Second Edition

Transplantation of the Liver

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History of Liver and Multivisceral Transplantation*

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Between 1955 and the end of 1967, the framework of clinical organ transplantation that exists today was established in a small number of centers in continental Europe, Great Britain, and North America. The kidney was, at first, the forerunner organ, but liver transplantation soon became the driving force in discoveries and advances that were applicable for other kinds

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of organs. These accomplishments included the development of better methods of organ preservation, the evolution of present-day immunosuppression, and the elucidation of the seminal mechanisms of alloengraftment and acquired tolerance. In addition, research in liver transplantation is responsible for insight into the metabolic interrelations of the intra-abdominal viscera in disease and health, progress in the understanding and treatment of liver-based inborn errors of metabolism, and identification of growth factors that influence hepatic growth control and regeneration. Table 1–1 summarizes and annotates most of the major milestones and events in this complex chain of events.[1-58]

Table 1–1. MILESTONES OF LIVER TRANSPLANTATION

Year	Description	Reference
1955	First article in the literature on auxiliary liver transplantation	1
1956	First mention of concept of liver replacement	2
1958-1960	Formal research programs of total hepatectomy and liver replacement in dogs	3,4
1960	Abdominal multivisceral transplantation described in dogs	5
1963	Azathioprine-prednisone cocktail introduced (kidneys first, then livers) and recognition of organ-induced tolerance	6
1963	Description of in situ preservation-procurement method	7
1963	First human liver transplantations (University of Colorado)	8
1964-1965	Evidence of hepatropic (liver-supporting) factor(s) in portal venous blood	9,10
1965	First clear evidence of hepatic tolerogenicity	11
1966	First liver xenotransplantation on July 15, 1966 (chimpanzee donor)	12
1966	Clinical introduction of antilymphocyte globulin (ALG) (kidneys, then livers)	13
1966-1970	Proof that human leukocyte antigen (HLA) matching would not be a major factor in organ transplantation	14,15
1967	First successful human liver replacements: under azathioprine, prednisone, and ALG	16
1967-1968	Acceptance of brain death concept	17
1969	First use of liver transplantation to cure inborn error of metabolism	18
1973	Recognition that the liver resists antibody-mediated rejection	19
1973-1975	Principal portal venous hepatotrophic factor identified as insulin	20,21
1976	Improved slush liver preservation permits long-distance procurement	22,23
1979	Systematic use of arterial and venous grafts for cadaver organ revascularization	24
1979	Cyclosporine introduced for organ transplantation including two liver recipients	25
1980	Cyclosporine-steroid cocktail introduced clinically	26
1981	80% 1-year liver recipient survival reported using cyclosporine-prednisone	27
1983	Introduction of pump-driven venovenous bypass without anticoagulation	28-30
1983-1984	US consensus development conference conclusion that liver transplantation is a service (1983) is followed by rapid proliferation of transplant centers worldwide	31
1984	Standardization of in situ preservation-procurement-preservation techniques for multiple cadaver organs	32,33
1984	Reversibility demonstrated of B-cell malignancies—post-transplant lymphoproliferative disease (PTLD)—in liver and other organ recipients	34
1984	First reports of reduced-size liver grafts	35,36
1987-1989	First successful transplantation of liver-containing multivisceral grafts	37,38
1987	University of Wisconsin (UW) solution improves liver and other organ preservation	39-41
1987	Report of successful extensive use of livers from marginal donors	42
1988	Compliance with Organ Transplant Act of 1984 by national adoption of Pittsburgh point system for cadaver kidney and liver distribution	43,44

Continued

Table 1-1. MILESTONES OF LIVER TRANSPLANTATION—cont'd

Year	Description	Reference
1989	Popularization of the piggyback variation of liver transplantation	45
1989	Clinical introduction of FK506 (tacrolimus)-based immunosuppression	46,47
1989	First report of splitting cadaver livers for 2 recipients	48
1990	First successful use of live liver donors (left-side fragments)	49,50
1992-1998	Discovery of donor leukocyte microchimerism in liver (and other organ) recipients with recognition of clonal exhaustion-deletion as the seminal mechanism of organ engraftment	51-53
1994-1999	Live-donor transplantation of right-side liver fragments	54-56
2001	Development of mechanism-based tolerogenic immunosuppression	57
2003	Double knockout of porcine α1,3-galactosyltransferase (GT) gene, revitalizing hopes of clinical xenotransplantation	58

Genesis of Liver Transplantation

Transplantation of all the major organs except the liver can be traced back to the early 1900s.[59,60] In contrast, the first report of liver transplantation did not appear until 1955 in a journal called *Transplantation Bulletin*, the forerunner of the present day *Transplantation*.

The Auxiliary Liver Concept. In a one-page article, C. Stuart Welch of Albany Medical College described the insertion of a hepatic allograft in the right paravertebral gutter of dogs, without disturbing the native liver.[1] More complete information was published in *Surgery* the following year.[61] The auxiliary livers were revascularized by anastomosing the graft hepatic artery to the recipient aortoiliac system and by end-to-end anastomosis of the graft portal vein to the host inferior vena cava (Fig. 1-1). Welch obviated the need to anastomose multiple hepatic veins by including the short length of donor retrohepatic vena cava into which all of these hepatic veins empty as part of his auxiliary allografts. The upper end of the caval segment of the graft was anastomosed to the recipient vena cava, and the lower end was ligated or sutured (see Fig. 1-1).

Unlike other kinds of transplanted organs, the auxiliary allografts underwent dramatic shrinkage. The atrophy, which began within 3 or 4 days, was attributed at the time to liver rejection. The view was consistent with the current dogma of the time, that liver size and regeneration are governed by the volume of portal venous inflow (the "flow hypothesis" of hepatic homeostasis). Because the portal vein of the transplanted extra livers had been provided with an ample amount of systemic (i.e., vena caval) blood (see Fig. 1-1), the acute allograft atrophy was ascribed to immunological factors. A decade passed before it was demonstrated that the liver shrinkage actually was due to the dearth in vena caval and other systemic blood of molecules (especially

