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The French Heritage in Clinical Kidney Transplantation

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The different starting points and uneven emphasis of historical accounts of transplantation[1] have tended to obscure the contributions to this field of some of the grand figures of French medicine and science. Clinical transplantation activity began in France within the first few years of the 20th century, when Jaboulay in Lyon[2] and other investigators in France and Germany performed subhuman primate to human kidney heterotransplantation.[3-5] In 1936, the Russian Yu Yu Voronoy of Kiev made the first known attempt at renal allotransplantation.[6]

The field of transplantation lay largely dormant until 1951 when Rene Kuss[7] and Charles Dubost[8] of Paris and Marceau Servelle of Strasbourg[9] performed a series of cadaveric renal transplantations. The kidneys were removed from convict donors after their execution by guillotine. The next year, French physician Jean Hamburger, working with urologist Louis Michon at the Hopital Necker (Paris) reported the now commonplace transplantation of a kidney from a live volunteer donor.[10] The pelvic kidney transplant procedure originally used by Kuss and refined subsequently by the French surgeons has been used hundreds of thousands of times since then including for the celebrated identical (monozygotic) twin transplantations performed by Murray (Nobel laureate 1990) and his associates[11] in Boston.

Visitors flocked to France in the early 1950s to learn first hand from this experience, including John Merrill of Boston, as Hume described in the classical account of his own clinical trials at the Peter Bent Brigham Hospital.[12] The extensive discussion of the French experience by Hume was typical of this man whose awareness and acknowledgment of other people's work was noteworthy throughout his illustrious career. As important as these and later contributions of Kuss[13] and Hamburger[14] were, the scientific basis for transplantation in France went far deeper. The roots of histocompatibility research were nourished in France by Jean Dausset (Nobel Laureate 1980).[15] In addition, George Mathe, the father of cell transplantation, was part of the Paris clique of the 1950s and early 1960s.

The skills necessary to transplant the kidney (the only candidate organ until the 1960s) were applications of what were becoming conventional surgical practices after World War II. The vascular surgical technology came from the Frenchman Alexis Carrell[16] and had a pervasive effect on essentially all surgical specialties. Although Carrell understood that transplanted organs were not permanently accepted, the biological specificity of the field of transplantation was defined by Medawar when he showed that rejection is an immunologic event.[17,18] In retrospect, every further development was a logical and inevitable step from this beginning. If rejection was in fact an immune reaction, what could be more logical than to protect the organ transplant by weakening the immune system? Medawar's conclusion about the nature of rejection was strengthened when it was shown more than 40 years ago that adrenal corticosteroids[19,20] and total body irradia-

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tion,[21] which already were known to diminish immunologic responses, significantly prolonged skin graft survival.

The relatively modest delay of rejection of rodent skin grafts made possible with corticosteroids and total body irradiation was not an open invitation for clinical application. Nor was there a clinical mandate in the 1953 article by Billingham et al[22] that described permanent skin graft acceptance in a special circumstance not involving iatrogenic immunosuppression. The unique circumstance was the inoculation of fetal or perinatal mice with immunocompetent spleen cells. Instead of being rejected, these cells survived and endowed the recipient with the ability in later life to accept other allogeneic tissues (in their experiments skin) from the original donor strain.[22,23]

As Billingham, Brent, and Medawar (later referred to as the "holy trinity") meticulously annotated, the impetus and rationale for these experiments came originally from the observation by Owen[24] 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[25] 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 whose definition of tolerance was that it "is due to a primary central failure of the mechanism of the immunological reaction, and not to some intercession, at a peripheral level."[23]

The surgical interest generated by the demonstration that tolerance could be acquired was quickly dampened when it was learned by Billingham and Brent[26] with further experiments in mice that the penalty for the prophylactic infusion of such donor cells could be lethal graft-versus-host disease (GVHD). Many of the inoculated mice failed to thrive ("runt disease") and had skin erosions, hair loss, diarrhea, diffuse pneumonitis, and characteristic changes in their lymphoid organs. Donor immune cells were found everywhere in the recipient tissues.

