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Renal Transplantation

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History of Renal Transplantation

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Renal transplantation came from a series of steps that began to appear in the literature at the beginning of the 20th century. The steps were small, widely spread in time, and usually 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 antigenetically 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 opinion was published on the eve of the successful clinical renal transplantations in 1962 and 1963 that extended this procedure beyond the occasional identical and fraternal twin cases of the mid and late 1950s. Even then, these efforts provoked editorials questioning their inherent feasibility as well as their ethical basis.[2]

▲ TWENTIETH CENTURY BEGINNINGS

Heterotransplantation (Xenotransplantation)

In fact, the trials of the early 1960s were already late in a long, but at first slowly unfolding, story of whole-organ transplantation. The first known attempts at clinical renal transplantation by vascular anastomoses were made between 1906 and 1923 with pig, sheep, goat, and subhuman primate donors. The first of these efforts were in France[3] and Germany,[4] but others followed as summarized elsewhere.[5–7] None of the kidneys functioned for long, if at all, and the human recipients died a few hours to 9 days later. Although the biologic barrier to success was not understood, the applicability of vascular suture techniques (from Alexis Carrel) and even the possibility of using pelvic implantation sites were either envisioned or actually practiced. No further animal to human transplantations were tried again until 1963, when systematic

and surprisingly successful clinical trials were made with chimpanzee[6] and baboon[7,8] kidneys. The eventual death of all of the recipients of animal organs ended renal xenotransplantation trials until the Baby Fae baboon heart xenotransplantation in the mid 1980s.[9]

Homotransplantation (Allotransplantation)

In 1936 Voronoy of Kiev, Russia,[10] reported the transplantation of 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.[11] In addition, the donor had been dead for 6 hours. The recipient died 48 hours later without making urine. Sporadic further efforts at renal allotransplantation were made in the ensuing 15 years without effective immunosuppression, as documented by Groth[5] and Hume et al.[12]

This was the dawn of renal transplantation. However, the stage was being set for the sunrise. Although renal transplantation lay largely dormant until 1951, Rene Kuss et al[13] and Charles Dubost et al[14] of Paris and Marceau Servelle et al of Strasbourg[15] carried out a series of cadaveric renal transplantations from convict donors after execution by guillotine. The next year, the French physician, Jean Hamburger, working with the urologist Louis Michon at the Hospital Necker, Paris, reported transplanting a kidney from a live volunteer donor.[16] The kidney, which was donated to a young man (named Marius) from his mother, functioned well and for 3 weeks before being rejected by the nonimmunosuppressed recipient. The kidney transplant procedure originally developed by Kuss and the other French surgeons was used for this patient. It has been performed hundreds of thousands of times since then, including for the celebrated identical (monozygotic) twin transplantations performed by Murray (Nobel Laureate, 1990) et al[17] in Boston.

Visitors flocked to France in the early 1950s to learn first hand from this experience, including John Merrill, who observed the extraperitoneal pelvic operation (often called the Kuss procedure in Europe). This was described in the classic account by Hume and Merrill et al[12] of their first clinical trials at the Peter Bent Brigham Hospital. In the Boston operations, all but one of the transplants were placed in the thigh and revascularized from the femoral vessels, with urine drainage by skin ureterostomies.[12] The extensive discussion of the French experience by Hume et al[12] included acknowledgment of the French source of the vascular surgical technology in the person of Alexis Carrel (Nobel Laureate, 1912),[18] who had spent much of his professional life in the United States in transplantation research. Carrel understood that transplanted organ allografts were not permanently accepted, but he did not know why.