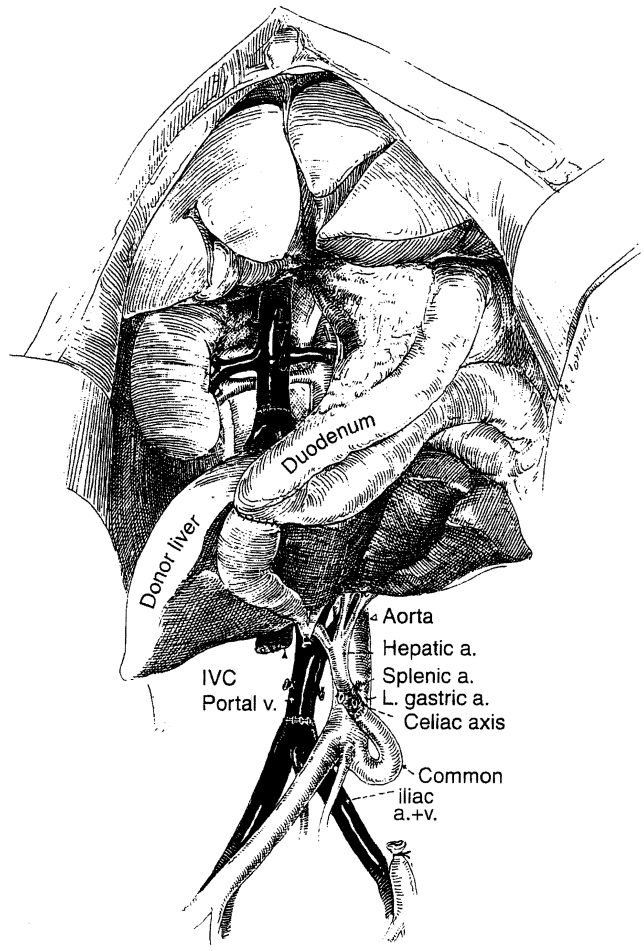

FIGURE 1-1

Auxiliary liver homotransplantation in dogs (the Welch procedure). Note that the reconstituted portal venous inflow is from the inferior vena caval bed rather than from the splanchnic organs. Biliary drainage was with cholecystoduodenostomy. (From Starzl TE, Marchioro TL, Rowlands DT Jr, et al: Immunosuppression after experimental and clinical homotransplantation of the liver. Ann Surg 160:411-439, 1964.)

insulin) that are normally presented to liver in high concentrations in splanchnic venous blood (see Reassessment of the Auxiliary Liver Graft).[9,10,20,21]

Orthotopic Liver Transplantation. The concept of liver replacement (orthotopic transplantation) was first mentioned by Jack Cannon in a one-page account of the transplant activities in the surgery department of the recently founded University of California, Los Angeles (UCLA) School of Medicine.[2] The species studied was not mentioned (presumably dog), and there was no specific information about the procedure. It is noteworthy that Cannon's article (entitled "Brief Report") and the two articles on auxiliary hepatic transplantation by Welch and colleagues[1,61] were the sole references to the liver in M.F.A. Woodruff's compendium of work in the transplantation field up to 1959.[62]

By the time Woodruff's book was published in 1960, extensive investigations of liver replacement in dogs had been completed in independent studies started in the summer of 1958 at both Northwestern University in Chicago[3] and the Peter Bent Brigham Hospital in Boston.[4] The Boston studies,[4,63,64] under the direction of Francis D. Moore, were a natural extension of an immunologically oriented institutional commitment to organ transplantation that initially was preoccupied with the kidney. In contrast, the Northwestern initiative[3,65] stemmed from an earlier investigation at the University of Miami of the metabolic interrelationships of the liver with the pancreas and intestine.[66,67] To facilitate these studies, a new method of total hepatectomy was developed in which the unique feature was preservation of the host retrohepatic inferior vena cava.[68]

The canine host hepatectomy developed in Miami was essentially the same as that in today's *piggyback* variation of liver transplantation.[45,69,70] For liver transplantation in the dog, however, it was simpler to excise the host retrohepatic vena cava along with the native liver and to replace it with the comparable caval segment of the donor liver into which the hepatic veins empty. After completing the vena caval anastomoses above and below the liver, hepatic arterial and biliary tract anastomoses were performed with conventional methods (Fig. 1–2).[3,4] When different means of portal revascularization were systematically tested in the Northwestern laboratory (Fig. 1–3), any deviation from normal of the portal supply resulted in reduced survival.

The research teams at Northwestern and Brigham Hospital were unaware of each other's activities until late 1959, and direct contact was not established until the 1960 meeting of the American Surgical Association. By then, the cumulative total of liver replacements in unmodified (nonimmunosuppressed) dogs had increased to 80 in Chicago[3] and 31 in Boston.[4] The results were published separately in 1960 in different journals.

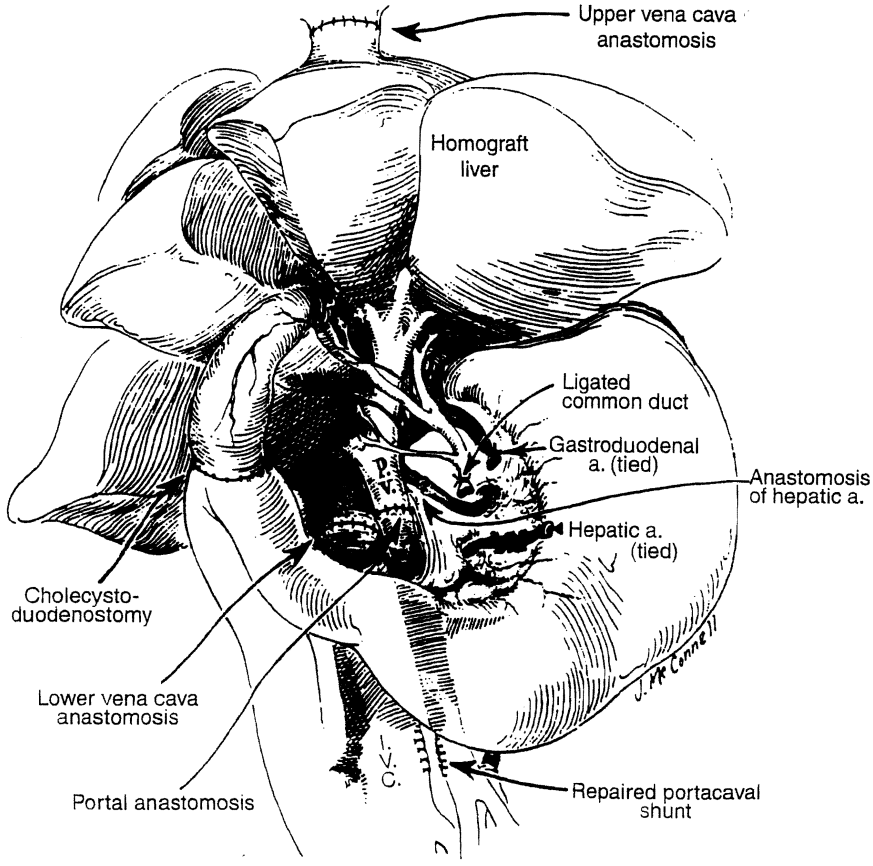

FIGURE 1–2

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. (From Brettschneider L, Daloze PM, Huguet C, et al: The use of combined preservation techniques for extended storage of orthotopic liver homografts. Surg Gynecol Obstet 126:263-274, 1968.)

