The Development of Clinical Renal Transplantation

Thomas E. Starzl, MD, PhD

ANY TWO PEOPLE can travel the same road and see different things. Thus, others discussing the history of renal transplantation might have noted different landmarks. Valuable personal reminiscences have been written by R.Y. Calne of England[1] and J.E. Murray of Boston,[2] whose initially separate careers came together in a remarkable joint venture at Harvard in 1960. In addition, original articles, which are usually cited in historical reviews, but rarely read because of their inaccessibility, were republished recently in a volume of the *Clio Chirurgica* series.[3] Perusal of this material gives unusual insight into the process of discovery and development. Another prime source of historical information was published in 1972 by Professor Carl Groth, the Swedish transplantation surgeon who examined the medical literature from the crucial period of 1950 to 1970 and interviewed or corresponded with almost all of the physicians and surgeons who were working during this time.[4]

Kidney transplantation as a practical therapeutic option came from a series of steps that began to appear in the literature at the turn of this century. At first, the steps were small, widely spread in time, and often quixotic enough to be overlooked or condemned. As late as 1961, the Nobel Laureate Macfarland 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 . . . ."[5] This opinion was published on the eve of the successful clinical renal transplantations in 1962 and 1963 that extended such procedures beyond the occasional identical and fraternal twin cases of the mid and late 1950s. These clinical trials in 1962 and 1963 provoked editorials questioning the inherent feasibility of such efforts, as well as their ethical basis.[6] Yet, these trials were already late in a long, but at first slowly unfolding, story of whole organ transplantation, which was dominated by but not confined to the kidney.

THE EARLIEST BEGINNINGS

Heterotransplantation

The first known attempts at clinical renal transplantation by vascular anastomoses were made without immunosuppression between 1906 and 1923 with pig, sheep, goat, and subhuman primate donors. The first of these efforts were in France[7] and Germany,[8] but others followed as summarized elsewhere.[4,9] None of the kidneys functioned for long, if at all, and the human recipients died from a few hours to 9 days later. Although there was little or no understanding of the biologic barrier to success, 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 renal heterotransplantations (animal to man) were tried again until 1963 when systematic and surprisingly successful clinical trials were made with chimpanzee[9] and baboon[10,11] kidneys. The eventual death of all of the recipients of animals organs ended renal heterotransplantation trials.

Homotransplantation

The first human to human kidney transplantation (homotransplantation) was reported in 1936 by the Russian, Voronoy,[12] who transplanted a kidney from a cadaver donor of B + blood type to a recipient of O + blood type in violation of what have become accepted rules of tissue transfer.[13] A further adverse factor was that the donor had been dead for 6 hours. The recipient died 48 hours later without making urine.

Sporadic further efforts at renal homotransplantation were made in the 20 ensuing years without effective immunosuppression as documented by Groth.[4] The heterotopic extraperitoneal technique

From the Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, PA.

Supported by Research Grants from the Veterans Administration and Project Grant No. DK 29961 from the National Institutes of Health, Bethesda, MD.

Address reprint requests to Thomas E. Starzl, MD, PhD, Department of Surgery, 3601 Fifth Ave, Falk Clinic, Pittsburgh, PA 15213.

0272-6386/90/1606-0007$3.00/0

of renal transplantation that became today's standard was developed by the French surgeons Dubost,[14] Kuss,[15] and Servelle[16] and their associates. John Merrill, a Boston nephrologist, had seen the extraperitoneal operation while traveling in France in the early 1950s, as was mentioned by Hume et al.[17] This technique was adapted for the historically important identical and fraternal twin cases in Boston.[18,19] Today, variations of the operation shown in Fig 1 are used worldwide.

As isolated events, or even in combination, none of the foregoing efforts would have had a major impact on medical practice. The principal ingredients of organ transplantation, namely immunosuppression, tissue matching, and organ procurement (and preservation), were either unknown or so undeveloped that grafting of the kidney at a practical level was only a dream. Only two patients may have derived some benefit. The first example of probable extended homograft function was in a patient of Lawler et al.[20] The only other example of prolonged homograft function through 1954 was in a nonimmunosuppressed patient of Hume et al[17] whose graft was placed in the thigh, with function for 5 months.