The objective of producing specific and stable allogeneic (often called Medawarian) nonresponsiveness became the holy grail of transplantation when in 1955, Main and Prehn[27] simulated in adult mice an environment that they likened to that in 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 (creating a chimera), and finally to engraft skin from the bone marrow donor. Their efforts were successful. When the results of Main and Prehn were confirmed by Trentin,[28] the prototype strategy for induction of tolerance in large animals and in humans seemed at first to be obvious. Bad news was close behind. Within a few months, it became clear that GVHD similar to that in the perinatal mouse model could be expected almost invariably after all bone marrow engraftments that "took" following irradiation, except those from perfectly histocompatible donors.

Although the bubble had burst, Mannick, Lochte, Ashley, Thomas, and Ferrebee at Cooperstown, NY (an affiliate of Columbia University), produced bone marrow chimerism in 1958 in an irradiated beagle dog, followed by successful kidney allotransplantation from the original marrow donor.[29] The animal lived for 73 days before dying from pneumonitis and was the first "successful" marrow-kidney chimera in a large animal. However, efforts by Hume et al[30] and others to extend the Main-Prehn irradiation plus bone marrow technology to mongrel dog kidney transplantation was totally unsuccessfully. Later, in summarizing his many years of collaborative research with the Cooperstown group, Rapaport confirmed that this strategy could not work in dogs unless perfectly tissue-matched marrow donors were used—usually litter mates.[31] Under all other conditions, lethal GVHD, rejection, or both were to be expected. Appreciation of this dilemma by the clinicians caused a break in ranks in the late 1950s between those interested in bone marrow transplantation for the treatment of hematologic disorders and those to whom the bone marrow was only the means to the end of transplantation of a needed solid organ of which the kidney was the sole candidate at the time.

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 classical tolerance induction. In spite of the consequent donor pool limitations (essentially only perfectly matched siblings being permissible), bone marrow transplantation, which was first accomplished clinically in 1968 by Robert Good of the University of Minnesota[32] and soon thereafter by Thomas (Nobel Laureate 1990)[33] and van Bekkum,[34] matured into accepted clinical therapy for hematologic diseases and an assortment of other indications.

In contrast, solid organ transplant surgeons were quick to abandon effort to produce specific allogeneic unresponsiveness with bone marrow. In Boston, Mur-

ray and Merrill[35] used the Main-Prehn principle of recipient preparation in their first two attempts at human kidney allotransplantation in 1958, but eliminated the bone marrow component for the next 10 recipients, using sublethal total body irradiation alone.[35,36] Although 11 of their 12 irradiated recipients died after 0 to 28 days, the survivor, the recipient of a fraternal twin kidney in January 1959, lived until 1979 and was the first example of a successful transplantation beyond the identical twin.[35-37]

Five months later, Hamburger et al[14,38,39] added a second successful fraternal (dizygotic) twin case. This patient had good renal function until his death 26 years later from carcinoma of the urinary bladder. However, in the Boston and Paris fraternal twin recipients, the possibility remained that their individual placentas had cross-circulated with those of their kidney donors, like the conditions in Owen's freemartin cattle. This possibility was precluded in the further extraordinary kidney transplant experience in France during 1960 and 1961 using total body irradiation without bone marrow reconstitution. Hamburger et al[14,39] succeeded with kidney transplantation from a sibling and a first cousin. The cousin kidney functioned for 18 years before retransplantation was performed without interim dialysis in a patient who now is a member of the French parliament and the longest surviving kidney allograft recipient (32 years) from that heroic and primitive era.[40]

Also in Paris, Rene Kuss had long-term survival of three of six irradiated patients treated with kidney transplantation from January 1960 through 1961.[13,41] This was a truly extraordinary achievement because two of Kuss's long surviving patients were given nonrelated kidneys (the first in June 1960) that functioned for 17 and 18 months. During the critical period of 1959 through early 1962, the cumulative French experience was the principal (and perhaps the only) justification to continue clinical kidney transplantation trials.[42] 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 and steroids as adjuvant therapy in his patients as early as 1960.[13]