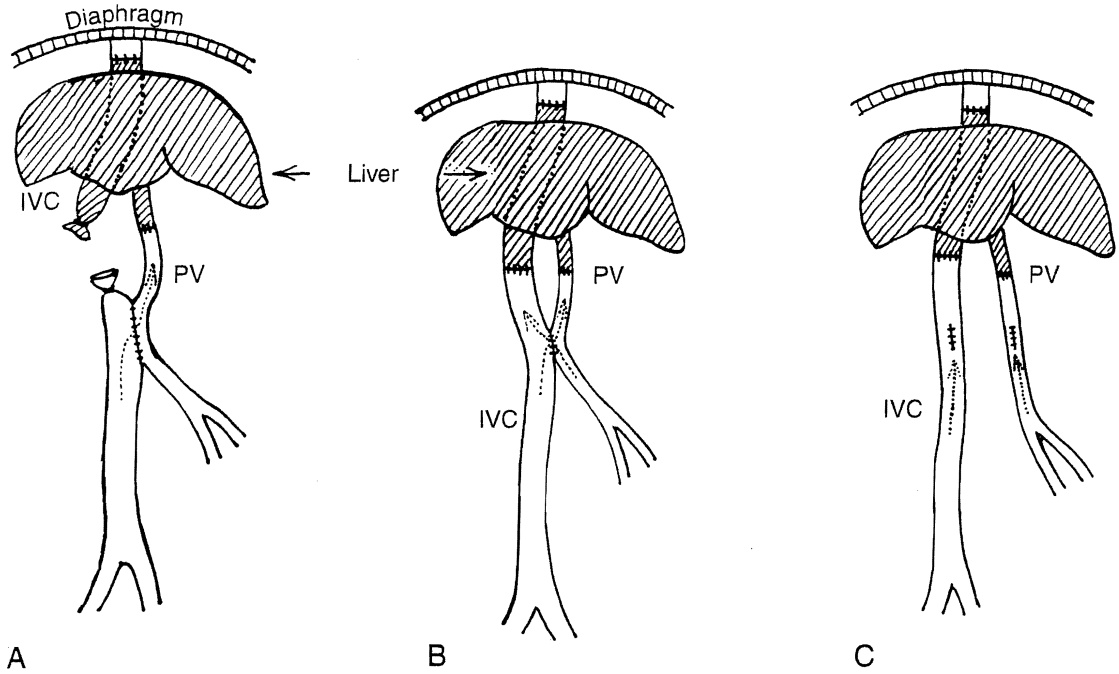

FIGURE 1–3

Alternative methods of portal vein revascularization: *A*, reverse Eck fistula; *B*, with small side-to-side portacaval shunt; *C*, anatomically normal. Survival was best with C. (From Starzl TE, Kaupp HA Jr, Brock DR, et al: Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. Surg Gynecol Obstet 111:733-743, 1960.) IVC, inferior vena cava; PV, portal vein.

Prerequisites for Canine Liver Replacement

The two prerequisites for perioperative survival of the canine recipients had been identified in both laboratories. The first requirement was prevention of ischemic injury to the allograft. This was accomplished in Boston by immersing the liver in iced saline. At Northwestern, the livers were cooled by the intravascular infusion of chilled lactated Ringer's solution (Fig. 1–4). This now universal first step in preservation of all organs had never been used before, apparently because of fear of damaging the microcirculation. Better liver preservation was later obtained with infusates of differing osmotic, oncotic, and electrolyte composition (e.g., the Collins,[22] Schalm,[23] and University of Wisconsin [UW] solutions).[39-41]

The second prerequisite for successful canine liver transplantation 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 in both laboratories by decompressing external venovenous bypasses, which differed in detail.

Pathology of Liver Rejection

Until 1960, the kidney had been the only organ allograft whose unmodified rejection had been systematically studied. Most of the transplanted canine livers were destroyed in 5 to 10 days. Typically, a heavy concentration of mononuclear cells was seen in the portal triads and within and around the central veins. Hepatocyte necrosis was extensive.[64,65] A curious exception was noted, however, in the 63rd liver replacement experiment.

In the exceptional recipient, the serum bilirubin reached a peak at 11 days, but then progressively declined (Fig. 1–5, dashed line).[65] The predominant histopathological findings in the allograft by day 21 were more those of repair and regeneration than of rejection. *This was the first recorded exception to the existing dogma (based on skin graft research) that rejection, once begun, was inexorable.* Five years later, similar observations were made in allografts of long-surviving canine liver recipients in Denver, whose rejections had developed and then spontaneously reversed under stable daily doses of azathioprine.[11]

Variant Liver Transplant Procedures

The studies completed by the end of 1959 in Boston and Chicago defined almost to the last detail the liver replacement operation soon to be performed in humans. The operation of multivisceral transplantation, in which the allograft consisted of the liver and all of the other intraperitoneal organs, also was perfected (Fig. 1–6, center).[5] It was noted that rejection of the different splanchnic organs transplanted with the liver was

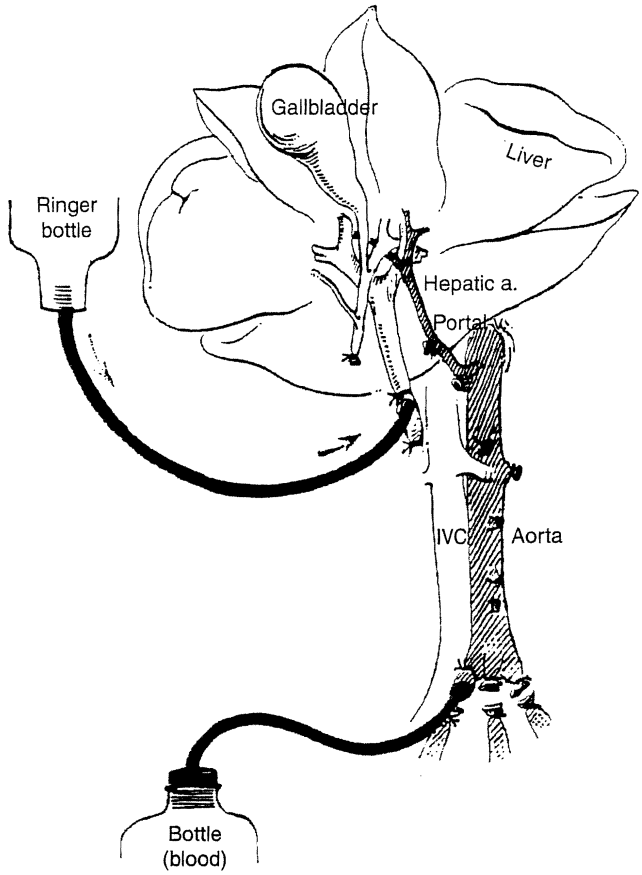

FIGURE 1–4

Cooling of the canine hepatic allograft by infusion of chilled lactated Ringer's solution into the donor portal vein. The animals were simultaneously exsanguinated. (From Starzl TE, Kaupp HA Jr, Brock DR, et al: Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. Surg Gynecol Obstet 111:733-743, 1960.)

much less severe than the rejection of the individual organs transplanted alone,[71] an observation that was validated much later in rodent studies[72,73] and in humans.[74] In addition, the recipients had histopathological evidence of a widespread graft-versus-host reaction in their tissues, but without overt graft-versus-host disease (GVHD). This was the first clue that GVHD might not blight intestinal or liver transplantation, or both, if such procedures were ever to become feasible.