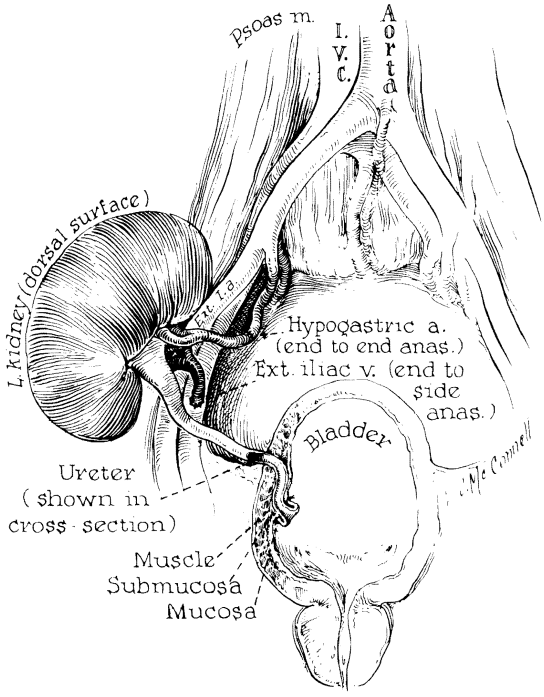

Fig 1. Extraperitoneal renal transplantation to pelvic site. (Reprinted with permission.[38])

The Identical Twin Cases

Two days before Christmas 1954, an identical twin transplantation was performed at the Peter Bent Brigham Hospital in Boston by the surgeons J.E. Murray and J.H. Harrison in collaboration with the nephrologist J.P. Merrill.[2,18] They used the ectopic extraperitoneal technique originally described by the French surgeons.[14-16] The recipient survived for more than two decades. Living-donor nephrectomy was an unusual operation at that time, and except for the ultimately unsuccessful mother-to-offspring transplantation reported by Michon et al,[21] it had been limited to the removal of "expendable" kidneys excised during creation of ventriculoureteric cerebral spinal fluid shunts or for other reasons. No effort was made to preserve the excised identical twin kidney, which functioned promptly even though it underwent 82 minutes of warm ischemia time. Merrill et al[18] gave credit for originally suggesting the transplantation to the recipients's physician, David C. Miller of the Public Health Service Hospital, Boston. It was already known that skin grafts between identical twins were not rejected.[22]

The application of this information in the transplantation of a vital organ was a bold extension of this principle and one that depended in the absence of immunosuppression on the perfect tissue match that could be obtained only with genetic identity of the donor and recipient. The efforts that were made to be sure of this condition were extraordinary, and ultimately included skin grafting. Further progress in the presence of an immunologic barrier would require effective immunosuppression.

IMMUNOSUPPRESSION FROM 1959 to 1980

Appreciation by Medawar[23] that rejection is an immunologic phenomenon made inevitable almost everything that followed. By 1960, the possibility of weakening the recipient immune system in order to mitigate rejection had been established in animals with corticosteroids,[24] total body irradiation,[25,26] and the cytotoxic drug 6-mercaptopurine[27-30] or its imidazole derivative, azathioprine.[31] However, prolonged survival of skin or kidney grafts in experimental animals was a relatively uncommon achievement. Sporadic attempts to use these techniques for renal homotransplantation in humans were so unsuccessful[4,19,32-34] that it was widely thought that the immunosuppression

requisite to prevent rejection would inevitably lead to immunologic invalidism and lethal infections.

There are no surviving patients from the era preceding 1962 during which immunosuppression usually was provided by total body irradiation (Table 1). However, the long survival of two fraternal twin recipients studied during this earlier period provided an exceptional incentive for continuing efforts during an otherwise bleak time. The first of these irradiated fraternal (nonidentical) twins, received his brother's kidney in Boston on January 24, 1959.[19,32,35] He died in August 1979 of arteriosclerotic heart disease (personal communication, Robert Kirkman, August 1989). The second irradiated fraternal twin was transplanted in Paris on June 29, 1959,[36] and died on July 13, 1985 of carcinoma of the bladder (personal communication, Henri Kreis, August 1989). Although a few patients treated in 1960 and 1961 in Paris and Boston with 6-mercaptopurine or azathioprine with or without irradiation had extended survival, they also died within 18 months. One of the Boston cadaveric kidney recipients, a patient of Murray and Merrill, was the first to have extended survival under drug therapy only.[33]

The pessimism that resulted from these clinical trials was changed drastically in 1962 and 1963 when it was discovered at the University of Colorado that azathioprine and prednisone had at least additive, and probably synergistic, effects which allowed the prevention or reversal of renal homograft rejection in most clinical cases.[37] The impetus given to renal transplantation as this information became known was reflected in the startling proliferation of centers in 1962 to 1964.