Those examining this period historically have been inclined to consider irradiation-induced and drug-induced graft acceptance as different phenomena.[4,36,37] However, it seems certain that the Boston and Paris fraternal twin kidney recipients, as well as the five long-surviving nontwin 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 in the last few months when it was realized that extensive migration and repopulation of sessile tissue leukocytes (most obviously of dendritic cells) from graft to host and vice versa are events common to the "acceptance" of all solid organs using any immunosuppressive modality—creating chimerism in the graft but also systemically in the recipient.[43] What has been achieved with drugs and antilymphoid agents compared with sublethal irradiation is a greater ease and reliability of achieving this transition.

In view of the historic developments through 1960, it was not surprising that the search for immunosuppressive drugs was focused at first on myelotoxic agents that were viewed as "space makers" for new donor or recovering recipient bone marrow, and thus the pharmacologic equivalent of total body irradiation. Willard Goodwin of Los Angeles achieved sublethal bone marrow "burn out" with methotrexate and cyclosphamide in a living related-kidney recipient in September 1960, who subsequently developed rejection that was reversed with prednisone. This was the first example of protracted human kidney graft survival (143 days) with drug treatment alone.[44]

Kidney transplant surgeons were quick to appreciate that myelotoxicity should be avoided, not deliberatey imposed. The most important step in this evolution was the discovery by Schwartz and Dameschek that 6-mercaptopurine was immunosuppressive without bone marrow depression in nontransplant models.[45] Within a few months, Schwartz and Dameschek[46] and Meeker (working with Good)[47] showed that this drug could mitigate skin graft rejection in rats. Close behind, Calne[48] and Zukoski[49] demonstrated independently of each other that kidney rejection in dogs also was ameliorated.

What was achieved in the earliest kidney transplant experiments using drugs was delay of the inevitable rejection or else death of the animal from over immunosuppression. However, occasional examples of long-term or seemingly permanent allograft acceptance were observed throughout 1962 and 1963[50-53]—defined as long survival of transplanted mongrel kidneys after a 4- to 12-month course of 6-mercaptopurine or azathioprine was stopped. Since then, each new major immunosuppressive agent (or drug cocktail regimen), including cyclosporine and

FK506, has generated excited claims of the same phenomenon. Throughout the years, the most potent agents for induction of this state have been the antilymphoid sera and globulins that at the beginning were polyclonal agents[54,55]—but later highly specific monoclonal preparations.[56] Although variable in its incidence, the graft acceptance observed with all these modalities was indistinguishable and thus was not a treatment-specific phenomenon.

This new kind of graft acceptance in outbred dogs was easier to produce with drugs than with total body irradiation, but the number of absolute examples was (and is) extremely small in contrast to what can be achieved today in small rodents. In summarizing his research with Calne, Alexandre, Sheil, and other investigators using azathioprine,[36] Murray described a 20-day mortality of approximately 50% and a 3-month mortality of 90% in a series of 120 mongrel dogs given daily treatment. Eventually a handful of long-surviving animals (<5%) was the distillation from 1,000 experiments with 6-mercaptopurine or azathioprine performed in Boston by Murray's team in work that was initiated with the arrival there of Sir Roy Calne in June 1960.[52]

The animals proudly displayed as chronic survivors in laboratories of Boston, Denver, Richmond, and Minneapolis were those precious few who had run the gauntlet of therapy to the point where treatment was stopped. Our results in Colorado were similar to those in Boston but with one striking difference. Adrenocortical steroids were shown to reverse rejection in 88% of our dogs, sometimes in spectacular fashion, before the steroids almost always caused fatal peptic erosions of the gastrointestinal tract.[57]

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 the clinical research climate of today, the rare exception 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 the dogs.[36,58] However, one of the Boston patients whose transplantation under azathioprine was 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.[58,59] Because cardiopulmonary bypass was in effect, the physiologic conditions for procurement were unusually advantageous and were in fact comparable to those with a "heart beating cadaver".[60] At 12 months, the blood urea nitrogen in this patient was 100 mg%. The allograft failed between 18 and 24 months, and the patient died at 27 months. However, this pioneer recipient was the first to achieve long survival with azathioprine, and thus he was an opening wedge into a new era.