Multivisceral transplantation and its modifications (see Fig. 1-6) were applied in humans 30 years later[37,38,75,76] and are now part of the conventional armamentarium of advanced organ transplant centers. However, when the canine operation was first presented at the Surgical Forum of the American College of Surgeons in October 1960,[5] it was ridiculed. In fact, all research in whole-organ transplantation (including of the kidney) during 1958 to 1960 was considered naïve or wasteful by many critics and especially by basic

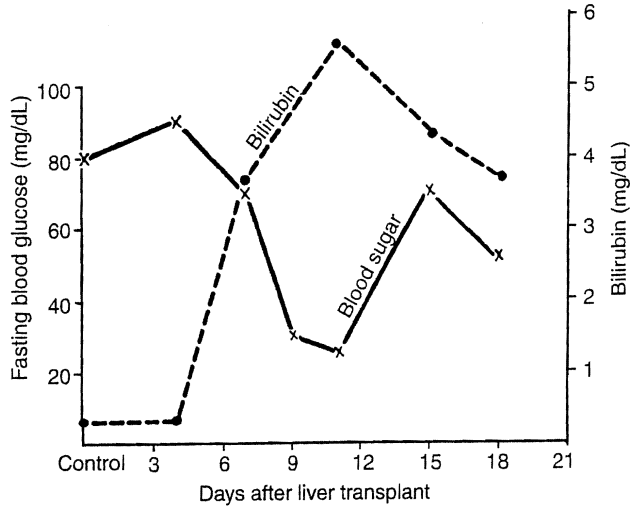

FIGURE 1–5

Serial blood glucose and serum bilirubin levels in a nonimmunosuppressed canine liver recipient who survived for 3 weeks. Note the decline of bilirubin after the eleventh day. This evidence of the spontaneous reversal of rejection was consistent with the histopathology of the autopsy liver at 21 days. (From Starzl TE, Kaupp HA Jr, Brock DR, Linman JW: Studies on the rejection of the transplanted homologous dog liver. Surg Gynecol Obstet 112: 135-144, 1961.)

immunologists, most of whom viewed the immune barrier to transplantation as impenetrable.

Immunosuppression by Host Cytoablation

Just as this kind of surgical research in unmodified dogs was losing momentum, it was dramatically revitalized by six successful human kidney transplantations performed between January 1959 and February 1962, first by Joseph Murray in Boston[77] and then five more times by the independent teams of Jean Hamburger[78] and Rene Kuss[79] in Paris. The first cases were compiled under circumstances that would not be acceptable in today's climate of institutional review board (IRB) regulation (i.e., before long-term survival had been accomplished in animals). All six patients were preconditioned with sublethal doses of 4.5 Gy total-body irradiation (Table 1-2, above the dashed line). Although *success* was defined as survival for at least 1 year, the first two recipients (both of fraternal twin kidneys) had continuous graft function for more than 2 decades without the need for posttransplant immunosuppression. These were the first examples of acquired immunological tolerance in humans. However, the drug-free state was not considered to be *real tolerance* for reasons described in Chapter 73, "Cell Migration, Chimerism, and Graft Acceptance, with Particular Reference to the Liver."

In an effort to replace irradiation for conditioning, the UCLA urologist Willard Goodwin pretreated six

