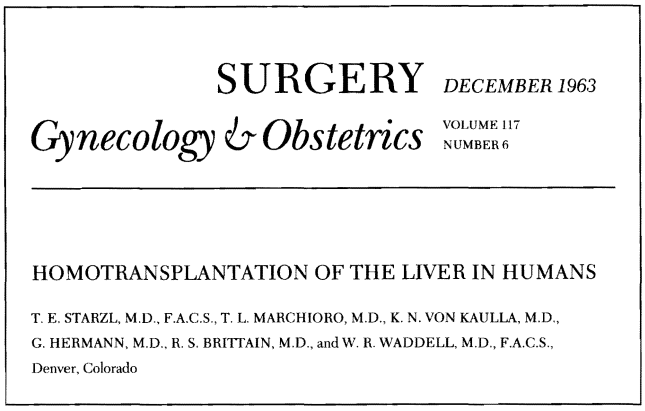
Liver Transplantation


SURGERY DECEMBER 1963
Gynecology & Obstetrics VOLUME 117 NUMBER 6

HOMOTRANSPLANTATION OF THE LIVER IN HUMANS

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The three attempts at human liver replacement reported in 1963[1] followed 7 years of research involving organ preservation, surgical technique, and the physiological interrelation of the liver with the pancreas and other intra-abdominal viscera. There were no means of preventing rejection at the beginning, but at the end, the decision to go forward hinged on a strategy of immunosuppression developed in 1962 that ultimately revolutionized transplantation of all organs.

The Genesis of the Idea

Engraftment of an Extra Liver

The first recorded mention of liver transplantation in either scientific or lay literature was in 1955, when C. Stuart Welch (Albany, NY) described the transplantation of an auxiliary liver to the right paravertebral gutter of mongrel dogs.[2] It was then thought that the volume rather then the source of blood delivered to the liver through its double blood supply was the critical determinant of normal hepatic homeostasis. Welch provided his allografts with a portal venous inflow of redirected host inferior vena caval blood. When they rapidly atrophied, he incorrectly ascribed this solely to rejection.

The Relevance of Hepatotrophic Factors

Between 1956 and 1958, at the University of Miami where I was a surgical resident, I had developed nontransplant dog models to test the hypothesis that the liver and pancreas cross-modulated. The first evidence suggesting that this was true came from studying the effect on insulin/carbohydrate metabolism of altering portal venous inflow with classical Eck or reverse Eck fistula in alloxan diabetic dogs.[3] One of the other procedures developed for the investigation was total hepatectomy,[4] the first stage of orthotopic liver transplantation.

Circumstances in Miami precluded further development. However, orthotopic liver transplantation after host hepatectomy was performed a few days after I moved to Northwestern University (Chicago) in late June 1958 and was performed once or twice a week throughout the rest of the summer. The poor performance of abnormally vascularized orthotopic livers[5] and the acute atrophy of Welch's auxiliary grafts were explained by the transplants' lack of access to an unknown factor (suspected to be insulin) present in high concentration in portal venous blood.[6]

Proving the insulin hypothesis and convincing skeptics that insulin was a true hepatic growth factor required nearly 15 years.[7] At the end, however, a precise explanation could be provided for the previously enigmatic pathophysiology of Eck's fistula. Eventually, the identification of a family of factors with insulin-like hepatotrophic properties that controlled liver structure, function, and the capacity for regeneration defined the new field of hepatotrophic physiology.[8]

Orthotopic Liver Transplantation

In 1956, Jack Cannon of the University of California, Los Angeles, was the first to report liver replacement, citing Welch's article as the stimulus for his work. Cannon alluded to "several successful operations" . . . "without survival of the patient" [dogs] but with no details.[9] Definitive information came from the canine experiments at Northwestern University and independently from the team of Francis D. Moore at the Peter Bent Brigham Hospital ("The Brigham," Boston).[10] In

contrast to the metabolic basis of the Chicago initiative, Moore's liver research was an offshoot of an institutional commitment to kidney transplantation that had begun a decade earlier.