Considering the end of this explosive new phase as March 1964 was natural. The 64 cases accumulated by that time at the University of Colorado provided the basis for the first textbook on renal transplantation.[38] This same time frame was used to collect all 342 renal homotransplants performed in the world.[39] The impetus for this extraordinary compilation came from Joseph E. Murray of Boston, following a conference sponsored by the National Research Council and the National Academy of Sciences on September 26 and 27, 1963 in Washington, DC. About 25 early workers (surgeons, physicians, and pathologists) who had contributed to the embryonal new specialty of renal transplantation were the participants.

The meticulousness of the first registry report[39] made it possible 25 years later in the summer of 1989 to trace the fate of all non-twin kidney recipients who had been alive at the end of March 1964.[40] There were 24 25-year survivors, of whom 15 were from the original Colorado series. Nine were still alive at six other centers (Table 2). These included three of David Hume's original patients at the Medical College of Virginia.[41]

It is noteworthy that none of the world's 24 quarter-century survivors had been given an unrelated donor kidney. Nor was there an example in the world of a 25-year survival of a cadaver donor kidney allograft at the time of this report.[40] A cadaver recipient in Paris who had maintained perfect renal function was expected to pass this barrier on October 12, 1989 (personal communication, Henri Kreis, August 1989). This French recipient was 31 years old at the time of

Table 1. Principal Immunosuppressive Regimens Used for Clinical Kidney Transplantation

Agents	Year Reported	Place	Reference
Total body irradiation	1960	Boston	19,35
Azathioprine	1962	Boston	32,33
Azathioprine-steroids	1963	Denver	37
Antilymphoid globulin (ALG) as adjunct*	1966	Denver	42
Cyclosporine	1978-1979	Cambridge	47
Cyclosporine-steroids	1980	Denver	50
FK 506	1989	Pittsburgh	57

*Polyclonal ALG has been largely replaced by monoclonal anti–T-lymphocyte antibodies.[45]

Table 2. 25-Year Survivors (Non-Twin) From Era Before March 31, 1964

	No.	Original Grafts	Program Chief
University of Colorado*	15	11	Thomas Starzl
Medical College of Virginia (Richmond)	3	3	David Hume
University of Minnesota	2	2	William Kelly
Necker Hospital (Paris)	1	0	Jean Hamburger
Peter Bent Brigham Hospital (Boston)	1	1	Joseph Murray
Western Infirmary (Edinburgh)	1	0	Michael Woodruff
Cleveland Clinic	1	1	Wilhelm Kolff
Total	24	18	

NOTE: Full documentation in reference 40.

*Fourteen of these patients are still alive after 26 to 29 years. The other died of a myocardial infarction in postoperative year 26.

her transplantation in 1964 under the care of Professor Jean Hamburger.

Because of dissatisfaction with azathioprine-prednisone therapy, particularly for cadaveric renal transplantation, modifications of or additions to the original double-drug treatment were made during the next 16 years (Table 1). Most of the modifications were designed to blunt the attack of the lymphocytes, which had been recognized as the mediators of rejection. The most significant addition was antilymphocyte globulin (ALG), which was used as an adjunct to azathioprine and prednisone.[42] ALG consisted of polyclonal antibodies raised in horses, rabbits, goats, or other animals by immunizing them to human lymphocytes.[43] When thymic lymphocytes were used for immunization, the product was called antithymocyte globulin (ATG). The active γ-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. Alternatively, it was used for the specific indication of rejection.

In spite of its great potential value, polyclonal ALG was not universally employed as a part of the antirejection armamentarium because of severely limiting features, including its inability to be standardized.[43] This latter problem and other deficiencies were eliminated with the hybridoma technology introduced by Kohler and Milstein.[44] With hybridoma cells injected into the peritoneum of mice, a homogeneous (monoclonal) antihuman-lymphocyte antibody could be produced. Therapy with monoclonal antibodies was introduced into clinical medicine by Cosimi et al[45] using the so-called OKT3 antibodies, which selectively deplete mature T lymphocytes. Their prime objective was to reverse kidney graft rejection that was nonresponsive or poorly responsive to conventional corticosteroid therapy and azathioprine. OKT3 therapy has been proved to be of value clinically, and it was released in 1986 for general use in the United States by the Food and Drug Administration (FDA). There has been much interest subsequently in even more specific monoclonal antibodies that target highly specific subpopulations of lymphocytes.

