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Organ Transplantation— Then and Now

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The last 25 years have seen amazing progress in transplantation—from the development of techniques for immunosuppression to methods for organ removal and preservation. Our distinguished authors focus on these developments and discuss how the momentum seen during the last quarter century can be accelerated.

Introduction

The success of whole organ transplantation has been one of the least expected events in the history of medicine. In 1961 the Nobel Laureate Burnet wrote in the *New England Journal of Medicine* that "much thought has been given to ways by which tissues or organs not genetically and antigenically identical with the patient might be made to survive and function in the alien environment. On the whole, the present outlook is highly unfavorable to success..."[1] This pessimistic view was published more than a year before the avalanche of successful clinical renal transplantations

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in 1962 and 1963 that extended such procedures beyond the occasional transplantation cases between identical and fraternal twins in the mid- and late 1950s.

The first sporadic clinical efforts at renal transplantation predated the watershed years of 1962 and 1963 by a half century. The first known attempts at clinical renal transplantation by vascular anastomoses were made between 1906 and 1923 without immunosuppression with sheep, pig, goat, and subhuman primate donors.[2,3] None of the kidneys functioned and the human recipients died within a few hours to nine days later.

Despite the climate of ignorance in which the trials were conducted, some principles were clearly delineated. The applicability of vascular suture techniques and even the possibility of using pelvic implantation sites were either envisioned or actually practiced. No further clinical renal heterotransplantations (animal to man) were tried again until 1963.

The first human-to-human kidney transplantation (homotransplantation) was reported in 1936 by the Russian Voronoy, who transplanted a kidney from a cadaver donor of B+ blood type to a recipient of O+ blood type, violating what are now well accepted rules of tissue transfer.[4] The patient died 48 hours later without making urine. The possibility that there would be an immune barrier to success was apparently not obvious to early clinicians. This realization awaited the classical studies of Medawar with rodent skin grafts, which established the immunologic basis of rejection.[5]

In the 20 years following Voronoy's case, sporadic further efforts at renal homotransplantation were made without effective immunosuppression as documented by Groth.[3] The heterotopic extraperitoneal technique of renal transplantation, which became today's standard, was developed

by the French surgeons Dubost,[6] Kuss,[7] and Servelle[8] and their associates. Merrill observed the extraperitoneal operation while visiting France in the early 1950s, as was mentioned by Hume et al,[9] and the technique was adopted for the first identical and fraternal twin cases performed in Boston.[10,11]

None of the foregoing efforts, singly or together, had major significance in the procedure's development as the principal ingredients of organ transplantation—namely immunosuppression, tissue matching, and organ procurement and preservation —were either unknown or undeveloped.

This discussion will focus on the astonishing developments in transplantation during the last quarter century, speculate about how the momentum of this progress can be sustained and accelerated, and discuss how government policies have influenced past events or could influence further developments. Although the principles of organ transplantation were developed with the simple kidney model, it was natural that transplantation technology would be applied to the grafting of other organs, including the liver, heart, lung, and pancreas.

Immunosuppression
The Earliest Efforts
By 1960 the possibility of weakening the recipient's immune process with corticosteroids,[12] total body irradiation,[13,14] the cytotoxic drug 6-mercaptopurine,[15,16] or its imidazole derivative, azathioprine,[17] had been established in animals. Sporadic attempts to use these techniques for renal homotransplantation in humans were so unsuccessful[3,11,18,19,20] that it was widely thought that the use of immunosuppression to prevent rejection inevitably led to immunologic invalidism and lethal infections.

Double-Drug Therapy
Renal transplantation became a practical reality in 1962

Dr Starzl, Director of Transplant Services at Presbyterian-University Hospital of Pittsburgh, proceeds with a liver transplantation.

and 1963 with the marriage of corticosteroid therapy, usually prednisone or prednisolone, to baseline therapy with azathioprine.[2,21] The value of this synergistic drug combination was promptly confirmed,[22] permitting fundamental observations including the fact that rejection was a reversible process. A change in the relation between the graft and the host often occurred in the time after the operation, permitting eventual reduction of drug doses. Patients who did not require chronic high-dose corticosteroid therapy to retain their grafts could return to useful social and vocational function without the fear of immunological invalidism. Double-drug therapy with azathioprine and prednisone remained the gold standard of transplantation for many years.

