

## The Landmark Identical Twin Case\*

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In the autumn of 1979, the 25th anniversary was observed in Boston of the kidney transplantation that was the subject of the LANDMARK ARTICLE by Merrill and co-workers<sup>1</sup> that is reproduced in this issue. All of the authors of the article were members of the Harvard Medical School Faculty serving at the Peter Bent Brigham Hospital, where research in renal transplantation had been an important activity for several preceding years and where such work has continued to the present time. The decision at these institutions to focus for a historical celebration on the first identical twin transplantation rather than some earlier or subsequent event revealed an in-house perception of the importance of the case that has been shared by outside students of medical history such as Groth<sup>2</sup> of Stockholm.

Of the four authors, Merrill and Guild were internists. The specialty of nephrology was somewhere between nonexistent and fledgling. George Thorn had been given one of the first four artificial kidneys by Wilhelm Kolff, the Dutch physician-inventor. A Brigham version of this machine was built, and with this advantage the first renal dialysis center in the world was born under the direction of Merrill et al.<sup>3</sup> The use of hemodialysis to prepare the identical twin recipient for transplantation foreshadowed this practice for tens of thousands of patients in later years.

The availability of dialysis in the eventuality of poor or absent initial graft function was an obvious factor in the decision to proceed with transplantation. Thus, the Peter Bent Brigham Hospital in 1954 had all the ingredients of a modern nephrology support unit years ahead of its time. In this unit, under Merrill's direction, were trained many of the leaders in nephrology of the next three generations.

### The Twin Transplant

The transplantation was performed two days before Christmas, 1954, by Murray and Harrison, who modified the ectopic extraperitoneal technique originally described by the French surgeons Dubost,<sup>4</sup> Küss,<sup>5</sup> and Servelle<sup>6</sup> and their associates. Merrill had seen the extraperitoneal operation while visiting in France several years previously, as was mentioned by Hume et al<sup>7</sup> in an

earlier publication from the Boston group. On Hume's departure to take over the surgical chair in Richmond, Va, Murray had explored the use of the pelvic position of the transplanted kidney in the dog and had acquired extensive experience with that operation. A brief report of the identical twin case was given by Murray<sup>8</sup> at the American College of Surgeons and published in the *Surgical Forum* of 1955. Murray's legendary contributions to transplantation surgery continued until 1968, when he left this field to return to his first love, plastic surgery.

Living-donor nephrectomy was an unusual operation at that time, and, except for the mother-to-offspring transplantation reported by Michon et al,<sup>9</sup> it had been limited to the removal of "expendable" kidneys excised during creation of ventriculoureteric CSF 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. Core-cooling techniques with cold solution were not introduced until the next decade. It is possible that some of the abnormalities of renal function reported in the early identical twin recipients could have been late manifestations of ischemic damage.

In addition to the nephrology prototype and the operative procedures, the connection of the Boston activities of late 1954 with many present-day policies is not hard to identify, including the important (and in the identical twin case, crucial) role of tissue matching.

### Tissue Matching, Heterotransplantation, Immunosuppression

In the account by Merrill et al,<sup>1</sup> credit for originally suggesting the transplantation was given to the recipient's physician, Dr David C. Miller of the Public Health Service Hospital, Boston. It had been known for almost two decades that skin grafts between identical twins were not rejected.<sup>10,11</sup> The application of this information in the transplantation of a vital organ was a bold extension of the same 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. It is no distortion of concept to say that the tissue matching of today between nontwin donors and recipients is an attempt to come as close as possible to the ideal circumstances of the landmark Boston Case.

In their summary, Merrill et al<sup>1</sup> wrote, "Tissue transplantation including that of a functioning kidney appears to be a feasible procedure in identical twins, but to date

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successful permanently functioning homografts appear to be limited to such individuals." Thus, as an isolated event, this transplantation would have had little significance. The real meaning came from the continuity of effort at the Brigham that had begun earlier with the work of Hufnagel<sup>12</sup> and Hume et al<sup>7</sup> that had as the ultimate objective the transplantation of kidneys from nonidentical donors including cadavers or even animals (heterotransplantation). Renal heterotransplantation was given a surprisingly extensive trial at the beginning of this century, as summarized elsewhere.<sup>2,13</sup> Renal homotransplantation was first attempted by Voronoy<sup>14</sup> of Russia in 1936. The first example of probable extended homograft function was in a patient of Lawler<sup>15,16</sup>; the only other example of prolonged homograft function through 1954 was in a patient of Hume and Merrill<sup>7</sup> whose graft was placed in the thigh with function for five months.

Immunosuppression was to be a necessary condition for the fulfillment of the dreams of early transplanters. The deliberate obtundation of recipient immunologic activity became theoretically feasible with the demonstration that total-body irradiation was immunosuppressive.<sup>17,18</sup> Pharmacologic immunosuppression with steroids<sup>19</sup> and cytotoxic drugs<sup>20,21</sup> provided the basis for the new era of renal transplantation that began in 1962 and 1963. The first demonstration of the possible value of cytotoxic drug therapy in large animals was by a young English surgeon, Roy Calne,<sup>22</sup> who brought his subsequent animal investigations to the Harvard facility.