In spite of what had been achieved by 1978 with most of the foregoing drugs and drug combinations, renal transplantation remained an unpredictable and dangerous undertaking, especially if cadaver donors were used. The margin between effective and toxic immunosuppression was too narrow. Consequently, the field of transplantation had a relative growth arrest throughout the 1970s, and there seemed to be little hope of major improvement. The clinical transplant sessions at scientific society meetings had become tedious expositions in which claims of results, counterclaims, and shuffling of details of management filled the programs. The boredom was relieved with the arrival of cyclosporine.

IMMUNOSUPPRESSION IN THE 1980s

The immunosuppressive qualities of the fungus extract cyclosporine were delineated by Borel et al[46] of Switzerland, and the first clinical trials for solid organ transplantation were performed by Calne and his associated in Cambridge, England, beginning in the spring of 1978.[47] There was a high mortality in the 1978 to 1979 trials at Cambridge, using cyclosporine with other drugs, and three of the first 34 recipients developed lymphomas. Calne recommended that cyclosporine be used alone for future trials. However, nephrotoxicity almost invariably was observed at the doses that were required. The complications of cyclosporine used with other agents were even more severe in further English trials of renal transplantation by Sweny et al.[48]

Trials in the United States of cadaver renal transplantation with cyclosporine were begun in late 1979 at the Peter Bent Brigham Hospital in Boston and at the University of Colorado, Denver. Disappointing results, no better than with azathioprine and prednisone, were reported from Boston using cyclosporine as the sole drug for the first two postoperative months.[49] Case accrual was slow and only 16 patients had been treated with cyclosporine at the Brigham by September 1981. In the other, and far more encouraging American trial, at the University of Colorado, cyclosporine was systematically combined with steroids.[50] The ability to control rejection of cadaver organs with this drug combination was greatly improved compared with any therapy in the past. Of equal importance, the maintenance steroid doses generally were low enough to allow survival with a considerable reduction in morbidity. By late May 1980, more than 40 renal recipients of cadaver kidneys had been treated in Colorado. Later in 1980, two more American trials of cyclosporine-steroid therapy

were started in Minneapolis[51] and Houston.[52] With the strategy of employing drug combinations with additive or synergistic immunosuppression, the doses of individual agents usually could be kept in the nontoxic range. Cyclosporine and steroids also have been combined in later years with azathioprine, and polyclonal or monoclonal ALG (OKT3). In November 1983, cyclosporine was released by the FDA for general use in the United States.

By the time cyclosporine became generally available, the lymphomas that threatened the outlook for cyclosporine at the outset were better understood. Similar lymphoproliferative tumors, earlier called reticulum cell sarcomas, had been seen frequently under azathioprine-steroid therapy with or without ALG.[53] It was realized in the patients treated with cyclosporine that these lesions usually were caused by Epstein-Barr virus infections. By stopping or lightening immunosuppressive therapy, most of the lesions melted away quickly without regard for their clonality.[54] These observations removed the specter of an overwhelming cyclosporine mortality caused by de novo lymphoid malignancies.

The advent of cyclosporine improved the prospects after living-related and especially cadaver renal transplantation. It also had an impact on transplantation of extrarenal organs. Cyclosporine changed liver and heart transplantation from exotic experimental procedures to patient-service, and made possible the previously unattainable objectives of transplanting the heart and lungs, or single lungs. In spite of these attainments, better drugs and immunosuppressive techniques have been eagerly looked for because of the side effects of cyclosporine, of which the most serious have been nephrotoxicity, arterial hypertension, neurotoxicity, the production of diabetes mellitus, and cosmetic deformity from hirsutism, brutalization of the physiognomy in some children, gynecomastia in men, and gum hyperplasia.[55] Most of these complications were already observed by Calne by 1980.

A new drug called FK 506 was a product of this search. FK 506 was discovered in Japan by Kino et al[56] in 1984 during systematic screening for drugs with antimicrobial, antineoplastic, or immunosuppressive qualities. FK 506 has no structural similarity to cyclosporine, but it has in common the ability to prevent T-lymphocyte activation by inhibiting the synthesis and expression of interleukin 2 and other cytokines, including interferon gamma. It has been used clinically since February 1989 for kidney, liver, heart, and lung recipients.[57,58] Because FK 506 appears to be less nephrotoxic than cyclosporine, has little effect on blood pressure, does not increase serum cholesterol, and often can be used as monotherapy (without steroids), it seems destined to permit further improvements in the care of renal transplant recipients in the 1990s.

