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The Ascension of Clinical Organ Transplantation

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DURING 1958 and 1959 at Northwestern University (Chicago), we developed transplantation of the canine liver alone,[1] parallel to similar independent investigations in Boston by Francis Moore.[2,3] The liver also was transplanted as a component of abdominal multivisceral grafts.[4] At the beginning, these were technical and physiologic exercises, because long-term survival of an organ allograft had never been achieved in any species.

The possibility of clinically exploiting transplantation brightened, however, between January 1959 and the date of our first human liver replacement in March 1963. During this 4-year period, Joseph Murray in Boston[5–7] and the French teams of Jean Hamburger[8] and Rene Kuss[9] produced the 7 examples shown in Table 1 of survival exceeding 6 months following human kidney transplantation. All of the patients except the last one had received total body irradiation, and in addition, 4 of the 5 French patients were treated with unstipulated doses of adrenal cortical steroids (Table 1) whose weak antirejection effect had been demonstrated by Billingham, Krohn, and Medawar[10] in a rabbit skin graft model. The seventh recipient was treated with the 6-mercaptopurine derivative (6-MP), azathioprine, Bob Schwartz's gift to transplantation.[11,12]

It had been recognized during 1959 to 1962 that total body irradiation would permit successful renal transplantation in only a small percent of cases. Consequently, the option of immunosuppression with 6-MP or its derivative, azathioprine was greeted initially with feverish enthusiasm. However, the preclinical studies of the new drugs by Calne[13,14] and Zukoski,[15] as well as Murray's human trials[5–7] cautioned that the clinical results might not be substantially better than with irradiation, even when azathioprine was combined with other cytotoxic agents. The seventh patient in Table 1 was the only recipient of the first 10 treated in Boston with 6-MP (n = 2) or azathioprine (n = 8) whose kidney allograft eventually survived more than 6 months.

Table 1. Kidney Transplantation: ≥6 Months Survival as of March 1963

Case	City[Ref]	Date	Donor	Survival (months)†
1	Boston[5]	1-24-59	Frat twin	>50
2	Paris[8]	6-29-59	Frat twin	>45
3	Paris[9]	6-22-60	Unrelated*	18(died)
4	Paris[8]	12-19-60	Mother*	12(died)
5	Paris[9]	3-12-61	Unrelated*	18(died)
6	Paris[8]	2-12-62	Cousin*	>13
7	Boston[6,7]	4-5-62	Unrelated	10

*Adjunct steroid therapy.
†The kidneys in patients 1, 2, and 6 functioned for 20.5, 25, and 15 years, respectively. Patient 7 rejected his graft after 17 months and died after return to dialysis.
Boston: J.E. Murray (1 and 7).
Paris: J. Hamburger (2, 4, and 6); R. Kuss (3 and 5).

At the nadir of the resulting pessimism, we made our most important contribution to transplantation.[16] Realizing that clinical liver transplantation could never be attempted without first succeeding with the simpler renal procedure, we had turned our laboratory research to the canine kidney transplant model at the University of Colorado (where I had moved in November, 1961). Two reproducible observations were made, first in the mongrel dogs, and then in humans, that came to dominate future developments in organ transplantation.

First, rejection, which had been considered to be one of nature's strongest and most irrevocable reaction, could be readily reversed by adding high doses of prednisone to recipients under primary immunosuppression with azathioprine. Second, successfully treated recipients appeared to develop donor specific tolerance. This was manifested by the ability later on to wean the doses of drugs to levels below those which had failed at the outset to prevent the onset of rejection.

Using azathioprine plus dose maneuverable prednisone, we began our clinical kidney transplant service in the autumn of 1962 at about the same time as David Hume, who was informed on a day to day basis of our research and clinical findings, initiated his program at the Medical College of Virginia (Richmond).[17] Nine of the first 10 recipients of live donor kidney allografts had prolonged graft survival,[16] including two who bear the longest continuously functioning allografts in the world today (>35.5 years). The two longest surviving patients have been off of all immunosuppression for 32 and 4 years.

