INTRODUCTION

Historical Perspective on Organ Transplantation and Donation


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Successful organ transplantation is one of the many medical miracles that have occurred in our extraordinary century. The dream is ancient. The well-known story of Cosmos and Damian, the martyred twin physicians who replaced the gangrenous limb of a white sacristan with that of a dead Moor, is visually recorded by many artists. However, it was not until the 1900s that scientifically documented attempts at organ replacement were made, and not until the last half of this century that success was achieved.

Although there was much faltering along the way, continuous advances in surgical technique, preservation, immunosuppression, and control of infectious diseases have now made success routine, so much so that the demand for human organs far exceeds the supply. This shortage has prompted a resurgence in xenotransplantation research (1), an avenue with the potential to lead us full circle. The first recorded organ transplants in humans (during the first quarter of the century) were from animal sources (2). All failed immediately. With a few exceptions (3), so did subsequent transplants from human donors until the landmark identical twin cases carried out at the Brigham Hospital in Boston during the mid-1950s by Murray, Harrison, Merrill, and associates (4).

Cadaver kidney transplants, however, continued to fail, as did most nonidentical twin related donor transplants, until the introduction of chemical immunosuppression in the 1960s (5). When azathioprine and steroids were used together, reversal of rejection episodes and long-term graft function became possible (6), feeding the stream that grew into the torrent we see today.

The sequential introduction of more effective immunosuppressants (polyclonal antilymphocyte preparations in the late 1960s and 1970s (7,8), and cyclosporine (9,10,11) and monoclonal antibodies (12) in the 1980s) were associated with
continuous improvement of results. By the early 1970s, well organized transplant teams were in place in several institutions, reimbursement for kidney transplants was assured by Medicare, and liver and heart transplants were beginning to be successful through the pioneering efforts of Starzl, Calne, Barnard, Shumway, and others (13-16).

In the 1980s extra-renal organ transplantation came into its own, with a success rate similar to that of cadaveric kidney transplants (17). By 1990, pancreas transplant results were also similar to that of the other organs (18).

The number of candidates for transplants of all organs dictates long and sometimes futile waits. Xenotransplantation has not yet become clinically applicable. There is a shortage of donors from closely related species (where success can be achieved in animals), while preformed natural antibodies against the more abundant but distantly related species remain an impenetrable barrier. Although these problems may be solvable and warrant vigorous investigational efforts, it is almost certain that during the next decade clinical transplants will still require human organs. Therefore, vigorous efforts are needed to increase their supply.

The history of organ donation is complex. As mentioned, the first successful kidney transplants were from living related donors. Although generally accepted as a legitimate act of altruism in the United States, there is still controversy over, and discomfort with, violating the medical imperative "primum non nocere" -- first do no harm (referring to the donor, of course). Variations in the prevalence of this attitude are reflected by the different rates that living related donor transplants are performed throughout the country. Historically, living related donors were successful because a fresh, undamaged kidney that would function immediately was available, and the close genetic matches mitigated against rejection during a time when the immuno-suppressive armamentarium was less than it is today. Nevertheless, it was apparent early on that it would be necessary to transplant cadaver kidneys to meet the needs of patients with end stage renal disease.

Many of the first cadaver organs were procured from individuals who were unable to come off the pump during open heart surgery, and the kidneys were removed during circulatory and respiratory support. The use of respiratory support systems for individuals with brain damage ultimately led to the concept and definition of "brain death." Formalizing criteria for brain death was necessary both to manage this tragic situation and to allow removal of organs for transplantation in the presence of circulatory and respiratory support. The publication of the Harvard Brain Death Criteria in the late 1960s (19), passage of legislation on the Uniform Anatomical Gift Act, evolution of relations between transplant centers and a network of hospitals and neurosurgeons who would identify brain dead cadaver donors, and employment of nurses designated specifically to coordinate the donation process, resulted in the process by which procurement of cadaver organs
became a standard procedure throughout the country by the early 1970s. Ad hoc sharing arrangements were made, organ procurement foundations (e.g., the Southeast Organ Procurement Foundation) and organ banks (e.g., Midwest) emerged. By the 1980s, about 2000-3000 brain dead cadavers per year were utilized for organ transplantation.