KIDNEY PROCUREMENT AND PRESERVATION

The fact that Voronoy's first cadaver kidney donor (in 1936) had been dead for 6 hours illustrated the lack of insight 50 years ago about the requirements for successful organ preservation. The potential benefit of lowering the temperature of an excised organ was grasped instinctively by early workers. However, even such inefficient attempts as surface cooling were not made in any of the identical twin renal transplantations performed through 1962. The infusion of a cold solution into its blood supply (core cooling) was a simple concept that was introduced into the laboratory almost 30 years ago to make possible liver transplantation in the dog.[59] Core cooling was later applied clinically for transplantation of the kidney[60] and eventually for all other organs.

Today, the intraoperative infusion of cold fluids at the donor operation is the essential first step for effective organ removal and preservation. With all organs, the overriding objective is avoidance of warm ischemia. This is achieved by carefully timed in situ infusion of cold solutions into anatomical regions, the limits of which are defined by preliminary dissection of the abdominal and/or thoracic aorta and cross clamping at those levels.[61]

Lactated Ringer's solution, the first infusate to be used,[60] has a 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 et al[62] and by others to extend the permissible limit of cold renal ischemia beyond that achievable with isotonic solutions.

Preservation, which once seemed the component of transplantation most susceptible to improvement, changed slowly over the years. The approach exemplified by the original contribution of Collins et al[62] was to introduce novel ingre-

dients into the solution, which stays in the cold devascularized organ during storage, or to use agents to minimize the reperfusion injury after revascularization in the recipients. Then in 1987, Belzer and his associates[63] introduced the University of Wisconsin (UW) solution for static (so-called slush) storage. Among other constituents, the UW solution contains two sugars, lactobionate and raffinose, which prevent the imbibition of water by parenchymal and other cells in the graft. There is more and more evidence that the graft microvasculature also is better preserved with UW solution than with past techniques, meaning that self-perpetuating injury is reduced after revascularization in the recipient. The UW solution, which was first widely tested for liver transplantation, is a generic advance that has also had an impact in renal transplantation. Now, kidneys can be preserved for 2 or 3 days with a high probability of prompt function.

The alternative to these simple refrigeration techniques is continuous perfusion. Ackerman and Barnard[64] of Capetown described perfusion with cold blood under hyperbaric oxygenation. A widely used perfusion technique for kidneys was described from San Francisco by Belzer et al,[65] using an asanguinous and oncotically controlled perfusate fluid. The method is a good one, but the quality of preservation in the first 2 days has not been markedly better than with the simpler and cheaper infusion and slush methods.

No matter what the ultimate method of preservation, the first step is quick cooling of the kidneys, which usually are removed as part of the multiple graft procurement in "heart beating" cadaver donors. Until 1981, transplantation of the extrarenal organs was a rare event. By late 1981, it had become obvious that liver and thoracic organ transplant procedures were going to be widespread, and that a method of multiple organ procurement would be required by which the kidneys, liver, heart, and lungs or various combinations of these organs could be removed without jeopardizing any of the individual organs. Such a system was developed at the Universities of Colorado and Pittsburgh, and aided by the efforts of the Surgeon General of the United States, C. Everett Koop, the technique was adopted as a worldwide standard almost overnight.[61] All organs to be used are cooled in situ, and after their cooling, they are rapidly removed by dissection in a bloodless field. The sharing of organs from a common donor by recipient teams from widely separated centers became routine in the 1980s.

TISSUE TYPING

Antigen Matching

Twenty-five years ago when the modern era of transplantation was in its infancy, it was predicted that tissue matching would have to be perfected if kidney grafting procedures were to succeed with any degree of reliability and predictability. The first prospective matching trials were started in 1964 by Paul I. Terasaki of Los Angeles[66,67] in collaboration with the University of Colorado transplantation team.

The results were disappointing. Since then, the validity of tissue matching, its genetic basis, and above all its complexity have become increasingly recognized. Although the value of tissue matching for transplantation between family members has been established, the complexity of the human histocompatibility system has militated against easy matching between nonrelated people. Close matching for transplantation of the cadaver kidney has not commonly been achieved, and lesser degrees of matching have not correlated well with the outcome. Whether these expensive efforts at matching should continue has become a matter of public policy because of the increasing use by the United Network of Organ Sharing (UNOS) of tissue matching as the overriding determinant of cadaver kidney distribution nationally. The inexplicable paradox continues of reports from two multicenter case compilations (one American and one European) having an overlapping data base which claim a slight but significant gain in survival of well-matched versus mismatched cadaver kidneys, whereas almost none of the major centers or consortia which contribute to these data pools are able to see this trend in their own material. HLA matching has faded as a factor in transplantation, because the results with modern day immunosuppression are almost as good with unmatched cadaveric kidneys as with kidneys from well-matched blood relatives.