However, consistently good transplantation results could be obtained only with transplantation from blood relatives, and even then only with good tissue matching. This unsatisfactory situation was a great stimulus to search for better immunosuppressive regimens.

Triple-Drug Therapy
Consequently, modifications of or additions to the original double-drug treatment were made as summarized elsewhere[23] during the next 16 years. Most modifications were designed to blunt the attack of lymphocytes, which were recognized as the mediators of rejection. The most significant addition was the use of antilymphocyte globulin (ALG) as an adjunct to azathioprine and prednisone.[24] The ALG consisted of polyclonal antibodies against human lymphoid tissue; the antibodies were raised in horses, rabbits, goats, or other animals by immunizing them to human lymphocytes. When thymic lymphocytes were used for immunization, the product was called antithymocyte globulin (ATG). The antibody-containing globulin was extracted, purified, and made ready for intramuscular or intravenous use. Usually, ALG was administered during the first few weeks or

months after transplantation.

In spite of its great potential value, polyclonal ALG was not universally employed as a part of the antirejection armamentarium because of several limiting features, including the fact that its quality could not be standardized. This latter problem, as well as other deficiencies, was eliminated with the new hybridoma technology introduced by Kohler and Milstein[25]; when hybridoma cells were injected into the peritoneum of mice, a homogeneous or monoclonal antihuman-lymphocyte antibody was produced. Clinical medicine therapy with monoclonal antibodies was introduced by Cosimi et al[26]; they used the so-called OKT3 (trademark, Ortho Pharmaceutical) antibodies, which selectively deplete mature T-lymphocytes. The objective of this therapy was to reverse kidney graft rejection previously nonresponsive or poorly responsive to corticosteroid therapy. OKT3 therapy has proved to be of value, and it was released in 1986 for general use in the United States by the Food and Drug Administration (FDA).

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In spite of the encouraging results with the foregoing drugs and drug combinations, the margin between effective and toxic immunosuppression was still too narrow. Whole organ transplantation remained an unpredictable and dangerous undertaking, especially if cadaver donors were used. Consequently, the field had a relative growth arrest throughout the 1970s, and there seemed to be little hope that transplantation of cadaver extrarenal organs, such as the liver or heart, could be considered on a large scale. Such pessimism was dispelled with the arrival of cyclosporine.

The Cyclosporine Era

The immunosuppressive qualities of this fungus extract were delineated by Borel et al[27] of Switzerland, and its first clinical trials for use in solid organ transplantation were carried out by Calne and his associates in Cambridge, England, beginning in the spring of 1978.[28] In late 1979, a large trial that systematically combined cyclosporine with steroids[29] was begun at the University of Colorado and later transferred to the University of Pittsburgh. This combination therapy greatly improved the ability to control cadaver kidney rejection compared with any therapy in the past.[30] Almost overnight a worldwide avalanche of activity began in renal as well as extrarenal transplantation programs, and the same drug combination was exploited

promptly for hepatic[23] and cardiac[31,32] transplantation. The FDA released cyclosporine for general use in the United States in November 1983.

In all programs cyclosporine administration is carefully guided by monitoring blood levels of the drug, necessitating the introduction of new and sophisticated radioimmunoassay (RIA) or high performance liquid chromatography (HPLC) techniques in clinical pathology laboratories.

Organ Procurement and Preservation

Practical immunosuppression was not perceived as feasible until the synergism of azathioprine and steroids was demonstrated with startling clarity in 1962 and 1963. A similar void existed at that time in organ procurement and preservation, as standard techniques did not exist for the removal of organs from either living or cadaver donors. Little thought or experimentation had been devoted to ways with which to treat the organ from the time of its removal to revascularization in the recipient. There was almost no understanding by the medical and legal professions, much less the public at large, of the conditions that should govern such activities.