Because effective immune suppression was not yet available in either laboratory, it was possible to do little more than develop the operation and study the events of unaltered rejection. Between 1958 and early 1960, 31 of these orthotopic procedures in dogs were performed in Boston[10] and 80 in Chicago.[5] All animals with survival of 4 or more days had histopathologic findings of allograft rejection. The technical principles that emerged from this collective experience were (1) the need for splanchnic venous blood for optimal portal revascularization, (2) core cooling of the allograft by infusion of chilled solutions into the portal vein as is practiced clinically today, and (3) decompression of the occluded splanchnic and systemic venous pools into the upper vena caval system through external venous bypasses during the anhepatic stage.

In addition to liver transplantation alone, modifications had been added by the end of 1959, including the multivisceral engraftment procedures[11] that would be used successfully in patients three decades later with essentially no change.

Movement to the Clinic

The Advent of Immunosuppression

Total body irradiation (TBI), adrenal cortical steroids, and the myelotoxic drug 6-mercaptopurine (6-MP) were shown between 1953 and 1959 to modestly prolong skin allograft survival in several animal species. Using TBI, successful kidney transplantation from fraternal (dizygotic) twin donors was accomplished in patients at the Brigham in January 1959 and again 5 months later in Paris. Although the genetic barrier to transplantation finally had been breached in humans, liver transplant surgery still had no conceivable application. Preoperative conditioning of hepatic canine recipients with TBI in our hands precluded even perioperative, much less extended, survival.

The drugs 6-MP[12] and its analogue, azathioprine, were viewed in a different light. Whereas kidney transplantation with long survival had never previously been achieved in mongrel dogs, approximately 5% of animals given one or the other of the new drugs by the Englishman Roy Calne[13] in collaboration with Joseph Murray at the Brigham[14] lived longer than 100 days. The objective of exploiting hepatic replacement to treat human liver disease was settled on as a high priority during my discussions in June 1961 with William R. Waddell, who left the Massachusetts General Hospital to assume the chairmanship of surgery at the University of Colorado 5 months before I joined him from Chicago. A prerequisite would be establishment of a track record in renal transplantation. In the United States, this procedure was under formal development only at the Brigham and at the Medical College of Virginia (David Hume). Willard Goodwin's early program at UCLA had been placed on hold.

Our clinical plans for both organs were shelved in January 1962. We had been following the tracks laid by the American kidney transplant pioneers and those in Paris (Rene Kuss and Jean Hamburger), only to eventually realize that we had joined them in a therapeutic cul-de-sac. Calne and Murray recognized the unacceptable therapeutic margin of azathioprine alone and had systematically tested drug combinations in their dog model. When prednisone given from the time of surgery had no additive effect,[13,14] they settled for clinical use on a triple-drug cocktail of azathioprine, azaserine, and actinomycin C. The results were little different than with TBI. In fact, as late as March 1, 1963, the date of our first liver transplantation, only 6 recipients of kidney allografts in the world had survived 1 year or longer (1 in Boston and 5 in Paris), all treated with TBI. The longest surviving kidney recipient treated solely with azathioprine- or 6-MP–based therapy from April 1960 to April 1962[15] was now 11 months postoperative, but we knew from contact with Murray that the patient had deteriorating renal function.

An Empirical Treatment Strategy

The experimental results in the Denver VA canine laboratory resembled those in Boston and Richmond until the summer of 1962 when a reproducible significant observation was made. Delayed high doses of prednisone were shown to reliably reverse the kidney (and, in pilot studies, liver) rejection that usually developed under primary azathioprine therapy. Most of the dogs died of complications of steroid-induced peptic ulceration, but several lived for years after discontinuance of prednisone and even when azathioprine also was stopped. Using the "double-drug cocktail," the Colorado clinical kidney transplant program finally was opened in November 1962.

The first 10 cases were compiled rapidly and reported in the October 1963 issue of *Surgery, Gynecology, and Obstetrics*,[16] preceding by 2 months the article on liver transplantation in the same journal.[1] Four of the 10 renal recipients survived ≥25 years including 2 who still bear the longest continuously functioning kidney allografts in the world after a third of a century. The first patients in the series had returned to a relatively unrestricted environment on reduced maintenance immunosuppres-

sion. We suggested that a state of relative host/graft nonreactivity had been accidentally but regularly induced by the renal allografts. The controversial, but as it turned out apposite, term "tolerance" (see later) was used to describe the change. This was the signal that triggered the liver trials.

