THE CO-DEVELOPMENT OF LIVER AND KIDNEY TRANSPLANTATION (1955-1967)

Thomas E Starzl

Thomas E Starzl Institute, Pittsburgh, PA, USA

Abstract. Between 1955 and the end of 1967, the framework of clinical transplantation that exists today was established in a small number of centers in continental Europe, Great Britain, and the United States. At first, the primary organ was the kidney, but efforts to transplant the kidney soon strongly influenced the development of liver and ultimately all other kinds of organ transplantation. This paper reviews the pertinent history of these developments as outlined in a lecture given in January 2003 in Bangkok on the occasion of the Prince Mahidol Award for a life's work in the field of organ transplantation.

DEVELOPMENT OF THE LIVER OPERATION

Liver transplantation was not mentioned in the literature until 1955 when C Stuart Welch of Albany Medical College described the insertion of an auxiliary hepatic allograft in the right paravertebral gutter of dogs, without disturbing the native liver (Welch, 1955). Three years later, total recipient hepatectomy and liver replacement in dogs was accomplished independently at Northwestern University in Chicago (Starzl *et al*, 1960) and at Harvard University in Boston (Moore *et al*, 1960). I first met the leader of the Boston team, Francis D Moore, at the 1960 meeting of the American Surgical Association, where I discussed his presentation of 31 dog experiments. By then, our total experience with this procedure had increased to 80.

The same two prerequisites for perioperative survival after canine liver replacement were identified in the two laboratories. The first was prevention of ischemic injury to the allograft. This was made possible in Boston by immersing the liver in iced saline (Moore *et al*, 1960). In contrast, our liver allografts were cooled by the intravascular infusion of chilled solutions in much the same way as in clinical practice today (Starzl *et al*, 1960). The second prerequisite was avoidance of damage to the recipient splanchnic and systemic venous beds, the drainage of which was obstructed during host hepatectomy and graft implantation. This was accomplished with decompressing external venovenous bypasses (Moore *et al*, 1960; Starzl *et al*, 1960).

These studies defined almost to the last detail the liver replacement operation (Fig 1) soon to be performed in humans. Also, by the end of 1959, we had developed the operation of multivisceral transplantation (Starzl and Kaupp, 1960). Here, the allograft consisted of the liver and all of the other intraperitoneal organs (Fig 2). The multivisceral operation and its modifications (Fig 3) were not applied in humans until 30 years later but they are now part of the conventional armamentarium of advanced organ transplant centers.

IMMUNOSUPPRESSION

These procedures were perfected between 1958-1960, preceding the availability of immunosuppression. All of the allografts in the unmodified animals were rejected within 3 weeks, usually after 5-10 days. Because the immune barrier to allografts as was thought by most immunologists to be impenetrable, our surgical research was considered by many critics to be naïve or wasteful.

Host cytoablation

Just as it was losing momentum, the work in liver transplantation was revitalized by 6 successful human kidney transplantations performed between January 1959 and February 1962: the first in Boston and the next 5 in Paris (summarized in Starzl, 2002). All 6 renal recipients had been conditioned prior to transplantation with

Correspondence: Thomas E Starzl, Thomas E Starzl Institute, Pittsburgh, PA, USA.

sublethal doses of 450R total body irradiation. It quickly became apparent, however, that the Boston and French successes with the kidney, remarkable though they were, would not be a bridge to liver transplantation. Total body irradiation precluded even perioperative, much less extended, survival of canine liver recipients (Starzl *et al*, 1962).

Drug immunosuppression

A sea change occurred with the arrival of the drug 6-mercaptopurine (6-MP)(Schwartz and Dameshek, 1959; 1960), and its derivative azathioprine. The drugs were first tested in a rabbit skin graft model (Schwartz and Demeshek, 1960) and subsequently by Roy Calne and Charles Zukoski in the canine kidney transplant model. The results with 6-MP and azathioprine in the first clinical trials of kidney transplantation were disappointing in that only one of the first 13 recipients survived >6 months (Murray *et al*, 1963; Hopewell *et al*, 1964). In the exceptional patient, whose operation was on April 6, 1962, the kidney was failing after 11 months (Murray *et al*, 1963). However, it was destined to support dialysis-free life of the recipient for a total of 17 months. This was the 7th human to survive more than one-year after kidney transplantation, and the first to do so without total body irradiation.

