will require increased involvement of the federal government by means of substantial support for relevant research. It will be one of the major roles of ASTS to convince the funding agencies, and perhaps more importantly Congress, that research in transplantation is cost-effective, using specific data derived from UNOS, the Renal Disease Data System, and HCFA. With aggressive investigation, tolerance induction with minimal or no immunosuppression after the first year should be possible within the next five years. This will be achieved by antigen presentation with or possibly even without lymphocyte reduction coupled to the administration of multimodality immunosuppressive therapy, based primarily upon the use of cyclosporine. Even small changes can make an impact on outcome. As an example, simply starting cyclosporine therapy 24 hours before transplant can result in a 53% reduction of the occurrence of any rejection episode in the first year after a living related donor renal transplant.

Within the next 15 years, active induction of suppressor networks as well as anti-idiotypic regulation will be possible in man prior to transplant. It will also he possible to perform ex vivo manipulation of regulatory networks with introduction of "educated" cells back into the patient. Posteducation driving of suppressor networks may be done with the use of certain agents such as prostaglandin E_2, prostacyclin and/or their analogues, or perhaps more important, by suppressor mediators produced in large quantity by recombinant technology. Monoclonal toxin-linked antibodies will be developed that can be used to treat rejection or delete selected subsets of cells, a technique that will be useful for preparation of a graft by reduction of antigen-presenting cells as well as for treatment of the recipient in preparation for grafting. Hybrid antibodies, as we have already heard, will have several important purposes in tolerance induction and will be useful for providing improved agents for treatment of rejection. Toxin-linked lymphokines may also be useful for the highly selective depletion of certain types of cells. Successful clonal deletion by activation of antigen-reactive cells or networks followed by their deletion using cytotoxic agents or toxin-linked monoclonals and/or lymphokines should prepare the way for the successful transplantation of the highly sensitized patient and also for the use of xenografts.

One extremely promising therapeutic approach is the use of gene therapy in transplantation. The human genome will be sequenced in the next 15 years. Even

using current technology it will be possible to insert genes into somatic cells, especially the bone marrow, which will offer several exciting possibilities. Immunoregulatory genes could be inserted that may alter the ease of acceptance of a graft, as well as change resistance to tumor or disease. More obvious is the use of gene therapy for treatment of genetic or metabolic diseases, such as diabetes mellitus or severe combined immunodeficiency disease that can occur because of absence of a single enzyme. Indeed, fewer people may need transplantation once gene therapy is fully developed and applied to humans—as it will begin to be in the next 15 years. It is important that ASTS members be first-line sources of information for Congress, the NIH, and other government funding agencies to encourage and develop support for the basic clinical research needed to accomplish such goals. Emphasis needs to be placed on the enormous cost savings because of improved outcomes. ASTS should also play an active role in the development of NIH-sponsored multicenter studies for the evaluation of new therapeutic techniques via the Scientific Studies Committee.

The next 15 years will see several important social as well as scientific changes. There will be increased federal and societal regulation of our practices. The End-Stage Renal Disease Program will serve as a model for outcome analysis that will require the development of accurate data. In this regard the data base of UNOS and the Renal Disease data system will be most helpful to both the government and ASTS. There is an effort by some to release center-specific data for outcome, but I believe such efforts should be vigorously opposed until there is a mechanism that is uniformly predictable that will properly weigh and adjust for various risk factors. We will see escalating pressures in the field of transplantation because of an increasingly insufficient availability of organs to meet the needs for transplantation. Through a concerted effort, however, I believe that in about three years there will be a modest increase in the availability of cadaver organs that will reach a maximum of about 8,000 to 9,000 solid organ donors per year 10 years from now.

Weighing all these factors and others for the four major organs discussed before, I will accept the risk of being wrong and make projections for the next 15 years. By 2004, the one-year graft survival rate for heart transplants will improve to 95%, and approximately 3,200 transplants will be performed per year. Transplantation will remain the preferred form of cardiac replacement, although totally implantable artificial hearts may be developed by then. The one-year survival rate for liver transplants will rise to 90% with twice as many being done. However, the needs will not be met partly because liver transplantation will be extended to more patients with Laennec's cirrhosis and to patients with malignant tumors using adjuvant chemotherapy protocols. For pancreas transplants, there will be a progressive rise in the success rate to 90% within the next 5 years and to 95% by the end of 15 years. The number transplanted will grow remarkably greater on a yearly basis, rising to 400 or 500 per year within the next five years and doubling again within the subsequent five years. However, following this there will be a leveling off of pancreas transplants and maybe even a fall because of the possibility of prevention of the disease by genetic engineering, which will have its greatest effect later than 2004, and because of the successful use of islet transplants in about 8 to 10 years.

As a result of task-directed research, the success rate will steadily rise to achieve an overall one-year renal graft survival of approximately 95%: 98% for living-related kidneys, 92% for cadaver kidneys. These results will occur despite an enlarging proportion of transplant recipients with increased risk factors or severe complicating disease. There should be more living donor kidney transplants done during the next five years because this will remain clearly the best method of treatment, and there is little documented risk to the donor. By the year 2004, it may be possible to reach a steady state for kidneys where the supply is roughly equal to the demand. Heart-lung and lung transplantation likewise will become increasingly successful. Clinical transplantation by 2004 clearly will be extended to skin transplantation for reconstructive surgery, small bowel transplantation, and limb transplantation.

Where should ASTS put its primary efforts during the next 15 years? I believe the major effort should be placed on improving the science of transplantation and rapid application of the laboratory advances to patient care. Strengthening the relationship with other scientific societies will be an important tool for increasing our effectiveness in dealing with federal and administrative issues. Because of this, I have appointed a scientific liaison committee to improve the strength of our communications and the effectiveness of our voice. There is a continued need for interaction with Congress, the NIH, and the public at large with particular regard to continued and improved ability to provide quality research in this exciting era. As an obvious example, we must take the responsibility along with others for the continued availability of animal research.

In conclusion, ASTS has the opportunity to continue at the cutting edge of scientific investigation and its application to patient care for the cure of disease and improvement in human suffering. We are living in an age of wonderment and expectation—wonderment of the advances that have already been made in our field and expectation that even our wildest dreams will someday, and perhaps soon, be achievable.

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