Within a few years after the watershed identical twin case, Merrill, Murray, and Harrison became responsible for clinical trials with immunosuppression for renal

homotransplantation using total-body irradiation<sup>23</sup> and drug therapy.<sup>24</sup> Almost all of these efforts failed, but they paved the way for the "cocktail" therapy with azathioprine and prednisone that opened the modern era of renal transplantation a little more than 20 years ago and that made it possible for the first time to consider the transplantation of extrarenal organs.<sup>13,25</sup>

When great deeds are performed, it is just to honor the heroes and especially those like the Harvard physicians and surgeons whose efforts were not transient; renal transplantation occupied much of their professional lifetimes, as Moore<sup>26</sup> has emphasized in his history of these events. The personal accolades for the members of the Boston team have been numerous.

If gold medals and prizes were awarded to institutions instead of individuals, the Peter Bent Brigham Hospital of 30 years ago would have qualified. The ruling board and administrative structure of that hospital did not falter in their support of the quixotic objective of treating end-stage renal disease despite the long list of tragic failures that resulted from these early efforts, leavened only by occasional encouraging notations such as those in the identical twin case. Those who were there at the time have credited Dr George Thorn, chairman of medicine, and Dr Francis D. Moore, chairman of surgery, with the qualities of leadership, creativity, courage, and unselfishness that made the Peter Bent Brigham Hospital a unique world resource for that moment of history.

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#### References

- Merrill JP, Murray JE, Harrison JH, et al: Successful homotransplantation of human kidney between identical twins. *JAMA* 1956;160:277-282.
- Groth CG: Landmarks in clinical renal transplantation. *Surg Gynecol Obstet* 1972;134:323-328.
- Merrill JP, Smith S III, Callahan EJ III, et al: The use of an artificial kidney: II. Clinical experience. *J Clin Invest* 1950;29:425-438.
- Dubost C, Oeconomos N, Nenna A, et al: Resultats d'une tentative de greffe renale. *Bull Soc Med Hop Paris* 1951;67:1372-1382.
- Küss R, Teinturier J, Milliez P: Quelques essais de greffe rein chez l'homme. *Mem Acad Chir* 1951;77:755-764.
- Servelle M, Soulie P, Rougeulle J, et al: Greffe d'un rein de supplicie a une malade avec rein unique congenital, atteinte de nephrite chronique hypotensive azotemique. *Bull Soc Med Hop Paris* 1951;67:99-104.
- Hume DM, Merrill JP, Miller BF, et al: Experiences with renal homotransplantation in the human: Report of nine cases. *J Clin Invest* 1955;34:327-382.
- Murray JE, Merrill JP, Harrison JH: Renal homotransplantation in identical twins. *Surg Forum* 1955;6:432-436.
- Michon L, Hamburger J, Oeconomos N, et al: Une tentative de transplantation renale chez l'homme. Aspects Medicaux et Biologiques. *Presse Med* 1953;61:1419-1423.
- Padgett EC: Is iso-skin grafting practicable? *South Med J* 1932;25:895-900.
- Brown JB: Homografting of skin: With report of success in identical twins. *Surgery* 1937;1:558-563.
- Hufnagel C, cited by Hume DM, Merrill JP, Miller BF, et al: Experiences with renal homotransplantation in the human: Report of nine cases. *J Clin Invest* 1955;34:327-382.
- Starzl TE: *Experience in Renal Transplantation*. Philadelphia, WB Saunders Co, 1964.
- Voronoy U: Sobre el bloqueo del aparato reticuloendotelial del hombre en algunas formas de intoxicacion por el sublimado y sobre la transplantation del rinon cadaverico como metodo de tratamiento de la anuria consecutiva a aquella intoxicacion. *Siglo Med* 1936;97:296.
- Lawler RH, West JW, McNulty PH, et al: Homotransplantation of the kidney in the human. *JAMA* 1950;144:844-845.
- Lawler RH, West JW, McNulty PH, et al: Homotransplantation of the kidney in the human: Supplemental report of a case. *JAMA* 1951;147:45-46.
- Dempster WJ, Lennox B, Boog JW: Prolongation of survival of skin homotransplants in the rabbit by irradiation of the host. *Br J Exp Pathol* 1950;31:669-670.
- Lindley DL, Odell TT Jr, Tausche FG: Implantation of functional erythropoietic elements following total body irradiation. *Proc Soc Exp Biol NY* 1955;90:512-515.
- Billingham RE, Krohn PL, Medawar PB: Effect of cortisone on survival of skin homografts in rabbits. *Br Med J* 1951;1:1157-1163.
- Hitchings GH, Elion GB: Activity of heterocyclic derivatives of 6-mercaptopurine and 6-thioguanine in adenocarcinoma 755. *Proc Am Assoc Cancer Res* 1959;3:27.
- Schwartz R, Dameshek W: Drug-induced immunological tolerance. *Nature* 1959;183:1682-1683.
- Calne RY: The rejection of renal homograft: Inhibition in dogs by 6-mercaptopurine. *Lancet* 1960;1:417-418.
- Murray JE, Merrill JP, Dammin GJ, et al: Study of transplantation immunity after total body irradiation: Clinical and experimental investigation. *Surgery* 1960;48:272-284.
- Murray JE, Merrill JP, Dammin GJ, et al: Kidney transplantation in modified recipients. *Ann Surg* 1962;156:337-355.
- Starzl TE, Marchioro TL, Waddell WR: The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. *Surg Gynecol Obstet* 1963;117:385-395.
- Moore FD: *Give and Take: The Development of Tissue Transplantation*. Philadelphia, WB Saunders Co, Garden City, NY, Doubleday & Co, 1964.