In Colorado, where the synergism of azathioprine and prednisone was known from the animal work, these two drugs were used together from the outset with results that exceeded everyone's expectations[61,62] and precipitated a revolution in clinical transplantation. Success hinged on the fact that acute rejection usually could be reversed with prednisone as had been shown in our dogs under baseline therapy with azathioprine[57] and as Goodwin had observed in a kidney recipient whose primary treatment had been with methotrexate and cyclophosphamide.[44] Both Hamburger[14] and Kuss[13] had administered steroids to their irradiated patients although no details were given. In a lapse of scholarship in our 1963 article,[61] we failed to acknowledge the French use of steroids or the earlier experimental work of Billingham et al[19] and the American, Morgan.[20] Although these oversights were corrected in our experimental report,[57] we already had unwittingly distorted all subsequent literature on this subject.

The second and far more fundamental observation in these patients was that the amount of drug treatment required to prevent rejection often became less in time,[61] allowing the lifetime rehabilitation of some of the patients. Of the first 64 patients in the Colorado series compiled between 1962 and March 1964,[62] 15 survived for the next 25 years. Two stopped all immunosuppression without rejection for 25 and 27 years, thus mimicking completely the phenomenon occasionally observed in dogs and in the irradiated Boston and Paris fraternal twins. Nine other patients from the era preceding early 1964 including three treated by David Hume of Richmond were still alive in six other centers in the summer of 1989.[40] It was noteworthy that none of these quarter century survivors had been given a nonrelated kidney. The first such example in the world was a cadaver kidney recipient treated in Paris by Hamburger in October 1964 who passed the 25 year mark in October 1989.[40]

The reversibility of rejection and change in host-graft relationship eventually were verified with all other transplanted organs, beginning with the liver.[63] Although immunosuppression has improved, the central therapeutic dogma for solid organ transplantation that had emerged by 1963[61,62] has changed

Table 1. Drug Cocktail Formulation

Central Therapeutic Dogma	*Baseline Agents*
Baseline therapy with one or two drugs	Azathioprine Cyclophosphamide
Secondary adjustments with steroids or anti-lymphoid agents	Cyclosporine Cyclosporine-azathioprine FK506
Case-to-case trial (and potential error) of weaning	FK506-azathioprine

very little in nearly 30 years. The dogma calls for daily treatment with one or two baseline drugs with further immune modulation by the highly dose-maneuverable adrenal cortical steroids to whatever level is required to maintain stable graft function (Table 1). The strategy readily incorporated the antilymphoid drugs in 1966,[54] and after Calne's introduction of cyclosporine[64] the dogma again was found applicable.[65]

A truly amazing period in the history of transplantation was 1959 through 1963, which led to successes that exceeded the wildest expectations of the immunologists. At the outset, the Peter Bent Brigham Hospital was the sole American forerunner of the new field of transplantation, soon to be joined by Will Goodwin's University of California at Los Angeles program in 1960. By January 1963, Goodwin's program had self-imposed a moratorium, but the number of active clinical centers in America had grown to three—the Brigham, the Medical College of Virginia, and the University of Colorado. There were scarcely more in all of Europe, but by this time the two in Paris already had been in existence for more than a dozen years. At the end of 1963, the gold rush was on with a wild proliferation of kidney transplant centers on both sides of the Atlantic. Trials with the liver, the next vital organ beyond the kidney, had started[66] and clinical heterotransplantation with chimpanzee[67] and baboon[68] donors had been systematically tried with encouraging although ultimately unsatisfactory results.