This was the first series of successful clinical kidney

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transplantations to be compiled in any center. At the time, the only programs in the United States where this procedure was being offered to patients were in Richmond (David Hume) and in Boston at the Peter Bent Brigham Hospital (Joseph Murray). An earlier program directed by Willard Goodwin at UCLA had been closed because of poor results, but not before making a significant contribution. In September, 1960, Goodwin had produced profound bone marrow suppression with methotrexate and cyclophosphamide (rather than with irradiation) in the daughter recipient of a maternal kidney. During the 143 days of her survival, the patient developed severe rejections that were temporarily reversed with prednisone. This was the first example of protracted function of a human allograft using drug treatment only, but the case was not reported until 1963[18] and was unknown during accrual of the Colorado series.

In Europe, total body irradiation remained the preferred treatment at the long-standing Paris centers of Jean Hamburger and Rene Kuss, while Michael Woodruff of Edinburgh had begun testing azathioprine.[19] Within 12 months after the effectiveness of the double drug treatment became known, a proliferation occurred of new kidney transplant centers in North America, and also in Europe.

The early kidney experience triggered our attempts beginning in March of 1963 to replace the liver, the first extrarenal organ to be transplanted in humans. After the first three reported patients,[20] two more in Boston and Paris, and an additional two in Denver all died within 23 posttransplant days, clinical liver transplantation ceased worldwide. During the 3-½ year moratorium, we developed antilymphocyte globulin (ALG) and tested it for the first time in kidney recipients, combined with azathioprine and prednisone.[21]

When the triple drug immunosuppression proved encouraging in the kidney trial, the Colorado liver program was restarted in July 1967. A number of long survivals were obtained,[22] including the three children shown in Figure 1 with their doctor, Carl Groth from the Karolinska Institute, then an NIH fellow in Denver, and now the President elect of the Transplantation Society. Another child from that early era whose operation was in January, 1970, is the longest surviving liver recipient in the world, married and in perfect health today.

The successful liver transplantations in the summer of 1967 expanded the horizon of transplantation from the kidney to all of the vital extrarenal organs. Within the succeeding 12 months, long survival was accomplished in other centers using variations of the same immunosuppression for heart, lung, and pancreas recipients. Another decade would pass, however, before the advent of cyclosporine[23,24] would make transplantation of the liver[25] or other cadaver organs a reliable service. Tacrolimus, the first immunosuppressant to be evaluated primarily with liver transplantation,[26] has allowed further improved survival of all transplanted organs including the intestine.

Fig 1. The first three long-surviving liver recipients shown in Denver in the summer of 1967 with Carl Groth, president-elect in 1998 of the Transplantation Society.

In later years, the management strategy originally developed with azathioprine and prednisone (Table 2) accommodated more potent baseline drugs as these came along (i.e., cyclosporine and tacrolimus in place of azathioprine) and adjunct agents (e.g., ALG and increasingly selective antilymphoid antibody preparations, mycophenolate mofetil, and other second line drugs). Despite the failure to understand what was being accomplished, the easily taught

Table 2. Central Therapeutic Dogma of Immunosuppression

Strategy	Baseline Agents	Sites of Inhibition
1. Baseline therapy with one or two drugs	Azathioprine*	DNA synthesis
2. Secondary adjustments with steroids or antilymphoid agents	Cyclosporine	Interleukin-2 production
3. Case to case trial (and potential error) of weaning	Tacrolimus	Interleukin-2 production

*Equivalent results with cyclophosphamide.

algorithm became the base upon which clinical transplantation of all organs was developed.

The treatment regimens were shown 3 decades later to have been effective because they fostered chimerism-dependent tolerance mechanisms[27,28] which were the same as in the neonatal models of Billingham, Brent, and Medawar.[29] The liver, which is more tolerogenic than other organs,[30,31] ultimately became the key organ in solving the immunologic mystery of allograft acceptance and acquired tolerance.[27,28]

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