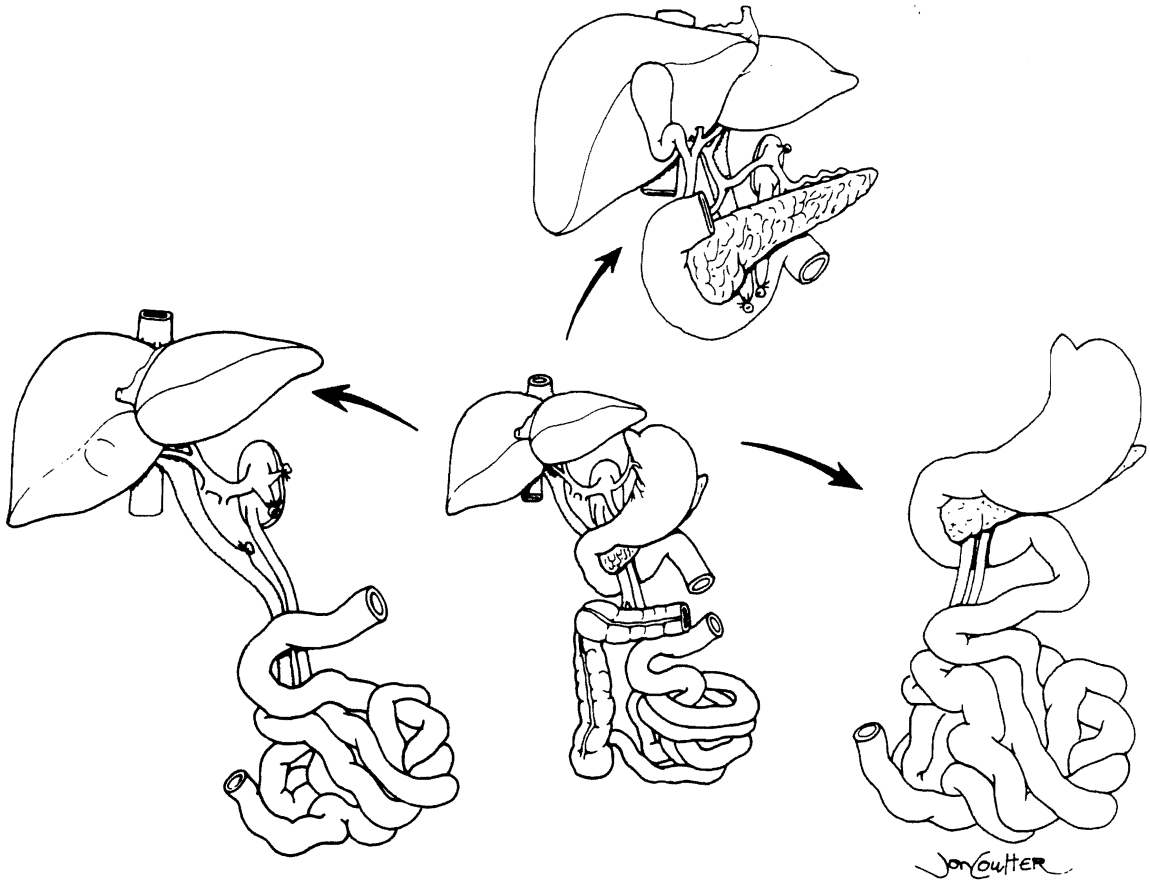

FIGURE 1–6

The original canine multivisceral allograft (*bottom center*) and its variations (*arrows*). All are used clinically today. (From Starzl TE: The saga of liver replacement, with particular reference to the reciprocal influence of liver and kidney transplantation (1955-1967). J Am Coll Surg 195:587-610, 2002.)

human kidney recipients in 1960 to 1961 with myelotoxic doses of cyclophosphamide and methotrexate.[80] One patient had prolonged survival (143 days), during which rejection was successfully reversed several times with prednisone. This important observation was not reported until 1963. In any event, it quickly became apparent that cytoablation would not be the means by which liver transplantation could be accomplished. In our hands, total-body irradiation precluded even perioperative, much less extended, survival of canine liver recipients.[81]

Table 1–2. KIDNEY TRANSPLANTATION: 6 MONTHS OR GREATER SURVIVAL AS OF MARCH 1963

	City (Ref)*	Date	Donor	Survival (mo)
1	Boston (77)	1/24/59	Fraternal twin	>50
2	Paris (78)	6/29/59	Fraternal twin	>45
3	Paris (79)	6/22/60	Unrelated	18 (Died)
4	Paris (78)	12/19/60	Mother	>12 (Died)
5	Paris (79)	3/12/61	Unrelated	18 (Died)
6	Paris (78)	2/12/62	Cousin	>13
7	Boston (93)	4/5/62	Unrelated	11

*Boston: Joseph E Murray (patients 1 and 7); Paris: Jean Hamburger (patients 2, 4, and 6), R Küss (patients 3 and 5).

Drug Immunosuppression for Clinical Kidney Transplantation

Since the early 1950s, skin graft survival in rabbits was slightly prolonged by treatment with adrenal cortical steroids.[82,83] However, the era of drug immunosuppression usually is designated to begin on the arrival of the drug 6-mercaptopurine (6-MP). After establishing that 6-MP was immunosuppressive without a need for overt bone marrow depression,[84] Schwartz and Dameshek at Tufts Medical School in Boston[85] and Meeker and Good and colleagues at the University of Minnesota[86] demonstrated modest prolongation of skin allograft survival in rabbits. Survival of canine kidney allografts for up to 40 days under 6-MP was then reported by Calne in London[87] and independently for similar times by Zukoski in Richmond.[88] By the end of 1960, Calne

(by now in Boston with Murray)[89,90] and Zukoski (with David Hume in Richmond)[91] obtained even longer survival of canine kidney recipients. In Calne's report, the best results were obtained with the imidazole derivative of 6-MP, azathioprine (Imuran).[89] However, survival for as long as 100 days was unusual (i.e., < 5% of the experiments).

When clinical kidney transplant trials with the new drugs were begun in Boston in 1960 to 1961 with initially high expectations,[92] the possibility of transplanting the human liver no longer seemed so remote. In 1961, William R. Waddell left Massachusetts General Hospital to become Chair of Surgery at the University of Colorado, where one of us (T.E.S) joined him from Northwestern. Armed with more than 3 years of experience in Chicago with canine hepatic replacement, we settled on liver transplantation as our highest priority for clinical development. The plan was tabled when we learned that the Boston clinical trial of kidney transplantation had yielded disappointing results. A ray of hope could be found, however, in a report by the future Nobel laureate, Joseph Murray, in the September 1962 issue of *Annals of Surgery*.[92]

The article included a description of a kidney allograft that was still functioning under azathioprine immunosuppression 120 days after its transplantation from an unrelated donor on April 6, 1962. The kidney was still functioning at 10 months when next reported in June 1963.[93] Although the patient's blood urea nitrogen (BUN) was now elevated (110 mg/dL), the graft was destined to support dialysis-free life for another 7 months (total of 17 months). It was the first example of 1-year survival of a human organ allograft without host conditioning with total-body irradiation (see Table 1–2, number 7). However, this was the only kidney recipient of the first 13 treated solely with chemical immunosuppression who survived for as long as 6 months.[92-94]

In the meantime, we had obtained our own supply of azathioprine in the spring of 1962 and began systematically evaluating it at the Denver VA Hospital laboratory with the simpler canine kidney model instead of liver transplantation. As in other laboratories, our yield of survivals of as long as 100 days was small. However, two crucial findings were clinically relevant. The first was that the kidney rejections that developed with azathioprine invariably could be reversed by the delayed addition of large doses of prednisone.[95]

The second key observation was that a mean survival of 36 days in dogs treated with azathioprine was almost doubled when the animals also were pretreated with the drug for 7 to 30 days.[96] We now committed to clinical trials of kidney and liver transplantation, in that order. Daily doses of azathioprine were given to the kidney recipients for 1 to 2 weeks before, as well as after, kidney transplantation from living donors, adding prednisone only to treat rejection. The human renal transplantation program was opened in the autumn of 1962.

The two features of the adaptive immune response to allografts that would make transplantation of all kinds of organs feasible were described in the title of the report of the first 10 kidney cases: "The Reversal of Rejection in Human Renal Homografts with Subsequent Development of Homograft Tolerance."[6] The term *tolerance* referred to the time-related decline of need for maintenance immunosuppression. Largely because of this observation, we already had concluded that renal transplantation had reached the level of a bona fide, albeit still flawed, clinical service. At the time, there were only three clinically active kidney transplant centers in the United States: the long-standing Brigham program and the two centers opened in 1962—ours at the University of Colorado and David Hume's in Richmond, Virginia.