Although the Peter Bent Brigham program postdated the early French efforts, the depth and serious intentions of the Harvard group were obvious in the report by Hume et al.[12] It contained observations on nine kidney allografts in nonimmunosuppressed recipients. The first of these kidneys was transplanted into the normal location in the recipient after its removal for a lower ureteral carcinoma on March 30, 1951, by Dr. L. H. Doolittle, of Springfield, Massachusetts. The patient had

been undergoing short-term dialysis care at the Brigham, where the first artificial kidney in the United States had been brought from Holland by Wilhelm Kolff and modified by Harvard engineers, as described in detail by Moore.[19]

The next eight renal allografts, all placed in the thigh location, were transplanted between April 23, 1951, and December 3, 1952. Hume's description of this experience stands as one of the great medical classics of the 20th century. It provides a nearly complete clinical and pathologic profile of renal allograft rejection in an untreated human recipient. None of the European and American efforts to this time, however, or all together, would have had any lasting impact on medical practice were it not for what lay ahead. The principal ingredients of organ transplantation—immunosuppression, tissue matching, and organ procurement (and preservation)—were still unknown or undeveloped. The only examples of probable allograft function through 1954 were provided first by one of the nonimmunosuppressed patients of Hume et al[12] whose graft in the thigh location functioned for 5 months and an even earlier patient treated in Chicago by Lawler et al[20] about whom similar claims were considered implausible by later critics. Hume's career lasted well into the next era of transplantation, until his death in May, 1973, near Los Angeles in the crash of a private plane. John Merrill drowned off the beach of a Caribbean island in 1984.

The perception, if not the reality, of hopelessness was changed at the Peter Bent Brigham Hospital 2 days before Christmas 1954, when a kidney was removed from a healthy man by the urologist J. Hartwell Harrison and transplanted by Joseph E. Murray to the pelvic location of the donor's uremic identical twin brother; the nephrologist was John P. Merrill.[17,21] As in the earlier mother-to-son transplant in France,[16] no effort was made to preserve the transplanted kidney, which functioned promptly even though it underwent 82 minutes of warm ischemia time. According to Merrill et al,[17] the bold step of exploiting the principle of genetic identity for whole-organ transplantation had been suggested by the recipient's physician, David C. Miller, of the Public Health Service Hospital, Boston. It already was well known that identical twins did not reject each others' skin grafts.[22] To ensure identity, reciprocal skin grafting was performed on the Boston twins. Although the identical twin cases attracted worldwide attention, organ transplantation had reached a dead end. Further progress in the presence of an immunologic barrier would require effective immunosuppression.

THE CONCEPT OF IMMUNOSUPPRESSION

With Recipient Irradiation

For Bone Marrow Transplantation

The transition of tissue and organ transplantation from an exercise in futility to tenuous practicality was a slow process that began more than 10 years before Murray's identical twin case. The fundamental problem of transplantation was defined by Medawar (Nobel Laureate with Burnet, 1960) when he provided evidence in 1944 that

rejection is an immunologic event.[23,24] In retrospect, every further development was a logical and inevitable extension of this concept. If rejection was an immune reaction, why not protect the organ transplant by weakening the immune system? This was done with adrenal corticosteroids[25,26] and total body irradiation,[27] both of which prolonged skin graft survival in animals.

However, the delay of rejection of rodent skin grafts was modest at best. Hopes were fanned when Billingham, Brent, and Medawar[28] accomplished permanent skin allograft acceptance in a special circumstance not involving any immunosuppression; namely, the inoculation of fetal or perinatal mice with immunocompetent spleen cells from adult donors. Instead of being rejected, these cells survived in the immunologically immature recipients, who were endowed with the ability in later life to accept skin from the original donor strain.[28,29] This was the first example of acquired transplantation tolerance.

The impetus and rationale for these experiments came originally from the observation by Owen[30] that freemartin cattle (the calf equivalents of human fraternal twins) were permanent hematopoietic chimeras if placental fusion and fetal cross circulation had existed in utero. Burnet and Fenner[31] predicted that such chimerism and the ability to exchange other tissues could be induced by the kind of experiment eventually performed with Medawar by Billingham and Brent. However, the surgical interest generated by the mouse tolerance experiments was quickly dampened when Billingham and Brent[32] learned that the penalty for the infusion of donor splenocytes was lethal graft versus host disease (GVHD) unless there was close histocompatibility between the donor and the immunologically defenseless recipients.