The Principle of Core Cooling

The potential benefit of lowering the temperature of an excised organ was grasped instinctively by early researchers. In some of the most deliberate applications of cooling that occurred almost 30 years ago, intestinal and cardiac grafts were preserved by simple immersion in ice-cold saline in Owen Wangensteen's laboratory at the University of Minnesota. However, even such inefficient attempts at surface cooling were not made in any of the identical twin renal transplantations performed through 1962.

A far more effective way to cool an organ is by infusion of a cold solution into its blood supply. This simple concept—core cooling—was introduced into the laboratory almost 30 years ago to make possible liver transplantation in dogs.[33] Without core cooling, liver transplantation was not possible; with core cooling, usually through the portal vein, success became the rule. Such clear evidence prompted the clinical application of core cooling for transplantation of the kidney[2] and all other organs.

Even today, the intraoperative infusion of cold fluids is the essential first step to effective organ removal and preservation. The overriding objective with all organ transplantation is avoidance of warm ischemia. This is achieved by carefully timed and controlled in situ infusion of cold solutions into anatomical regions, the limits of which are defined by preliminary dissection of the abdominal and thoracic aorta.

Organ graft cooling by the intravascular infusion of chilled solutions at the time of circulatory arrest increases the duration of organ viability and allows unhurried appli-

cation, if desired, of other, more sophisticated organ preservation measures. Different solutions, for example, may be used; lactated Ringer's solution has low potassium content and is nearly isotonic. Chilled special solutions with an electrolyte composition similar to that in cells were shown in 1969 by Collins, Bravo-Shugarman, and Terasaki[34] to extend the permissible limit of cold renal ischemia beyond that achievable with isotonic solutions. The same effect has also been shown with donor livers.[35] Cardiac surgeons have cooled the heart with various cardioplegic solutions having potassium concentrations of 20 to 30 mEq/L.

Procedures for Multiple Organ Removal

Until 1981, transplantation of extrarenal organs was a rare event, and one that was confined to a handful of institutions. Although renal transplant surgeons were concerned that removal of the liver and heart could damage kidneys from cadaver renal donors, these anxieties were muted by the small number of cases involved. However, by late 1981 it became obvious that liver and thoracic organ transplant procedures were becoming widespread and that a method of multiple organ procurement would be required so that kidneys, liver, heart, and lung, or various combinations of these organs, could be removed without jeopardizing any individual organs.

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Such a system was developed at the University of Pittsburgh's affiliated hospitals, and, at the request of the US Surgeon General C. Everett Koop, MD, the technique was described in detail[36]: Preliminary dissection of the great vessels of the abdomen and chest of the donor is performed so that the organs to be removed can be core cooled in situ with cold intra-aortic and intraportal infusates, once the aorta has been crossclamped at preplanned levels. This technique was adopted as a worldwide standard almost overnight. A simplified modification of this original procurement procedure has since come into use; it entails virtually no preliminary dissection of any of the organs to be removed.[37] All organs are cooled in situ, after which they are rapidly removed by dissection in a bloodless field. The incidence of well-functioning donor kidneys, livers, and hearts has been better with this simplified method than with previous ones.

The collegiality between collaborating transplantation groups (often from different cities) has been greatly improved with the use of the rapid procurement operation.

Furthermore, the new procedure can usually be carried out in less than 60 minutes from beginning to end,[37] uniformly pleasing the personnel at hospitals visited by the transplantation teams.

Preservation by Continuous Perfusion

After removal, organs harvested with these techniques can be packed in ice chests and kept in special cold solutions near 0 °C until transplantation. The heart, liver, and kidneys can remain cold-packed within pre-procedure time limits of six, eight, and 48 hours, respectively. Sophisticated techniques for continuous perfusion of all these organs have been developed, but have been widely used only for kidney grafts. The perfusion technique for kidneys, described by Belzer et al,[38] uses an asanguineous and oncotically controlled fluid. Though the method is a good one, the quality of preservation in the first two days is not markedly better than that achieved with the simpler infusion and "slush" method, whereby the organs are simply refrigerated after the initial cooling with special chilled solutions.