The passage of the National Organ Transplant Act in the mid-1980s led to the creation of the United Network for Organ Sharing (UNOS), standardizing and formalizing organ procurement agencies throughout the country. Most of them served more than one transplant center. There was hope that this kind of organization would, by itself, lead to an increase in organ donation, a hope which unfortunately was not fulfilled. About 4000 donors per year have been registered with UNOS from their inception (1986) through the end of the 1980s. Studies by Bart, et al (20) in the early 1980s indicated that the potential for organ donation greatly exceeded actual achievement. In two areas of the United States that he surveyed, only one in six brain dead cadavers were used. Whether the figure is similar today is not yet known, but new studies are under way. Some cadavers used in 1980 might not be used today, e.g., those with histories placing them at risk for HIV. Tests for HIV or hepatitis C were not available in 1980 but they are today, leading to further (and appropriate) exclusions. Thus, the proportion of cadavers that would be classified as suitable today may differ from the number judged suitable at the time of the Bart study. What is certain is that the number of cadavers used for donation is substantially less than the potential, and the need to increase cadaver organ donation is pressing. The potential to increase living related donation also exists. Strategies to increase donation are intertwined with ethical, financial, racial, demographic, and other considerations. It is to discuss and explore these issues that the Surgeon General's Workshop is convened.

Over the years many conferences have been held on the many issues involved in organ donation. The first was sponsored by the CIBA Foundation in 1965 (21). The extraordinary document that emerged from that conference contains discussions touching on virtually all the issues that are still of concern to us now, including living donation and the concept of brain death (the term being first used at this conference) in cadavers that allows organs to be removed while still under respiratory support. The issues raised then continue to be debated and many examples of such debates can be cited (22,23).

The most recent conferences specifically devoted to donor issues include one held in Munich in December 1990, entitled "Commerce, Ethics and Justice in Transplantation." Another, sponsored by the National Kidney Foundation (NKF) in February 1991 was entitled "Controversies in Organ Donation." The latter was designated as a consensus conference and, after intense discussion, issued statements on living donation, financial incentives, presumed consent, and minority donation. (All participants in the Surgeon General's Workshop should be familiar
with the consensus statements from the NKF Conference.)* In this instance, "consensus" does not imply complete agreement on all the issues raised, but rather gives an indication of the evolved thinking of experts over the last 25 years.

However, in general, everyone agrees that efforts are needed to increase the supply of human organs. Difference of opinion involves only the means, not the ends.

The purpose of this introduction is not to expand on the background papers for the workshop, since the papers themselves were designed to be comprehensive. The first set of papers all address the issue of how to increase donation by focusing on the individual. Campaigns that reach the general public are needed. In the final analysis, it is education that will lead to positive attitudes toward organ donation. Educational efforts must be tailored toward the various socio-economic and cultural groups that exist in this country. This will be particularly important for increasing donations among racial groups who are disproportionately affected by the diseases for which transplantation is the optimal therapy. For example, blacks comprise only 12 percent of the total United States population, but they constitute 30 percent of patients on dialysis waiting for a kidney transplant. There has been much publicity about the fact that blacks have received less than 30 percent of cadaver donor kidneys (24). This is, at least in part, attributable to the fact that kidneys are distributed according to HLA matching; 92 percent of cadaver kidneys procured in the United States have come from non-black donors, making a match less likely. Efforts to increase donation among blacks are being made, but we clearly cannot expect organ donations greater than their proportion in the population. Distribution of organs must be made equitable without having a negative impact on transplant results. Ultimately the goal should be to improve anti-rejection strategies so that HLA matching becomes less important. Distribution could then be on a basis other than the chance inheritance of certain HLA antigens.

The second set of papers discusses how to increase donation by focusing on the health care environment. Besides regulatory issues, education of our professional groups is also needed. Impediments to donation do not always spring from the attitudes of the families of potential donors, but from environments where donation is not even discussed. Professional attitudes can make a difference.

A third set of papers discusses donor criteria. The criteria for being a donor have become more stringent - and appropriately so - with regard to assuring against transmission of diseases such as HIV or hepatitis C. On the other hand, criteria for being a donor could be more liberal in regard to factors such as age. Arbitrarily

*Available on request from The National Kidney Foundation, Inc., 30 East 33rd Street, New York, NY 10016; (800) 622-9010.
chosen exclusion criteria need to be examined scientifically. The very important issue of using non-heart beating cadaver donors is also addressed. Most deaths occur with the cessation of heart beat. Can the logistical aspects be solved to make these cadavers also sources of organs? These considerations involve legal and ethical issues. Presumed consent might be necessary for use of non-heart beating donation to be possible.

Finally, the use of living unrelated as well as related donors is discussed. Some of us feel that the use of living donors is justified only if the results are superior to those of cadaver donors, while others think that the use of living donors is justified if the results are at least equal, as long as there is a shortage of cadaver donors. Not using living donors is to deny someone a transplant, and why should the results have to be superior to justify their use? Thus, the debate goes on.

In summary, this workshop brings together all the groups and disciplines that are necessary to make transplantation the highly successful enterprise it is today. The challenge now is to expand the enterprise through increased donations, so that all who could benefit from transplantation will benefit.

REFERENCES


18. Terasaki PI. *Clinical Transplants 1990.* Los Angeles, CA UCLA Tissue Typing Laboratory; 1990.