In the meanwhile, I had moved from Northwestern to the University of Colorado (Denver) where we had obtained our own supply of azathioprine. We systematically evaluated the new drug with the simpler canine kidney model rather than with liver transplantation. As in other laboratories, our yield of 100-day canine kidney transplant survivors treated with azathioprine was small. However, two crucial findings were clinically relevant. First, kidney rejection developing in the dog under azathioprine invariably could be reversed by the addition of large doses of prednisone (Marchioro *et al*, 1964). Second, mean survival of the dog recipients was doubled when the animals were treated with the drug before as well as after operation (Starzl,1964).

We now undertook clinical trials of kidney and liver transplantation, in that order. Daily doses of azathioprine were give for one to two weeks before as well as after transplantation, with the addition of prednisone only to treat rejection. The two features of the adaptive immune response to allografts that eventually would make transplantation of all kinds of organs feasible and practical were promptly recognized in kidney recipients. These were described in the title of the report of the first Colorado kidney recipients (Starzl *et al*, 1963 b): first, the reversibility of rejection, and

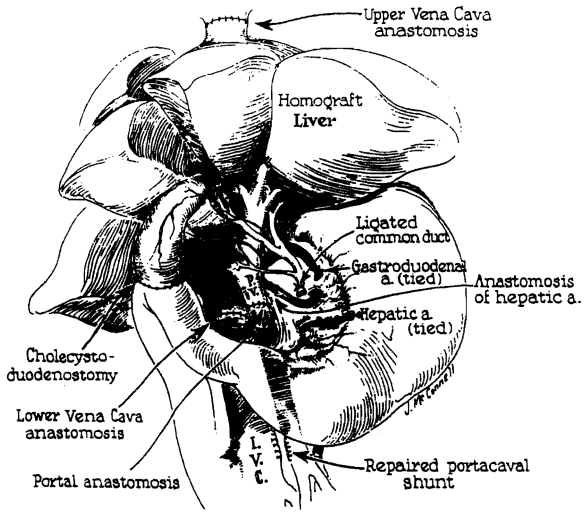

Fig 1–Completed liver replacement in the dog. The fact that the recipient was a dog rather than a human is identifiable only by the multilobar appearance of the liver.

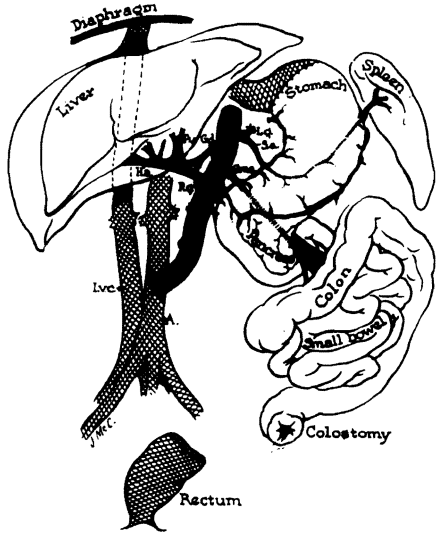

Fig 2 –Canine multivisceral transplantation. The organs of the composite allograft are not shaded. With permission of *Surg Forum* 1960;11:28-30.

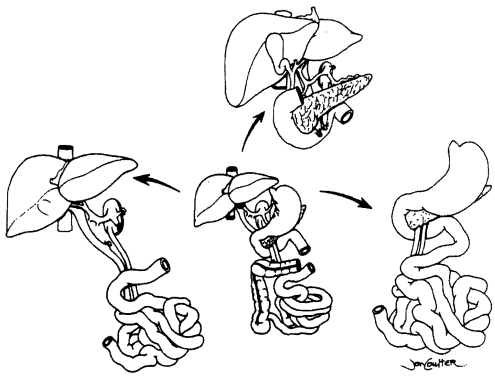

Fig 3–The original canine multivisceral allograft (bottom center) and some of its variations (arrows) that are used clinically today.