Better continuous perfusion techniques should permit the extension of perservation times of all organs; however, experimental efforts at continuous perfusion of hearts and livers usually have yielded results inferior to those with the simple infusion and refrigeration methods.

Tissue Typing

Twenty-five years ago when transplantation was in its infancy, it was predicted that tissue matching would have to be perfected if the new grafting technology was to succeed. Since then, the validity of tissue matching, its genetic basis, and, above all, its complexity have become increasingly recognized.

The value of tissue matching for transplantation between family members has been established beyond any doubt. At the same time, the very complexity of the human histocompatibility system has militated against easy matching between nonrelated people. At a practical level, close matching for transplantation of cadaver kidneys has become less of a consideration, especially since the availability of cyclosporine. With transplantation of the liver, heart, and other extrarenal organs, tissue matching has not even been taken into consideration since the events leading to and connected with transplantation occur so quickly that a labored search for a well-matched organ is not possible. Surprisingly, good results can be obtained even with completely mismatched cadaver organs, and this fact has reduced progressive emphasis on antigen matching.

However, none of the immunosuppressive measures available today can prevent the immediate destruction of transplanted kidneys by preformed humoral antibodies in a condition that has been called "hyperacute rejection." Terasaki et al[39] described the first example of this pheno-

menon in 1965, with prompt confirmation by Kissmeyer-Nielsen[40] of Denmark and by many others. Hyperacute rejection is most commonly seen with kidney transplants, but the heart and liver (in that order of susceptibility) can also be similarly destroyed. Hyperacute rejection can be avoided by the so-called crossmatch test, which detects anti-donor antibodies in the recipient's serum before the procedure. Crossmatching has proved to be the single most important practical contribution of tissue typers to the practice of transplantation during the last quarter century.

Prospects of Improvement
The prognosis for improved transplantation care hinges upon improvements in immunosuppression, organ procurement and preservation, and tissue typing.

The most urgent need in transplantation is improved organ preservation. The techniques in common use today were developed two decades ago and have not undergone fundamental change since then.

There are hopes that immunosuppression can be improved. New drugs are being evaluated, some of which are far more potent than cyclosporine. Whether these agents have acceptable toxicity limits, and the extent to which they can be used in combination with other drugs, remains to be determined. The techniques for rapid assessment of drugs, including the most minute details of their mechanisms of action, have been a part of a pharmaceutical industry revolution that is sure to produce other promising drugs.

The most urgent need in transplantation is improved organ preservation. The techniques in common use today were developed two decades ago and have not undergone fundamental change since then. Worldwide linkage of donor networks would be possible overnight if ways could be found to store livers or hearts even for as long as one day. The prospects of this kind of breakthrough, though, are not bright at the present time.

With tissue matching, the objective of finding perfect antigen matches at the principal histocompatibility loci has come to be less important because of the great advances in immunosuppression; however, identification of potentially injurious preformed antibody states has become all the more important. Many examples of hyperacute rejection of kidneys, hearts, and even livers have occurred without preprocedure identification of the offending antibody system responsible for starting the process.

Government Policies, Past and Present
In indispensable ways, government has played a central role in the development of transplantation; a remarkable proportion of all such research in this field has been funded by the National Institutes of Health. When clinical trials were first attempted, the recipients of various organs (first kidneys, then livers, and finally hearts) were cared for on federally sponsored Clinical Research Center Wards. Renal transplantation was funded as a government service by Congress in 1973 with the creation of the End Stage Renal Disease Program, as well as the Network for Cadaver Organ Procurement, which remains in operation today.

The latter program was one of the key advances in clinical organ transplantation since it encouraged identification and early referral of potential organ donors. This orderly process depends upon widespread social and legal acceptance of what is known as brain death or, more precisely, irreversible central nervous system injury.