One year later, nearly 50 kidney teams had started or were gearing up, including the program at UCLA that had opened in 1960 and closed in 1961. A similar proliferation of kidney centers also was under way throughout Europe. Moreover, the benefits of kidney transplantation proved to be truly long-lasting in some cases. Eight of the Colorado kidney recipients of the 1962 to 1963 era still bear their original transplants 40 years later and are the longest surviving organ allograft recipients in the world.[97]

Human Liver Trials of 1963

Although the follow-ups were still short, our encouraging kidney experience triggered the decision to go forward with the infinitely more difficult initiative of liver transplantation. The first attempt on March 1, 1963 was in an unconscious and ventilator-bound child with biliary atresia who bled to death during operation. The next two 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 (Table 1–3). These two patients were found at autopsy to have extrahepatic micrometastases.[8]

As in the kidney recipients, azathioprine was administered before as well as after transplantation, adding a high-dose course of prednisone with the onset of rejections. The rejections were easily reversed (Fig. 1–7), and the transplanted livers retrieved at autopsy after 7.5 and 22 days were remarkably free of rejection. Good allograft preservation was accomplished by transfemoral infusion of a chilled perfusate into the aorta of the non-heart-beating donors after cross-clamping the aorta at the diaphragm (Fig. 1–8), in much the same way as in the first stage of the *flexible* multiple organ procurement operation used today.[32,33] There was little ischemic damage to the allografts during the cold ischemia of

Table 1-3. THE FIRST SEVEN HUMAN LIVER RECIPIENTS

Age	Date	City (Ref)	Liver Disease	Survival (Days)	Main Cause of Death
3	3/1/63	Denver (8)	Biliary atresia	0	Intraoperative bleeding
48	5/5/63	Denver (8)	Hepatoma, cirrhosis	22	Pulmonary emboli, sepsis
68	6/3/63	Denver (8)	Duct cell carcinoma	75	Pulmonary emboli
52	7/10/63	Denver (9)	Hepatoma, cirrhosis	65	Gastrointestinal bleeding, pulmonary emboli/edema, liver failure
58	9/16/63	Boston (98)	Colon metastases	11	Pneumonitis, hepatic abscesses, failure
29	10/4/63	Denver (9)	Hepatoma	23	Sepsis, bile peritonitis, pulmonary emboli
75	1/?/64	Paris (99)	Colon metastases	0	Intraoperative hemorrhage

2.5 and 8 hours, as judged by modest increases in the liver injury tests.

The various anastomoses were performed in the same way as in the dog experiments except for the biliary tract reconstruction. The complete operation was drawn in 1963 (Fig. 1-9). The picture could be used today, and often is, to depict a perfectly executed human liver transplantation. The flaw in the trial was the use of passive venovenous bypasses. Blood clots formed in the bypass tubing, migrated to the lungs, and caused or contributed to the deaths of all four of the 1963 Denver recipients who survived the operation (see Table 1-3). Overzealous correction of clotting abnormalities probably contributed to the formation of the emboli. Coagulation had been monitored with serial thromboelastograms and corrected with blood components and with ε-aminocaproic acid (an analogue of the currently used aprotinine).

Ironically, the venous decompression that had been critical for survival in the dog experiments is not mandatory in most human liver recipients. The motor-driven venovenous bypass system, which was introduced in Pittsburgh in the 1980s,[28-30] made the procedure easier; but in many centers, it now is used only selectively and

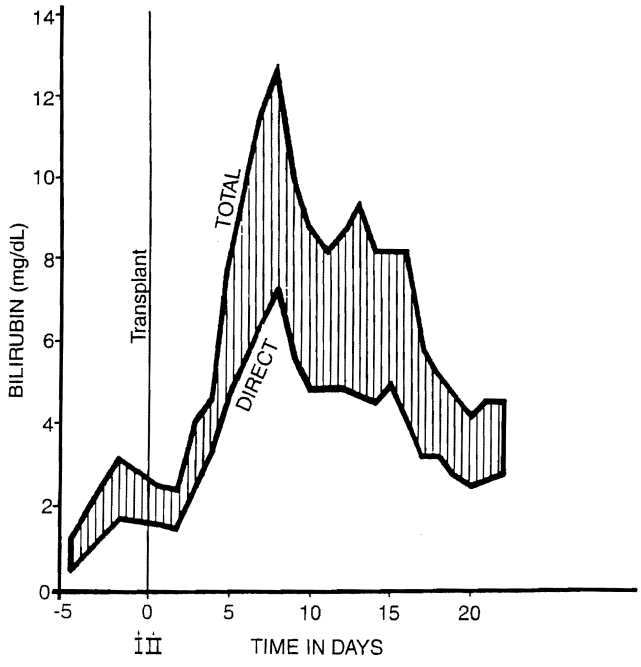

FIGURE 1-7

Rise in serum bilirubin to 12.8 mg/dL in the first patient who survived liver replacement. The bilirubin declined after institution of high-dose prednisone therapy. The patient died of pulmonary emboli after 22 days. (From Starzl TE, Marchioro TL, Von Kaulla KN, et al: Homotransplantation of the liver in humans. Surg Gynecol Obstet 117:659-676, 1963.)

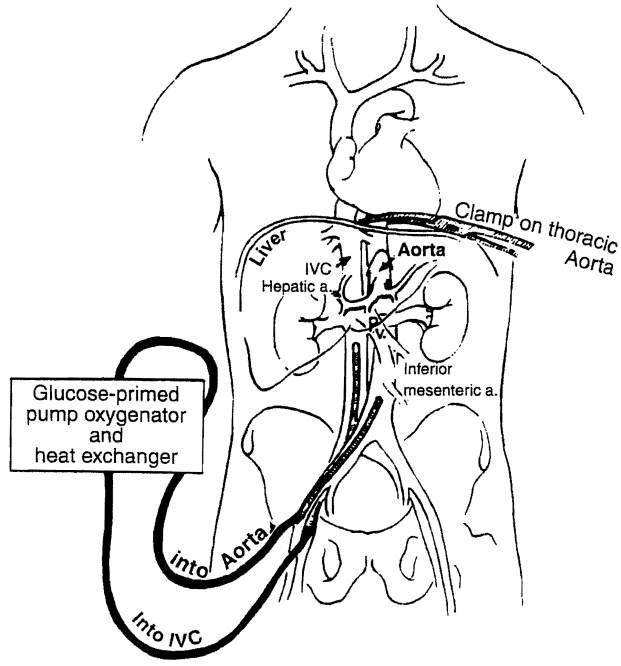

FIGURE 1-8

Extracorporeal perfusion of the deceased donors reported in 1963. "The venous drainage was from the inferior vena cava and the arterial inflow was through the aorta after insertion of the catheters through the femoral vessels. Note clamp on thoracic aorta to perfuse the lower half of the corpse selectively. A glucose-primed pump oxygenator was used with a heat exchanger."[8]