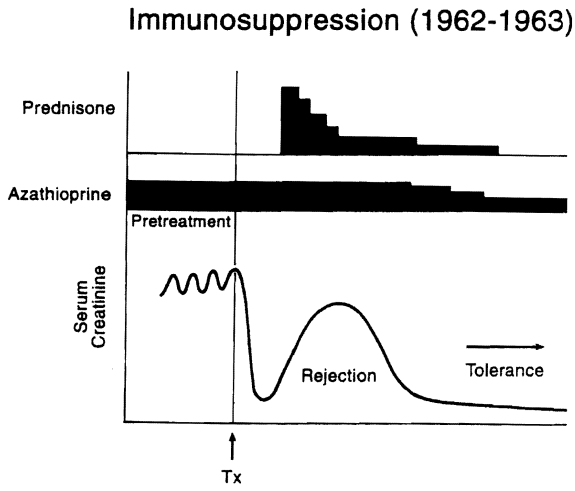

Fig 4–The strategy of double drug immunosuppression used for kidney transplant recipients in 1962-63. Note the reversal of rejection with the addition of prednisone to azathioprine. More than a third of a century later, it was realized that the timing and dosage policy of drug administration had been in accord with the principles of tolerogenic immunosuppression that were elucidated after the mechanisms of organ engraftment and acquired tolerance were discovered since 1992.

more importantly, the subsequent development of donor specific tolerance. "Tolerance" referred to the time-related decline of need for maintenance immunosuppression (Fig 4). Although the maximum follow-up of our first human renal transplantations was only six months in the Spring of 1963, nine of these patients still bear their original kidney allografts after 40 years and are the longest surviving allograff recipients in the world (Starzl, 2002).

HUMAN LIVER REPLACEMENT: 1963

Armed with the early kidney experience, the first attempt at liver transplantation was made on March 1, 1963, with a ventilator-bound child with biliary atresia. The patient bled to death during operation. The next 2 recipients, both adults, died 22 and 7.5 days after their transplantations on May 5 and June 3, 1963 for the indication of primary liver malignancies (Starzl *et al*, 1963a). As in kidney recipients, rejections were easily reversed with prednisone. Although the 2 adult operations were technically satisfactory, emboli formed in the bypass tubing of the veno-venous bypasses, migrated to the lungs, and caused or contributed to the deaths of these recipients.

During the last half of 1963, four more attempts to replace the human liver were made: two in Denver, and one each in Boston and Paris (summarized in Starzl, 2002). Clinical activity then ceased for 3-1/2 years. The worldwide moratorium was voluntary. The decision to stop was reinforced, however, by widespread criticism of attempting to replace an unpaired vital organ with an operation that had come to be perceived as too difficult to ever be tried again. In contrast, kidney transplantation thrived at the University of Colorado and elsewhere.

THE LIVER MORATORIUM

Advances were made during the moratorium that were applicable to all organs. First, it was shown, in a clinical collaboration with Paul Terasaki of UCLA that the quality of HLA matching short of perfect compatibility had little association with kidney transplant outcome. It could be assumed that the same would apply to the liver and to the other non-renal organs. Second, antilymphocyte globulin (ALG) was prepared from mouse antilymphocyte serum (ALS) and introduced clinically. Third, it was established that organs other than the kidney (especially the liver) could induce tolerance. Finally, an *ex vivo* perfusion system was developed in 1966 and 1967 that permitted reliable preservation of canine livers and other organs for as long as a day. Now, it was time to try liver transplantation again.

THE RESUMPTION OF HUMAN LIVER REPLACEMENT

When the liver program reopened in July, 1967, multiple examples of prolonged human liver recipient survival were produced, under triple drug immunosuppression: azathioprine, prednisone, and ALG (Starzl *et al*,1968). The liver transplant beachhead was reinforced by the opening of Roy Calne's clinical program in Cambridge, England, in February 1968. Transplantation of other extrarenal organs followed close behind the liver, using similar immunosuppression (catalogued in Starzl, 2002). Hearts were successfully transplanted in 1968 in Capetown by Christian Barnard, and in Palo Alto by Norman Shumway. In 1969, the first prolonged survival after human lung and pancreas transplantation was accomplished in Ghent and Minneapolis, respectively.

THE ARRIVAL OF BETTER DRUGS

Despite these successes, the widespread use of the liver and other extrarenal organs, and even of cadaveric kidneys, was precluded for another decade by the high mortality. The outlook for all organs improved with the advent of cyclosporine in 1978, and again when tacrolimus was substituted for cyclosporine in the 1990's. By the end of the 20th century, transplantation of the liver and all of the other vital organs had become an integral part of sophisticated medical practice in every developed country in the world.

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