Immunosuppression was first exploited to achieve tolerance when in 1955 Main and Prehn[33] simulated in adult (as opposed to fetal) mice an environment they likened to that in the perinatal Billingham-Brent-Medawar animals. The three steps were: first, to cripple the immune system with supralethal total body irradiation, next to rescue it with allogeneic bone marrow (producing a hematolymphopoietic chimera), and finally to engraft skin from the bone marrow donor strain. Although these efforts were successful,[33,34] lethal GVHD could be avoided, as in the perinatal mouse model only by using histocompatible donors. Mannick et al[35] extended these observations by producing bone marrow chimerism in a single irradiated beagle dog, followed by kidney allotransplantation from the original marrow donor. The dog survived for 73 days.[35] Rapaport et al[36] later showed that, as in the rodent models, this strategy could not work unless perfectly tissue-matched canine marrow donors were used, usually litter mates. Efforts by Hume et al,[37] Rapaport et al,[36] and others to broaden the acceptable histocompatibility requirements were totally unsuccessful—leading to lethal GVHD, rejection, or both.

Appreciation of the dilemma posed by the administration of bone marrow to cytoablated recipients caused a break in ranks in 1959–1962 between those interested in the treatment of hematologic disorders and those for whom bone marrow was only the means to the end of transplantation of a needed whole organ. From this point onward, the therapeutic philosophies of bone marrow and solid organ transplantation took separate pathways—one dependent and the other seemingly independent of classic chimerism-associated tolerance induction as defined by the

Billingham, Brent, and Medawar model.[29] In spite of the fact that only perfectly matched siblings could be used, clinical bone marrow transplantation was accomplished in 1963 by Mathe et al in Paris[38] and in 1968 by Gatti et al in Minneapolis[39] and Bach at the University of Wisconsin.[40] Successes by Thomas (Nobel Laureate, 1990),[41] van Bekkum,[42] and others fueled the maturation of bone marrow transplantation into accepted clinical therapy for hematologic diseases and an assortment of other indications.

For Whole Organs

In contrast to the hematologists, Murray et al[43] attempted to use the Main-Prehn principle of recipient cytoablation with total body irradiation (TBI) plus bone marrow and kidney transplantation in two patients only, both in 1958. Sublethal TBI[43,44] without bone marrow was used for the next 10 kidney recipients. Although 11 of 12 irradiated recipients died after 0–28 days, the survivor (who was not given bone marrow) had adequate renal function from the time his fraternal twin brother's kidney was transplanted in January 1959 until he died of arteriosclerotic heart disease in 1979. The detailed description of this patient by Merrill et al in the *New England Journal of Medicine*[45] was arguably the single most influential clinical case report in the transplantation literature, because this was the first time that the genetic barrier to transplantation had been breeched.[43,44,46] Five months later, Hamburger et al[47–49] added a similar fraternal twin case. The second recipient had good renal function until his death 26 years later from carcinoma of the urinary bladder.

However, it was conceivable with these fraternal (dizygotic) twin recipients that their individual placentas had cross-circulated with those of their kidney donors during gestation, like the circumstances in Owen's freemartin cattle. This suspicion was put to rest with the further extraordinary kidney transplant experience in France during 1960–1962 in which TBI was used *without* bone marrow reconstitution. Hamburger et al[48,49] succeeded with kidney transplantation from a sibling and a first-cousin donor. The latter kidney (transplanted in February 1962) functioned for 18 years before retransplantation was performed (without interim dialysis) on a patient who now is a member of the French parliament. He is the longest surviving kidney allograft recipient (34 years) from that heroic era.[50]

Also in Paris, Rene Kuss et al[51,52] had long-term survival of three of six irradiated patients treated with kidney transplantation from January 1960 through 1961. This was a monumental achievement, because two of Kuss's long-surviving patients were given kidneys from nonrelated donors (the first in June 1960) that functioned for 17 and 18 months. During the critical period from January 1959 through the spring of 1962, the cumulative French experience was the principal (and perhaps the only) justification to continue clinical kidney transplantation trials (Table 2–1). By showing that bone marrow infusion was *not* a necessary condition for substantial prolongation of kidney grafts, the stage was set for the transition to drug therapy. In fact, Kuss was using 6-mercaptopurine (6-MP) and steroids as adjuvant therapy as early as 1960.[51]