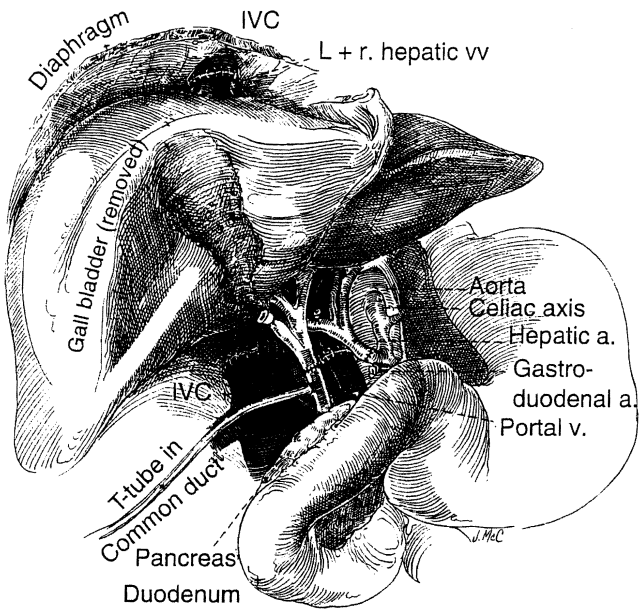

FIGURE 1–9

The operation carried out in the first two patients who survived liver replacement on May 5 and June 3, 1963. The patients lived for 22 and 7.5 days. (From Starzl TE: Experience in Hepatic Transplantation. Philadelphia, Saunders, 1969, p 138.)

almost never in infants or small children. In fact, venous decompression was later shown to be expendable in dogs that were submitted to common bile duct ligation several weeks in advance of transplantation. With the development of venous collaterals in these animals, it was possible at a second stage to carry out liver replacement without venovenous bypass.[100]

Liver Transplant Moratorium

During the last half of 1963, two more liver transplantations were performed in Denver,[9] and one each in Boston[98] and Paris[99] (see Table 1–3). After the deaths of these patients, clinical activity ceased for 3.5 years, between January 1964 and the summer of 1967. The worldwide moratorium was voluntary, but the decision to stop was reinforced by widespread criticism of attempting to replace an unpaired vital organ with an operation that had come to be perceived as too formidable to be practical. During the moratorium, advances were made, most of which were applicable to all organs.

Role of Human Leukocyte Antigen (HLA) Matching

In a clinical collaboration with Paul Terasaki of UCLA, it was shown that the quality of human leukocyte antigen (HLA) matching, short of perfect compatibility, had little association with kidney transplant outcome.[14,15,101] By inference, desperately ill liver, heart, and other transplant candidates who could not wait for a well-matched organ would not suffer a significant penalty by receiving a mismatched one.

Development of Antilymphocyte Globulin (ALG)

A second objective was to improve immunosuppression. Between 1963 and 1966, antilymphocyte globulin (ALG) was prepared from antilymphocyte serum (ALS) obtained from horses immunized against dog or human lymphoid cells.[102] After extensive preclinical studies, human-specific ALG was introduced clinically in 1966 in combination with azathioprine and prednisone (the *triple drug cocktail*).[13,16] In the preclinical canine studies, the efficacy of dog-specific ALG had been demonstrated when it was given before, at the time of, or after kidney and liver transplantation. Because pretreatment appeared to be valuable, it was incorporated for the patients whenever possible.

Demonstration of Hepatic Tolerogenicity

The feasibility of liver transplantation reflected during this period was increasingly evidenced by a growing kennel population of long-surviving canine recipients (Fig. 1–10), none of which was treated with more than a 4-month course of azathioprine[11] or a few doses of ALG.[13] In presenting the results of 143 canine liver replacements to the Society of University Surgeons in February 1965, it was emphasized that "Although the early recovery after liver homotransplantations has many hazards... the frequency and rapidity with which dogs could be withdrawn from immunosuppression without an ensuing fatal rejection is remarkable.... The consistency of this state of host-graft nonreactivity and the rapidity with which it seemed to develop exceeds that reported after canine renal homotransplantations."[11]

A year later, the French surgeon, Henri Garnier, reported (with Cordier) that a significant percentage of *untreated* outbred pig liver recipients did not reject their allografts.[103] This observation promptly was confirmed and extended in England by Calne at Cambridge,[104] Peacock and Terblanche in Bristol,[105] and us.[106] Calne and colleagues subsequently demonstrated that the tolerance self-induced by the liver extended to other tissues and organs from the liver donor, but not from third-party pigs.[107]

FIGURE 1–10

Canine recipient of an orthotopic liver homograft, 5 years later. The operation was on March 23, 1964. The dog was treated for only 120 days with azathioprine and died of old age 13 years after transplantation.

Reassessment of the Auxiliary Liver Graft

Although the primary focus during the moratorium was on liver replacement, the ostensibly less radical auxiliary liver transplantation (Welch's operation) was reevaluated. After showing that rejection could be completely prevented in some dogs with high doses of azathioprine, it was proved that the acute atrophy of Welch's auxiliary livers was caused by depriving the allografts of liver-supporting constituents of splanchnic venous blood (see Fig. 1–1).[9,10] The technical difficulties of obtaining optimal portal vein revascularization finalized the decision to proceed clinically with liver replacement.

However, the *hepatotropic* qualities of splanchnic venous blood were not fully explained until the mid-1970s. Eventually, it was established that endogenous insulin was the most important factor.[20,21] This was a decisive step in understanding the pathophysiology of Eck's fistula (portacaval shunt).[108] Only then could it be readily understood why total splanchnic venous diversion (i.e., portacaval shunting) was such a severe insult to the already damaged liver of patients with hepatic disease, particularly if there had been significant portal flow prior to the shunt. In addition, the demonstration that insulin is a liver growth factor was the beginning of the field of hepatotropic physiology (i.e., studies of the effect of growth factors on liver structure, size, function, and the capacity for regeneration).[109]

Improved Organ Preservation

The potential pitfall of organ preservation remained. It would still be necessary to obtain livers from non–heart-beating donors. To help surmount this difficulty, we developed an ex vivo perfusion system in 1966 and 1967 that permitted reliable preservation of canine livers for as long as a day.[110] Now, it was time to try again.

Resumption of Human Liver Replacement

The liver program was reopened in July 1967 and was reinforced by a powerful new member, Carl Gustav Groth, a 2-year National Institutes of Health (NIH) fellow

FIGURE 1-11

The first three human recipients to have prolonged survival after liver replacements in July and August, 1967. The adult, Carl Groth, was then an NIH-supported fellow.

from Stockholm. Multiple examples of prolonged human liver recipient survival promptly were produced under triple-drug immunosuppression with azathioprine, prednisone, and ALG (Fig. 1-11).[16]

The liver transplant beachhead was reinforced by the opening of Roy Calne's clinical program in Cambridge, England in February 1968.[69] By the time the first textbook on liver transplantation was written in 1969,[111] there had been 33 human liver replacements in the world: 25 in Denver and 8 elsewhere (4 by Calne). The German and French teams of Rudolf Pichlmayr and Henri Bismuth began to make important contributions to liver transplantation in the early 1970s, followed by the Dutch group of Rudi Krom later in the decade.

