The Origin of Clinical Organ Transplantation Revisited

SUMMARY OF THE ORIGINAL ARTICLE

Successful Homotransplantation of the Human Kidney Between Identical Twins

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A patient whose illness had begun with edema and hypertension was found to have extreme atrophy of both kidneys. Because of the steady worsening of the condition and the appearance of uremia with other unfavorable diagnostic signs, transplantation of 1 kidney from the patient's identical healthy twin brother was undertaken. Preparations included collection of evidence of monozygosity and experimental transplantation of a skin graft from the twin. During the transfer of the healthy kidney, it was totally ischemic for 82 minutes. Evidence of functional activity in the transplanted kidney was obtained. The hypertension persisted until the patient's diseased kidneys were both removed. The homograft has survived for 11 months, and the marked clinical improvement in the patient has included disappearance of the signs of malignant hypertension.

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Commentary by Thomas E. Starzl, MD, PhD, and Clyde Barker, MD

During the decade bracketed by 1953 and 1963, a beachhead for the clinical field of organ transplantation was established by a series of discoveries and events that included 3 milestone renal transplantations carried out by Murray and Merrill et al.[1] The first of these operations was performed with an identical twin's kidney on December 23, 1954, and published in *JAMA* 17 months later.[1] It already had been established that tissues were freely interchangeable between identical twins. In addition, the renal transplant procedure had been developed earlier in France by Küss, and subsequently used for the precedent-setting mother-to-son living kidney donation reported in 1953 by Michon and Hamburger et al. Thus, the widely publicized case of 1954 would have had minimal, if any, unique implications if viewed in isolation.

Instead, the landmark report by Merrill et al[1] mobilized physician and public support for transplantation research to a new level. Only 12 years earlier, Medawar had shown with skin allografts that rejection was an immunologic phenomenon. By the early 1950s, the main histopathologic features of renal allograft rejection in nonimmunosuppressed humans were delineated in studies of the kidney allograft of Michon and Hamburger, and of kidneys transplanted to the thigh by Hume and Merrill et al. Successful engraftment of the identical twin kidney now dramatically demonstrated what could be accomplished if rejection were prevented.

The only evidence that rejection might be avoidable had come from experiments reported in 1953 by Billingham, Brent, and Medawar,[2] in which allogeneic spleen cells were transplanted into immunologically immature mice. This was the forerunner model of bone marrow cell transplantation for humans with immune deficiency diseases. In a second model that ultimately evolved into clinical bone marrow transplantation for a wide range of hematologic and other indications, Main and Prehn[3] reduced the immune responsiveness of adult mice by irradiation, preceding the transplantation of bone marrow cells. Under both experimental circumstances, the mouse recipients endowed with donor cells (ie, donor leukocyte chimerism) could accept other tissues from the same donor throughout their lifetime.

A derivative 3-step strategy that could permit organ engraftment in patients was promptly envisioned. It consisted of weakening the recipient's immune system with total body irradiation as had been done by Main and Prehn, infusing donor hematolymphopoietic (eg, bone marrow) cells, and engrafting an organ from the leukocyte donor. Efforts to apply this strategy in outbred large animals failed because the donor leukocytes either were rejected or caused graft-vs-host disease. Human tissue antigens would not be sufficiently delineated to avoid these outcomes by histocompat-

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Table. Characteristics of the First Successful Transplantations of Kidney Allografts With ≥6 mo Survival as of March 1963

Physician	Site	Date	Donor Relationship	Outcome
Joseph E. Murray	Boston, Massachusetts	January 24, 1959	Fraternal twin	20 Years
Jean Hamburger	Paris, France	June 29, 1959	Fraternal twin	26 Years
René Küss[a]	Paris, France	June 22, 1960	Unrelated	18 Months[b]
Jean Hamburger[a]	Paris, France	December 19, 1960	Mother	22 Months[b]
René Küss[a]	Paris, France	March 12, 1961	Unrelated	18 Months[b]
Jean Hamburger[a]	Paris, France	February 12, 1962	Cousin	15 Years[c]
Joseph E. Murray	Boston, Massachusetts	April 5, 1962	Unrelated	17 Months[d]
Thomas Starzl	Denver, Colorado	1962-1963	Mixed series	>45 Years

[a] Küss[6] and Hamburger[5] described periodic administration of adrenal cortical steroids with these patients.
[b] Patient death occurred at listed time.
[c] Patient underwent successful retransplantation in the 1970s; elected to French Parliament.
[d] First success with drugs-only immunosuppression (no radiation).

ibility matching for another decade. Consequently, clinical bone marrow cell transplantation for any purpose was forestalled until 1968.

In contrast, kidney allografts were successfully transplanted in a small number of humans, beginning in 1959, without donor leukocyte infusion or tissue matching. Success of these procedures was defined as life-supporting graft function for 1 year or more. In the first of these epochal cases, Merrill and Murray et al[4] at the Peter Bent Brigham Hospital, Boston, Massachusetts, transplanted a kidney from a fraternal (dizygotic) twin to his sublethally irradiated brother (450 R). Five months later, Hamburger et al[5] duplicated the feat in a French fraternal twin (TABLE). Although 11 attempts by Merrill et al to move beyond fraternal twins were unsuccessful, 4 irradiated nontwin recipients were reported during 1960 to 1962 by the Paris teams of Hamburger et al[5] and Küss et al.[6] Two of the kidney donors were blood relatives and the other 2 were genetically unrelated (Table).

The transplanted fraternal twin kidneys had normal function without posttransplant immunosuppression until the recipients died 20 and 26 years later of nonrenal causes. None of the nontwin kidneys were spared rejection, although one of these allografts (Table) functioned for 15 years. In their nontwin recipients in the Table, Hamburger and Küss described periodic administration of adrenal cortical steroids. In addition, Küss secondarily administered the myelotoxic drug 6-mercaptopurine to one patient as early as August 1960, based on canine studies of the drug in London, England, by Calne[7] who had visited the Paris, France, center in 1960 shortly before joining Murray in Boston.