The first 3 patients entered were a moribund child with biliary atresia, a 48-year-old man with Laënnec's cirrhosis and an unresectable hepatoma, and a 67-year-old man with a completely obstructing bile duct carcinoma who had previously undergone bilateral above-knee amputations for peripheral vascular disease. Their high risk factors would preclude candidacy today. Although 2 survived the surgery, they died after 22 and 7.5 days of pulmonary emboli that were suspected to have originated from the plastic tubes used for the veno-venous bypass.

The Aftermath

The Colorado kidney center mushroomed overnight while the spark that had ignited it, liver transplantation, was consigned by the end of 1963 to a self-imposed $3^1/_2$-year worldwide moratorium after four more failures: two in Denver and one each in Boston and Paris. Three advances applicable to all organs were made during this period: (1) the purification and clinical introduction in 1966 of antilymphocyte globulin for use with azathioprine and prednisone in a triple-drug regimen[17]; (2) preservation techniques that allowed livers to be stored ex vivo for 1–2 days; and (3) demonstration (with Paul Terasaki of UCLA) that the quality of donor/recipient HLA matching had little association with kidney transplant outcome. When the liver program was reopened in July 1967 during the 2-year fellowship of Carl Groth (Stockholm), multiple examples of prolonged liver recipient survival were produced.[18,19]

A second liver transplant program was founded in 1968 by Roy Calne of Cambridge University and fostered by a long-lasting interuniversity collaboration with the hepatologist Roger Williams at King's College Hospital, London. The American and English teams sustained each other for the next dozen years, joined in the early 1970s by Rudolph Pichlmayr in Hannover and by Henri Bismuth in Paris, always tantalizingly close to making liver transplantation a service. In Denver, 170 patients underwent the procedure between 1963 and 1979. Although only 56 survived for 1 year, 25 were alive after 13–22 years at the end of 1992,[20] and 19 remain today with follow-ups of 17–27 years.

Although the feasibility of liver transplantation was established, the results remained unacceptable until Sir Roy Calne, who had presided over the preclinical development of the thiopurine drugs in Boston nearly two decades before, repeated the feat with cyclosporine and then reported the first clinical series that included 2 liver recipients. In another visit to the past, the full potential of the new drug was realized for transplantation of the kidney, liver, and eventually all organs when it was combined with prednisone or used in triple-drug cocktails.[21] The stampede to develop extrarenal transplant centers began. Nine years later, expectations moved up another notch with the substitution of tacrolimus for cyclosporine.[22]

In Retrospect

Most failed trials are doomed to be footnotes, if that much, in the pages of history. The 1963 liver transplant article escaped obscurity because it was based on principles that were enduring. Aside from the manifold details of the difficult operation, including the role of and complications from veno-venous bypass, there already was accurate insight into the importance of hepatotrophic physiology and into the cause and treatment of metabolic acidosis. The only nonsurgeon author, Kurt von Kaulla, anticipated the intraoperative coagulation disorders, monitored them with serial thromboelastograms, and provided treatment with blood components and epsilon amino caproic acid (an analogue of the currently used aprotinine). Lessons from the research preceding the clinical trial had long since cross-fertilized to kidney transplantation and eventually were exploited for all kinds of allografts: core cooling by infusion of chilled intravascular fluids, in situ procurement procedures that presaged the standard flexible procedures of today, and the intravascular techniques required for close-quarter anastomoses.

However, none of the generically applicable advances, or all together, remotely approached in importance the realization in the summer of 1962 that rejection could be engineered into prolonged allograft and recipient survival by the strategic use of existing agents. The cyclic pattern of convalescence and the consequent achievement of allograft acceptance remained enigmatic until it was discovered in 1992 that long-surviving organ recipients had donor leukocyte chimerism in their blood, skin, lymph nodes, and other sites as long as three decades after transplantation.[20,23] Then it could be seen that the prototypic postoperative events following transplantation of all organs were the product of a double immune reaction: host-versus-graft (rejection) and graft-versus-host. Potentially tolerogenic "passenger leukocytes" of bone marrow origin including pluripotent stem cells had migrated from organs and engrafted peripherally. This was the seminal mechanism of organ allograft acceptance, an insight that enlarged the tunnel leading to the future.

The epiphany ended the 35 years of speculation preceding it.

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0016-5085/97/$3.00