The clinical criteria of brain death have been extremely well standardized since 1968. Once the diagnosis of brain death has been established, the attending physician or neurologist can formally pronounce death in the patient's chart and can complete a death certificate even though the patient's circulation is intact. It is then possible, and in many states it is a legal requirement, to formally request consent for organ donation from the family. The physician should also determine that the relatives have a complete understanding of the diagnosis of brain death and the organ procurement process. Legislation giving legal sanction to the concept of brain death has been passed in 44 states and judicial precedents have been established in six other states.[41]

The shortage of suitable donor organs has prompted a new kind of legislative initiative called required request. These laws, which have been passed in almost all states, mandate each hospital to systematically approach the families of all donors who die under circumstances that might permit solid organ or tissue donation.

Support of organ donor programs has come from government leaders, most notably President Ronald Reagan, who has stressed the importance of private sector participation, even including the Boy Scouts of America in their Presidential Good Turn program.

These laws and other activities illustrate the support of both the state and federal governments in disseminating news to the public on the advantages of transplantation. Congress enacted legislation in 1984 that authorized a task force to study issues in organ procurement and distribution. The government then authorized the eventual funding of the United Organ Sharing Network (UNOS) by awarding this previously private organization a contract to operate a computer matching system to aid in the placement of renal and extrarenal organs in a systematic fashion. In addi-

tion, UNOS has been asked to look into the collection of careful data on all renal and extrarenal organs procured.

For extrarenal organs, UNOS presently acts in an advisory capacity by supplying a prioritized list of acceptable recipients to the organ procurement agency that is managing a specific donor. The final choice for utilization of available organs is made by the local procurement agency. At the present time, UNOS has many subcommittees at work developing recommendations for the efficient and fair distribution of organs. Many of these conditions will be proscribed by the limitations of preservation technology, which is too underdeveloped at present to permit extensive and time-consuming traffic of organs from city to city under any but the most urgent conditions.

The current trend of high legislative interest and activity in regulating transplantation could ultimately stifle the orderly progress and growth of this important branch of medicine.

Parallel to the rapidly growing success of organ transplantation has been an increasing interest in the regulation of transplantation medicine by state and federal governments. The transplantation community has attempted to collaborate with government in the development of new health policies; the current trend of high legislative interest and activity in regulating transplantation could ultimately stifle the orderly progress and growth of this important branch of medicine. Future emphasis in these efforts must be on the establishment of a climate of constructive collaboration, and not government domination or control of what primarily must remain a professional medical effort.

Media factors have encouraged public acceptance of transplantation as a fully established discipline, ready for mass clinical application. This deep misunderstanding of the complexity of organ transplantation and related problems has generated ambitious and sometimes premature legislation concerning organ retrieval and sharing, not taking into account that organ preservation is ten to 15 years behind proposed federal regulations. □

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Organic Transplantation

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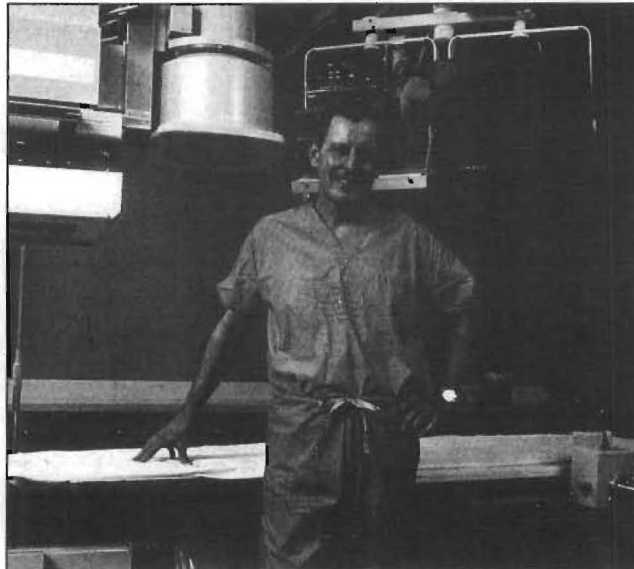
Dr Starzl will be honored by the International Organ Transplant Forum in September for his 25 years of research and clinical achievement.