Those examining this period historically have been inclined to consider

TABLE 2–1 ▲ LONG SURVIVING HUMAN KIDNEY ALLOGRAFTS (BEFORE MAY 1962)

Reported by	Reference	Date	Donor	Primary Immunosuppression	Kidney Survival (years)
Murray	43,44,46	January 24, 1959	Fraternal twin	X-ray	20.5[a]
Hamburger	47	June 29, 1959	Fraternal twin	X-ray	25[a]
Kuss	51	June 22, 1960	Unrelated	X-ray (also 6-MP, steroids)	1.5
Hamburger	48	December 19, 1960	Mother	Irradiation (also steroids)	>1
Kuss	51	March 12, 1961	Unrelated	Irradiation (also 6-MP, steroids)	1.5
Hamburger	49	February 12, 1962	Cousin	Irradiation (also steroids)	15[b]
Murray	53	April 5, 1962	Unrelated	Imuran (azathioprine)	1.5

6-MP, 6-mercaptopurine.
[a] Died of cancer.
[b] Patient alive after retransplantation of sister kidney (without interim dialysis) on March 28, 1977.

irradiation-induced and drug-induced graft acceptance as different phenomena.[5,44,46] However, it seems certain that the Boston and Paris fraternal twin kidney recipients, as well as the 5 long-surviving non-twin French recipients, had achieved to variable degrees the kind of graft acceptance that later was seen in tens of thousands of drug-treated humans after all kinds of whole-organ transplantation. The fact that the mechanism was the same has been appreciated only since it was discovered that extensive migration and survival of sessile tissue leukocytes (most obviously of dendritic cells) from graft to host (microchimerism) is the explanation of "acceptance" of all whole organs with any immunosuppressive modality.[54–58]

Chemical Immunosuppression

Because of the success (albeit limited) with kidney transplantation after TBI, it was not surprising that the search for immunosuppressive drugs was focused at first on myelotoxic agents that mimicked irradiation. They were viewed as "space makers" for donor marrow or for recovering recipient bone marrow. In September 1960, Goodwin et al produced profound bone marrow suppression with methotrexate and cyclophosphamide in a daughter recipient of a maternal kidney. The patient subsequently experienced several rejections that were temporarily reversed with prednisone during the 143 days of survival. This was the first example of protracted hu-

man kidney graft function with drug treatment alone.[59] However, the case was not reported until 1963.

Kidney transplant surgeons were quick to realize that myelotoxicity should be avoided, not deliberately imposed. The most important step in this appreciation followed the discovery by Schwartz and Dameschek[60] that 6-MP in nontransplant models was immunosuppressive without bone marrow depression. Within a few months, Schwartz and Dameschek[61] and Meeker et al[62] showed that 6-MP allowed a dose-related mitigation of skin-graft rejection in rats. Close behind, Calne[63] and Zukoski et al[64] independently demonstrated the same thing in dogs following kidney transplantation.

In June, 1960, Calne moved from the Royal Free Hospital, London, to Boston to be the team leader in Murray's Brigham laboratory for further preclinical development of 6-MP and its analogue, azathioprine.[65,66] What was achieved at first in Boston and in laboratories elsewhere with the canine kidney transplant model was delay of rejection or death of the animal from overimmunosuppression. However, occasional examples of long-term or seemingly permanent allograft acceptance were observed throughout 1962 and 1963[67–70]—defined as long survival of transplanted mongrel kidneys following completion of a 4- to 12-month course of 6-MP or azathioprine. The same thing has been observed since with each new major immunosuppressive agent (or drug cocktail regimen), including cyclosporine and tacrolimus (FK 506). Until the advent of cyclosporine and tacrolimus, the most potent agents for induction of this state have been the antilymphocyte sera (ALS) and antilymphocyte globulins (ALG) that at the beginning were polyclonal agents[71,72] and later the highly specific monoclonal preparations first used clinically by Cosimi et al.[73]