These events and subsequent ones could not have transpired in the way they did without the French

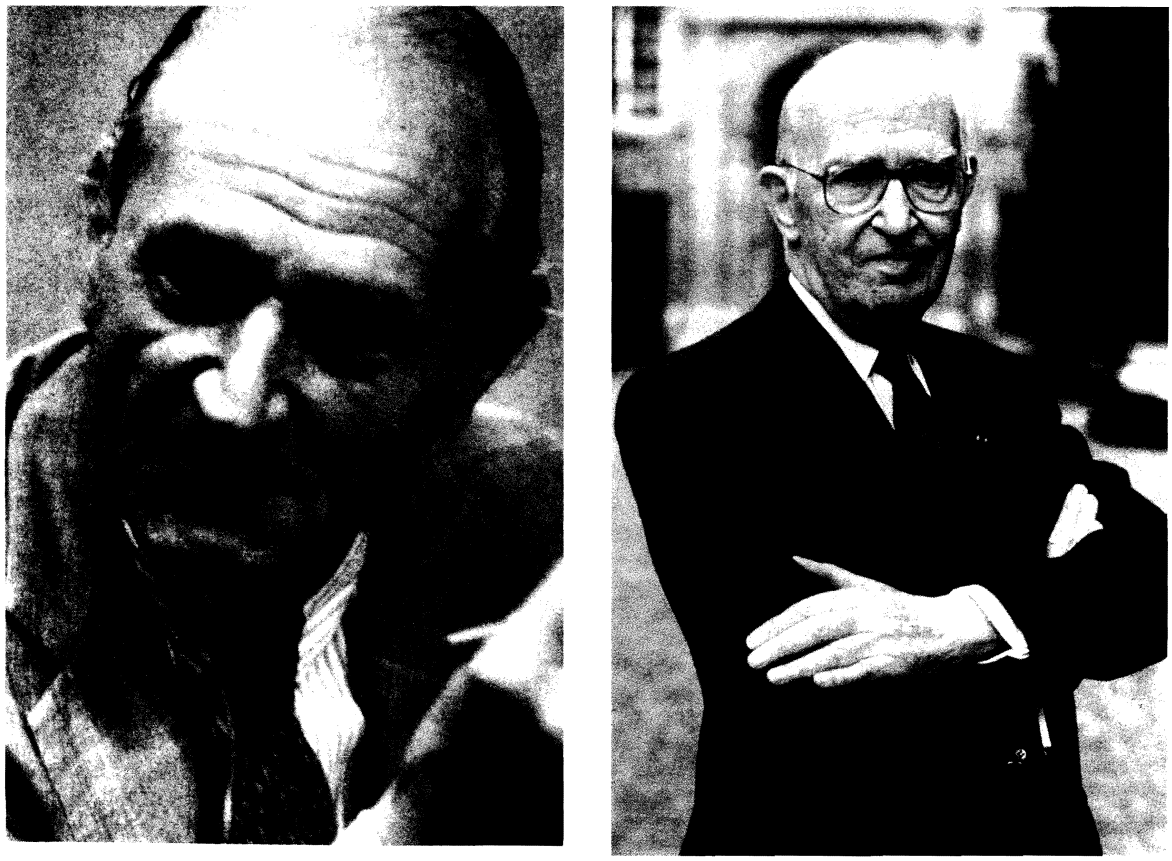

Figure 1. (Left) Rene Kuss (1913-), approximately 1966. (Right) Jean Hamburger (1909-1992), approximately 1985.

pioneers, Hamburger the physician and Kuss the surgeon (Fig 1), and their friends in Boston whose vision was greater than that given to most men and women. Workers in the two cities founded a clinical discipline where none existed before and then persisted despite allegations of folly or worse. The French successes with kidney transplantation over the three-year period from 1959 through early 1962 kept the flames alive when all other efforts were failing.

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