Cross-Matching

The importance of the cross-match concept remains undiminished 25 years after its description. None of the immunosuppressive measures available today can prevent the immediate destruction of

kidneys by preformed humoral antibodies in what has been called "hyperacute rejection." In 1965, Terasaki et al[66] described the first example of this phenomenon. Kissmeyer-Nielsen et al,[68] Williams et al,[69] and numerous other observers[70] have made valuable observations about hyperacute rejection, but except for its variable association with preformed antigraft antibodies, its exact pathogenesis is not understood. The process of sudden graft infarction with this kind of rejection is caused by occlusion of the graft microvasculature with formed blood elements and clot, presumably following an antigen-antibody reaction, which is not always measurable.[71] Hyperacute rejection usually, but not always, can be avoided by the cross-match test, which detects antidonor cytotoxic antibodies in the recipient serum in advance of operation. Understanding and prevention of hyperacute rejection could hold the key to successful heterotransplantation.

THE EFFECT OF TRANSPLANTATION ON NEPHROLOGY

Renal transplantation and nephrology came from the same mother and father (medicine and surgery), were raised in the same crib, survived sibling rivalries, and finally came to peace with each other. Eventually, the practice of nephrology was revolutionized by transplantation and vice versa. As great as it has been, the full impact of the relationship has yet to be felt. The immunosuppression that gives transplantation its specificity has become, or promises to be, so powerful and highly focused on discrete components of the immune apparatus that many of the diseases leading to transplantation, including autoimmune nephritides and diabetes mellitus, could be interdicted in the near future by treatment similar to that used to prevent graft rejection.

REFERENCES

1. Calne RY: Organ transplantation: From laborabory to clinic (Lister Oration). Br Med J 291:1751-1754, 1985
2. Murray JE: Discovery: Reflections on the first successful kidney transplantation. World J Surg 6:372-376, 1982
3. Hau T: Kidney Transplantation. Austin, TX, Landes, Clio Chirurgica, October 1990
4. Groth CG: Landmarks in clinical renal transplantation. Surg Gynecol Obstet 134:323-328, 1972
5. Burnet FM: The new approach to immunology. N Engl J Med 264:24-34, 1961
6. Elkinton JR: Moral problems in the use of borrowed organs artificial and transplanted. Ann Intern Med 60:309-313, 1964
7. Jaboulay M: Greffe du reins au pli du coude par soudures arterielles et veineuses. (Kidney grafts in the antecubital fossa by arterial and venous anastomosis.) Lyon Med 107:575-577, 1906
8. Unger E: Nierentransplantation. (Kidney Transplantation.) Wien Klin Wochenschr 47:573-578, 1910
9. Reemtsma K, McCracken BH, Schlegel JU, et al: Renal heterotransplantation in man. Ann Surg 160:384-410, 1964
10. Starzl TE: Experience in Renal Transplantation. Philadelhia, PA, Saunders, 1964, pp 262-298, 345-359
11. Starzl TE, Marchioro TL, Peters GN, et al: Renal heterotransplantation from baboon to man: Experience with 6 cases. Transplantation 2:752-776, 1964
12. Voronoy U: Sobre bloqueo del aparato reticuloendotelial del hombre en algunas formas de intoxicacion por el sublimado y sobre la transplantacion del rinon cadaverico como metodo de tratamiento de la anuria consecutiva a aquella intoxicacion. (Blocking the reticuloendothelial system in man in some forms of mercuric chloride intoxication and the transplantation of the cadaver kidney as a method of treatment for the anuria resulting from the intoxication.) Siglo Medico 97:296-297, 1937
13. Starzl TE: Experience in Renal Transplantation. Philadelphia, PA, Saunders, 1964, pp 37-47
14. Dubost C, Oeconomos N, Nenna A, et al: Resultats d'une tentative de greffe renale. Bull Soc Med Hop Paris 67:1372-1382, 1951
15. Kuss R, Teinturier J, Milliez P: Quelques essais de greffe rein chez l'homme. Mem Acad Chir 77:755-764, 1951
16. Servelle M, Soulie P, Rougeulle J: Greffe d'une rein de supplicie a une malade avec rein unique congenital, atteinte de nephrite chronique hypertensive azatemique. Bull Soc Med Hop Paris 67:99-104, 1951
17. Hume DM, Merrill JP, Miller BF, et al: Experience with renal homotransplantation in the human: Report of nine cases. J Clin Invest 34:327-382, 1955
18. Merrill JP, Murray JE, Harrison JH, et al: Successful homotransplantation of human kidney between identical twins. JAMA 160:277-282, 1956
19. Murray JE, Merrill JP, Dammin GJ, et al: Study of transplantation immunity after total body irradiation: Clinical and experimental investigation. Surgery 48:272-284, 1960
20. Lawler RH, West JW, McNulty PH, et al: Homotransplantation of the kidney in the human. JAMA 144:844-845, 1950
21. Michon L, Hamburger J, Oeconomos N, et al: Une tentative de transplantation renale chez l'homme. Aspects medicaux et biologiques. Presse Med 61:1419-1423, 1953
22. Brown JB: Homografting of skin: With report of success in identical twins. Surgery 1:558-563, 1937
23. Medawar PB: The behavior and fate of skin autografts and skin homografts in rabbits. J Anat 78:176-199, 1944
24. Billingham RE, Krohn PL, Medawar PB: Effect of cortisone on survival of skin homografts in rabbits. Br Med J 1:1157-1163, 1951
25. Dempster WJ, Lennox B, Boag JW: Prolongation of sur-