This new kind of graft acceptance in outbred dogs was easier to produce with drugs than with TBI, but the number of absolute examples was (and is) extremely small in contrast to what can be achieved in small rodents. In Murray's summary of his research with Calne and subsequent collaborators, a handful of long-surviving animals (<5%) was the distillation from 1000 experiments with 6-MP or azathioprine performed in the Boston laboratories.[67] The same was true everywhere. The animals proudly displayed as long-term survivors in laboratories in Boston, Denver, Richmond, and Minneapolis were limited to a few who had run the gauntlet of therapy to the point where treatment was stopped. However, a unique observation was made at the University of Colorado. Adrenocortical steroids were shown to reverse rejection in 88% of dogs, sometimes in a spectacular way, before the steroids in this species almost always caused fatal peptic erosions of the gastrointestinal tract.[74]

It was on this dismal record that the clinical kidney transplant trials of the early 1960s were based. In a display of optimism that would not be tolerated in today's clinical research climate, the rare exceptional survival was given more weight than the customary failure. Thus the poor results came as no surprise when the drugs were first used for patients in the same way as had been tried in dogs.[44,53] However, one of the Boston patients whose transplantation under azathioprine had been performed in April, 1962, had functional graft survival for more than 18 months after

receiving the kidney of a patient who could not be weaned from a heart-lung apparatus after open heart surgery[53,75] under conditions comparable to those of a "heart-beating cadaver."[76] Although the allograft failed after 18 months, this pioneer recipient was the first to achieve long survival with azathioprine, and this constituted the opening wedge into a new era.

▲ THE YEAR OF THE STAMPEDE: 1963

The Crucial Role of Steroids

The Reversibility of Rejection

At the University of Colorado, where the synergism of azathioprine and prednisone had been observed in dog experiments,[74] the two drugs were routinely used together from the origin of this program in early 1962. The results exceeded everyone's expectations[77,78] and precipitated a revolution in clinical transplantation. Acute rejection could readily be reversed with prednisone in almost all cases. The use of adrenocortical steroids in transplantation can be traced to the experimental work a decade earlier of Billingham et al[25] and Morgan.[26] Goodwin et al[59] had observed reversal of rejection in a kidney recipient whose primary treatment had been with methotrexate and cyclophosphamide. Hamburger et al[48] and Kuss et al[51] also had administered steroids to their irradiated patients under unknown circumstances. However, there was no hint in any of these reports suggesting either the profound effectiveness of prednisone or the indispensability of this dose-maneuverable drug, which remains an essential component of treatment regimens to the present day.

Host-Graft Nonreactivity

A second and equally fundamental observation in the Colorado kidney recipients was a subsequent diminution in the amount of drug treatment required to prevent rejection,[77] often allowing the life-time rehabilitation of many patients in an unrestricted environment. Of the first 64 patients in the Colorado series compiled between 1962 and March 1964,[78] 15 survived for the next 25 years, including the recipient with the longest surviving allograft in the world (now 33 years).[50] Two of the 15 patients stopped all immunosuppression without rejection for 28 and 30 years, recapitulating the phenomenon occasionally seen in dogs and in the irradiated Boston and Paris fraternal twins. Nine other patients from the era preceding early 1964, including three treated by Hume (who had moved to Richmond), were alive in six other centers in the summer of 1989. None of these quarter-century survivors had been given a kidney from a nonrelated donor. The first such example in the world passed the 25-year mark in October 1989.[50] This was a recipient of a cadaveric kidney treated in Paris by Hamburger et al in October 1964.

TABLE 2-2 ▲ THE FOUNDATION OF CLINICAL TRANSPLANTATION

Central Therapeutic Dogma	Principal Baseline Agents
Therapy with baseline drugs	Azathioprine
Secondary adjustments with steroids with or without antilymphoid agents	Cyclophosphamide
Case to case trial (and potential error) of weaning	Cyclosporine
	Tacrolimus (FK 506)

Evolution of a Treatment Dogma

The reversibility of rejection and change in the host-graft relationship eventually were verified with all other transplanted organs, beginning with the liver.[79,80] Although immunosuppression has improved, the central therapeutic dogma for solid-organ transplantation that had emerged by 1963[77,78] has changed very little in more than 30 years. The dogma calls for daily treatment with one or two baseline drugs with further immune modulation by the highly dose-maneuverable adrenocortical steroids to whatever level is required to maintain stable graft function (Table 2–2). This means that every recipient of a whole organ goes through a trial and potential error experience as drugs are weaned to maintenance levels.