The drug 6-mercaptopurine and its imidizole derivative azathioprine had been synthesized and shown to be immunosuppressive by Elion and Hitchings in a search for antileukemic agents. Interest in the use of these drugs for transplantation was generated by a report of Schwartz and Dameshek in 1958 that a 2-week course of 6-mercaptopurine inhibited the rabbit immune response to heterologous albumin. In 1959, they reported additional experiments showing that second and third albumin injections without further 6-mercaptopurine treatment failed to induce the typical anamnestic response induced by repetitive exposure to foreign proteins.[8] This observation revealed the possibility of drug-assisted antigen-specific tolerance. In addition, when rabbits were given daily doses of 6-mercaptopurine, skin allograft survival was prolonged but by only a few days.

Moreover, when outbred canine kidney recipients were given daily doses of 6-mercaptopurine or its analogue azathioprine, mean allograft survival was prolonged in most animals by only a few weeks.[7] Murray and Merrill et al[9] then produced the seventh example of successful kidney allograft transplantation, and the first ever with drugs only (without irradiation, Table). The patient who received a kidney from an unrelated donor in April 1962 was treated daily with azathioprine to which adjunct cytotoxic agents were added. The milestone renal allograft functioned for 17 months before being rejected.

Initial enthusiasm caused by news of this successful case was dampened when the recipient was the only one of the first 10 patients in the Boston azathioprine series to survive longer than 6 months. However, an overlapping series of living donor kidney transplantations in 1962 and 1963 at the University of Colorado, Denver (Table), showed that renal transplantation could be a practical, albeit flawed, clinical treatment when azathioprine was combined with prednisone.[10] The majority of these patients and their allografts (46 from blood relatives, 18 from unrelated individuals) survived more than 1 year. Close behind, Hume et al reported similar results in Richmond, Virginia, with a modified azathioprine-prednisone combination.

The Colorado experience revealed 2 features of the alloimmune response that permitted the rapid expansion of clinical renal transplantation, and because these features were not kidney specific, the transplantation soon after of other organs. First, rejection that developed with azathioprine was reversible with the addition of high doses of prednisone. Second, reversible rejection frequently was succeeded by what was proposed to be variable-acquired tolerance as evidenced by a time-related reduction of need for immunosuppression. The need for maintenance immunosuppressive therapy eventually was eliminated in some patients. Eight recipients in this series cur-

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rently have the world's longest functioning organ allografts after 45 or more years, and 6 of the 8 have not taken immunosuppression medications for 10 to 44 years.

By the end of 1963, a base had been laid by the experience with kidney transplants that readily accommodated new immunosuppressive drugs (eg, antilymphocyte globulin, cyclosporine, tacrolimus), and on which nonrenal transplant programs would be built. What was missing was an understanding of what had been accomplished. None of the vanguard kidney allograft recipients of 1959 to 1963 had been infused with donor lymphopoietic cells. It was assumed, therefore, that the requisite of donor leukocyte chimerism for tolerance in the mouse models played no role in organ engraftment. This dogma was not challenged until small numbers of multilineage donor leukocytes (microchimerism) were detected in 1992 in the tissues or blood of all 5 kidney recipients of the 1962 to 1963 Colorado series who were studied, and of all 25 liver recipients who by 1992 were 12 to 29 years posttransplantation.[11]

The microchimeric donor cells in these recipients were progeny of the transplanted organ's passenger leukocytes of bone marrow origin. Under an umbrella of immunosuppression or without this protection in the radiated fraternal twins of 1959, the ancestral donor leukocytes had migrated during the first few posttransplant weeks into the recipients. Thus, transplantation of an organ was the equivalent of bone marrow cell infusion.[11] Consistent with this view, Przepiorka and Thomas et al[12] contemporaneously discovered a small residual population of recipient cells (reverse microchimerism) in bone marrow recipients who previously were thought to have total hematolymphopoietic cell replacement.

In the transplantation immunology paradigm that evolved from the microchimerism findings, it is axiomatic that stable alloengraftment of either an organ or bone marrow cells means that bidirectional tolerance has evolved—the completeness of which can be inferred by the amount of maintenance immunosuppression required to avoid rejection or graft-vs-host disease.[11] The seminal tolerance mechanism of clonal activation-exhaustion-deletion coincided with the rejection and its reversal first recognized in organ recipients in 1962 to 1963. The additional mechanism of "immune ignorance" essential for maintenance of exhaustion-deletion achieved with the initial flood of migratory leukocytes was first demonstrated in a skin transplantation model in 1968.[13] A third of a century passed, however, before the role of this passive mechanism of organ engraftment (failure of the immune system to recognize the presence of antigen that does not reach host lymphoid organs) was recognized.

Concurrent with the microchimerism discoveries, Zinkernagel et al[14] independently formulated from infection studies a similar explanation of acquired tolerance to viruses and other noncytopathic microorganisms. In 1998, the analogies were described between essentially all clinical scenarios of transplantation and microorganism-specific infection syndromes, with further linkages to the immunology of neoplasms and autoimmune disorders.[15] It was also proposed as an overarching paradigm of immune regulation that immunologic responsiveness or unresponsiveness, no matter what the antigen, is governed by the migration and localization of the antigen.

The therapeutic implications of these generalizable immunologic paradigms in other medical disciplines have only begun to be explored. In transplantation, the immediate result has been reducing the burden of chronic immunosuppression with revised treatment regimens in which the timing and doses of antirejection drugs interfere less with natural mechanisms of tolerance.

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