vival of skin homotransplants in the rabbit by irradiation of the host. Br J Exp Pathol 31:670-679, 1950

26. Lindsley DL, Odell TT Jr, Tausche FG: Implantation of functional erythropoietic elements following total-body irradiation. Proc Soc Exp Biol 90:512-515, 1955

27. Schwartz R, Dameshek W: Drug-induced immunological tolerance. Nature 183:1682-1683, 1959

28. Calne RY: The rejection of renal homografts, inhibition in dogs by 6-mercaptopurine. Lancet 1:417-418, 1960

29. Zukoski CF, Lee HM, Hume DM: The prolongation of functional survival of canine renal homografts by 6-mercaptopurine. Surg Forum 11:470-472, 1960

30. Pierce JC, Varco RL: Induction of tolerance to a canine renal homotransplant with 6-mercaptopurine. Lancet 1:781-782, 1962

31. Calne RY, Murray JE: Inhibition of the rejection of renal homografts in dogs by Burroughs Wellcome 57-322. Surg Forum 12:118, 1961

32. Murray JE, Merrill JP, Dammin GJ, et al: Kidney transplantation in modified recipients. Ann Surg 156:337-355, 1962

33. Murray JE, Merrill JP, Harrison JH, et al: Prolonged survival of human-kidney homografts by immunosuppression drug therapy. N Engl J Med 268:1315-1323, 1963

34. Woodruff MFA, Robson JS, Nolan B, et al: Homotransplantation of kidney in patients treated by preoperative local irradiation and postoperative administration of an antimetabolite (Imuran). Lancet 2:675-682, 1963

35. Merrill JP, Murray JE, Harrison JH, et al: Successful homotransplantation of the kidney between non-identical twins. N Engl J Med 262:1251-1260, 1960

36. Hamburger J, Vaysse J, Crosnier J, et al: Transplantation of a kidney between nonmonozygotic twins after irradiation of the receiver. Good function at the fourth month. Presse Med 67:1771-1775, 1959

37. Starzl TE, Marchioro TL, Waddell WR: The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet 117:385-395, 1963

38. Starzl TE: Experience in Renal Transplantation. Philadelphia, PA, Saunders, 1964, pp 1-383

39. Murray JE, Gleason R, Bartholomay A: Second report of registry in human kidney transplantation. Transplantation 2:660-667, 1964

40. Starzl TE, Schroter GPJ, Hartmann NJ, et al: Long-term (25 year) survival after renal homotransplantation—The world experience. Transplant Proc 22:2361-2365, 1990

41. Hume DM, Magee JH, Kauffman HM Jr, et al: Renal homotransplantation in man in modified recipients. Ann Surg 158:608-644, 1963

42. Starzl TE, Marchioro TL, Porter KA, et al: The use of heterologous antilymphoid agents in canine renal and liver homotransplantation, and in human renal homotransplantation. Surg Gynecol Obstet 124:301-318, 1967

43. Starzl TE (with the assistance of Putnam CW): Experience in Hepatic Transplantation. Philadelphia, PA, Saunders, 1969, pp 207-225, 253-273

44. Kohler G, Milstein C: Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 256:495-497, 1975

45. Cosimi AB, Burton RC, Colvin RB, et al: Treatment of acute renal allograft rejection with OKT3 monoclonal antibody. Transplantation 32:535-539, 1981