When the news became known in 1963 of the successes with azathioprine and prednisone therapy, a proliferation of kidney transplant centers began on both sides of the Atlantic. In January 1963, there were only three active clinical kidney transplant centers in the United States. These were at the Brigham, the Medical College of Virginia (where Dave Hume moved from Boston in 1956), and the University of Colorado, where the first renal transplantation was performed in March 1962. Centers were equally scarce in Europe, where the two in Paris had been in existence for more than a dozen years. By year's end, more than 50 American kidney centers were gearing up, and some had already started. The same thing occurred in Europe. Trials with the liver, the next vital organ beyond the kidney, had started,[81] and clinical xenotransplantation with chimpanzee[6] and baboon[8] donors had been systematically tried with encouraging, although ultimately unsatisfactory results.

Failure to explain the reason for the empirically derived treatment regimen did not prevent its worldwide acceptance almost overnight and its refinement to an art form with each new agent beginning with the addition of ALG in 1966 as a third (adjuvant) agent[71] and continuing in 1989 with the addition of tacrolimus (FK 506).[82] The introduction of cyclosporine by Calne et al[83] in 1978 eventually led to a dramatic change in the field. However, the use of cyclosporine alone (or in combination with myelotoxic agents) was unacceptably toxic and suboptimally therapeutic. When combined with prednisone (with or without other agents),[84] the new drug narrowed the gap between the results of cadaveric versus living-related transplantation and opened the doors to further development of transplantation of the liver, heart, and other extrarenal organs.

▲ KIDNEY PROCUREMENT AND PRESERVATION

The sudden arrival of clinical kidney transplantation in 1963 was so unexpected that little collateral research or other formal preparation had been made to preserve the organs. The lack of insight 50 years ago about the requirements for successful kidney preservation was illustrated by the fact that Voronoy's first cadaveric kidney donor (in 1936) had been dead for 6 hours before procurement.[10] Even in the highly successful identical twin cases, kidneys were not protected from warm ischemia until 1962.

Yet the potential benefit of lowering the temperature of an excised organ was grasped instinctively by early workers, in part because cardiac surgeons were knowledgeable about hypothermia for open heart operations and had demonstrated a reduction of ischemic damage below the level of aortic cross clamping when the subdiaphagmatic organs were cooled.[85] Lillehei et al[86] simply immersed intestine in iced saline solution before its autotransplantation. The value of hypothermia for liver allografts was quantified chemically by Sicular and Moore,[87] who reported a slowed rate of enzyme degradation in cold hepatic slices. Thus the principle of hypothermia was understood, although not efficiently applied.

Hypothermia to protect human renal homografts was first systematically accomplished with the cumbersome and potentially dangerous method of ice-tub immersion of living volunteer donors.[88] Total body hypothermia was soon replaced by core (intravascular) cooling by means of infusion of chilled solutions into the renal artery after donor nephrectomy.[89] This technique (using lactated Ringer's solution) had been used for the first time during the development of experimental liver transplantation.[90] Its modification for the renal operation by the same team was an early example of the cross fertilization of procedures that continues today, despite the balkanization of transplantation along organ-defined specialty lines.

Core cooling remains the first step in the preservation of all whole-organ grafts. In cadaveric donors, this is most often done in situ by means of some variation of the technique described by Marchioro et al.[91] This method for the continuous hypothermic perfusion of cadaveric livers and kidneys was used clinically long before the acceptance of brain-death conditions.[92] Ackerman and Snell[93] and Merkel et al[94] popularized in situ cooling of cadaveric kidneys with simple infusion of cold electrolyte solutions into the distal aorta.

Until 1981, transplantation of the extrarenal organs was an unusual event. By late 1981, it had become clear that liver and thoracic-organ transplant procedures were going to be widespread. A method of multiple organ procurement was 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, called the *flexible technique*,[95] was developed at the University of Colorado and the University of Pittsburgh. Aided by the efforts of C. Everett Koop, the Surgeon General of the United States, the technique was adopted as a worldwide standard almost overnight. All organs to be used are cooled in situ, and after cooling they are rapidly removed by means of dissection in a bloodless field. The sharing of organs from a

common donor by recipient teams from widely separated centers became routine by the mid 1980s.

Extension of the safe period after initial cooling has followed one of two prototype strategies, developed in research conducted mainly with kidneys and applied secondarily to livers and other organs. One approach was to provide a limited and continuous renal arterial circulation, as was done by Ackerman and Barnard[96] with a perfusate primed with blood and oxygenated within a hyperbaric oxygen chamber. When Belzer et al[97] were able to eliminate the hemoglobin and hyperbaric chamber components, their asanguineous perfusion technique was immediately accepted but then slowly abandoned in most centers when it was learned that the quality of two-day preservation was not markedly better than with the simpler and less expensive infusion and slush methods. Nevertheless, it is expected that refinement of this approach will someday allow true organ banking.

The alternative strategy for the preservation of kidneys and other organs has been the instillation of special solutions such as that described by Collins et al[98] or plasma-like solutions.[99] The original Collins solution, or modifications of it, was used for almost 20 years for the so-called slush techniques of kidney preservation. The introduction of the University of Wisconsin (UW) solution was the first important development in kidney preservation in almost two decades.

The superiority of the UW solution to any of previous conventional solutions for preservation of kidney, liver, and other organs has been demonstrated in experimental kidney transplant test models[100–102] and confirmed in clinical trials.[103] The UW preservation allowed longer safe preservation (2 days), a higher rate of graft survival, and a lower rate of primary nonfunction. The day of economical and practical national organ sharing had finally arrived after 30 years of evolution.

▲ TISSUE TYPING

Antigen Matching

In the early 1960s, 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 Terasaki et al,[104] of Los Angeles, in collaboration with the University of Colorado transplantation team.

The results were disappointing. Since then, the genetics of the human major histocompatibility complex (MHC), its overriding importance in human biology, and above all its complexity have been established. Although the value of tissue matching for transplantation between highly compatible family or nonrelated donor members (the perfect match) was established as early as 1970,[105] the complexity of the human histocompatibility system has militated against perfect matching between nonrelated people for cadaveric kidney transplantation. Lesser degrees of matching have not correlated well with outcome.[106–109]

Whether these expensive efforts at matching should continue has become a debated public policy because of the increasing use by the United Network of Organ Sharing (UNOS) of tissue matching as the overriding determinant of national distribution of cadaveric kidneys. Reports from two American and European multicenter case compilations with an overlapping database have consistently claimed a slight but statistically significant gain in survival of well-matched versus mismatched cadaveric kidneys, but most of the centers or consortia that contribute to these data pools are unable to see this trend in their own material. In the meanwhile, the results with modern-day immunosuppression have become almost as good with unmatched cadaveric kidneys as with kidneys from less than perfectly matched (double haplotype identical) blood relatives.

The most nagging intellectual concern to kidney transplant surgeons and others who wanted to but could not see an influence of human leukocyte antigen (HLA) matching in their own practices was the knowledge that only a perfect or near perfect match had a significant effect on outcome, and even then a small one. It was difficult to see why HLA matching was so critical for success with bone marrow transplantation[41,110] but so inconsequential for whole organs. A plausible explanation for this dichotomy was provided with the discovery of systemic chimerism in organ recipients many years after organ transplantation.[54–56] How this chimeric state, which is believed to be the basis of renal graft acceptance, explains the blindfolding of an HLA matching effect is discussed in Chapter 9.

Cross Matching

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.* This catastrophic complication was first seen with transplantation from ABO incompatible donors and ascribed to antidonor isoagglutinins.[11] After the description by Terasaki et al[111] of hyperacute kidney rejection by a recipient with antidonor lymphocytotoxic antibodies, Kissmeyer-Nielsen et al[112] and others[113–115] confirmed the etiologic role of these antigraft antibodies. Although hyperacute rejection usually can be avoided with the "cross match" originally recommended by Terasaki et al,[111] its exact pathogenesis remains mysterious 30 years later. Understanding and prevention of the process is believed to be the key to successful xenotransplantation.[116]

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