46. Borel JF, Feurer C, Gubler HU, et al: Biological effects of cyclosporin A: A new antilymphocytic agent. Agents Actions 6:468-475, 1976

47. Calne RY, Rolles K, White DJG, et al: Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet 2:1033-1036, 1979

48. Sweny P, Farrington K, Younis F, et al: Sixteen months experience with cyclosporin-A in human kidney transplantation. Transplant Proc 13:365-367, 1981

49. Carpenter BJ, Tilney NL, Strom TB, et al: Cyclosorin-A in cadaver renal allografts. Kidney Int 19:265, 1981 (abstr)

50. Starzl TE, Weil R III, Iwatsuki S, et al: The use of cyclosporin A and prednisone in cadaver kidney transplantation. Surg Gynecol Obstet 151:17-26, 1980

51.Ferguson R, Rynasiewicz JJ, Sutherland D, et al: Cyclosporin A in renal transplantation: A prospective randomized trial. Surgery 92:175-182, 1982

52. Kahan BD, VanBuren CT, Lin S, et al: Immunopharmalogical monitoring of cyclosporine A treated recipients of cadaveric kidney allografts. Transplantation 34:36-45, 1982

53. Starzl TE, Penn I, Putnam CW, et al: Iatronenic alterations of immunologic surveillance in man and their influence on malignancy. Transplant Rev 7:112-145, 1971

54. Starzl TE, Nalesnik MA, Porter KA, et al: Reversibility of lymphomas and lymphoproliferative lesions developing under cyclosporin-steroid therapy. Lancet 1:583-587, 1984

55. Kahan BD: Cyclosporine. N Engl J Med 321:1725-1738, 1989

56. Kino T, Hatanaka H, Miyata S, et al: FK-506, a novel immunosuppressant isolated from a streptomyces. II. Immunosuppressive effect of FK-506 in vitro. J Antibiot 40:1256-1265, 1987

57. Starzl TE, Todo S, Fung J, et al: FK 506 for human liver, kidney, and pancreas transplantation. Lancet 2:1000-1004, 1989

58. Todo S, Fung JJ, Starzl TE, et al: Liver, kidney, and thoracic organ transplantation under FK 506. Ann Surg 212:295-305, 1990

59. Starzl TE, Kaupp HA Jr, Brock Dr, et al: Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. Surg Gynecol Obstet 111:733-743, 1960

60. Starzl TE: Experience in Renal Transplantation. Philadelphia, PA, Saunders, 1964, pp 68-71

61. Starzl TE, Hakala TR, Shaw BW Jr, et al: A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet 158:223-230, 1984

62. Collins GM, Bravo-Shugarman M, Terasaki PI: Kidney preservation for transportation: Initial perfusion and 30 hours ice storage. Lancet 2:1219-1224, 1969

63. Jamieson NV, Sundberg R, Lindell S, et al: Successful 24- to 30-hour preservation of the canine liver: A preliminary report. Transplant Proc 29:945-947, 1988 (suppl 1)

64. Ackerman JR, Barnard CN: A report on the successful storage of kidneys. Br J Surg 53:525-532, 1966

65. Belzer FO, Ashby BS, Dunphy JE: 24-hour and 72-hour preservation of canine kidneys. Lancet 2:536-538, 1967

66. Terasaki PI, Marchioro TL, Starzl TE: Sero-typing of human lymphocyte antigens: Preliminary trials on long-term kidney homograft survivors, in Russell PS, Winn HJ, Amos DB (eds): Histocompatibility Testing 1965. Washington, DC, National Academy of Science, 1965, pp 83-96

67. Terasaki PI, Porter KA, Marchioro TL, et al: Serotyping for homotransplantation. VII. Selection of kidney donors for thirty-two recipients. Ann NY Acad Sci 129:500-520, 1966

68. Kissmeyer-Nielsen F, Olsen S, Peterson VP, et al: Hyperacute rejection of kidney allografts, associated with preexisting humoral antibodies against donor cells. Lancet 2:662-665, 1966

69. Williams GM, Lee HM, Weymouth RF, et al: Studies in hyperacute and chronic renal homograft rejection in man. Surgery 62:204-212, 1967

70. Ting A: The lymphocytotoxic crossmatch test in clinical renal transplantation. Transplantation 35:403-407, 1983

71. Starzl TE, Lerner RA, Dixon FJ, et al: Shwartzman reaction after human renal transplantation. N Engl J Med 278:642-648, 1968