Transplantation of other extrarenal organs followed close behind the liver, using similar immunosuppression (Table 1-4). Hearts were successfully transplanted in 1968 in Capetown by Barnard[112] and in Palo Alto by Shumway.[113] In 1969, the first prolonged survival after human lung[114] and pancreas transplantation[115] was accomplished in Ghent, Belgium and Minneapolis, respectively. Despite these achievements, transplantation of the extrarenal organs, and especially of the liver, remained controversial for another decade, because of the high mortality rate. Only 34 (20%) of the 170 liver recipients treated at the University of Colorado through 1979 survived for 5 years or longer.[52]

The unusual tolerogenicity of the hepatic allograft previously demonstrated in dogs and pigs was evident in human liver recipients of the 1970s. In 1995, 12 (28%) of the 42 Colorado patients still surviving from this era already had been off all immunosuppression for 1 to 17 years.[116] Since then, the majority of the remaining 30, some of whom are now beyond the third of a century posttransplant milestone, also have stopped drugs without rejection.[117,118] Such drug-free tolerance was almost unheard of with the other kinds of deceased-donor organs.

Advent of Better Drugs

Although the feasibility of transplanting the liver and other extrarenal organs had been established, the widespread use of these procedures was precluded until cyclosporine was introduced clinically in England in 1978 by Calne[25] and combined with prednisone in Denver 1 year later.[26] Results further improved with all

Table 1-4. FIRST SUCCESSFUL TRANSPLANTATION OF HUMAN ALLOGRAFTS (SURVIVAL >6 MONTHS)

Organ	City	Date	Physician/Surgeon	Ref
Kidney	Boston	1/24/59	Murray	77
Liver	Denver	7/23/67	Starzl	16
Heart	Cape Town	1/2/68	Barnard/Shumway	112,113
Lung*	Ghent	11/14/68	Derom	114
Pancreas†	Minneapolis	6/3/69	Lillehei	115

*Patient died after 10 months; all others in table lived more than 1 year with functioning graft. The first more than 1-year survival of isolated lung recipients was not reported until 1987.

†Kidney and pancreas allografts in uremic patient.

organs when tacrolimus was substituted for cyclosporine in the 1990s.[46,47] The stepwise increases in liver recipient survival, first with cyclosporine-based[27,119] and then with tacrolimus-based immunosuppression,[46,47] were particularly striking (Fig. 1–12). Thus, 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. The dramatic spread of liver transplantation that began in the mid-1980s was made possible by a supremely talented new generation of surgeons who in turn began to instruct their own competent trainees.

There was, however, one disappointment. With the better immunosuppressants, drug-free liver recipients such as those treated with azathioprine (or cyclophosphamide), prednisone, and ALG in the mortality-plagued 1970s were expected to become common. Yet, this was seen less frequently than before. It was clear that the goal of deliberate production of drug-free liver recipients would remain out of reach until the mechanisms leading to organ-induced tolerance were understood. Insight into these mechanisms of tolerance began to emerge in 1992 when low-level donor leukocyte chimerism (microchimerism) was demonstrated in all 30 kidney and liver recipients studied from 3 to 30 years after successful transplantation. Chapter 73 describes how this new information permitted the development of more tolerogenic strategies of immunosuppression applicable to transplantation of all organ allografts.

Technical Innovations

Although the ascension of liver transplantation was dominated by improvements in immunosuppression, there were other significant developments, including modifications in the details of both the donor and recipient operations.

Donor Procedures

Cooling of deceased-donor organs is done today by variations of the in situ technique originally developed before the acceptance of brain death conditions (see Fig. 1–8), but with simple infusion without a bypass.[7] These methods[32,33] allow removal of all thoracic and abdominal organs, including the liver, without jeopardizing any of the individual organs—even with unstable donors, including those whose hearts have ceased

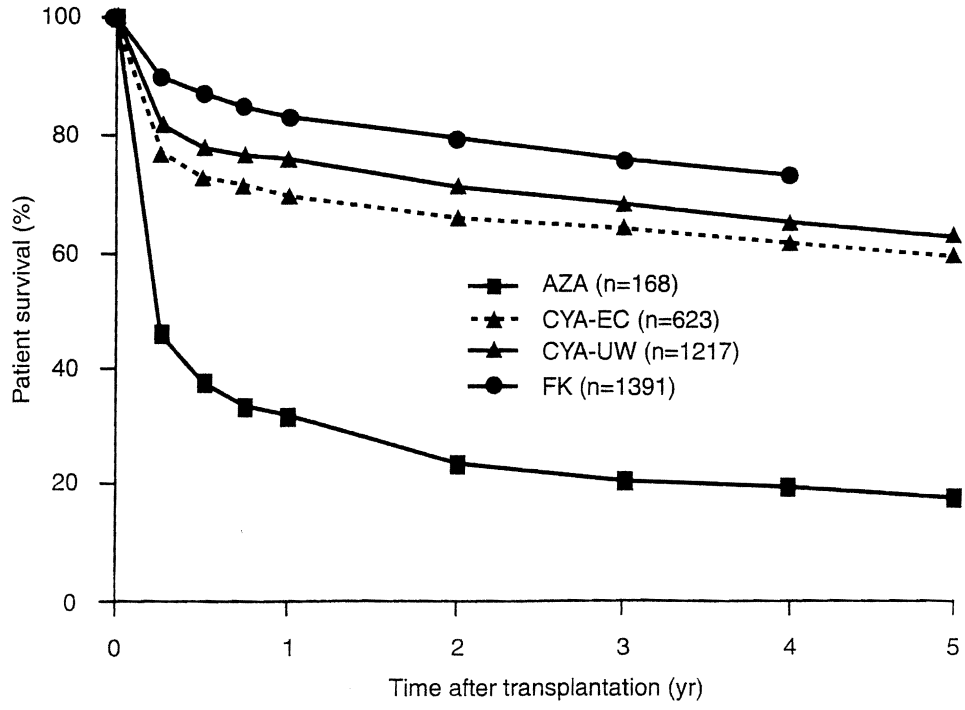

FIGURE 1–12

Stepwise improvements in patient survival after liver replacement. These were associated with the advent of increasingly potent immunosuppressive drugs. AZA, azathioprine; CYA, cyclosporine before [*dashed line*] and after [*continuous line*] the availability of UW solution; FK, tacrolimus. Most of the difference between the dashed and continuous lines was because of the availability of FK for the rescue of cyclosporine failures. The data shown here were presented to the American Surgical Association in April 1994.

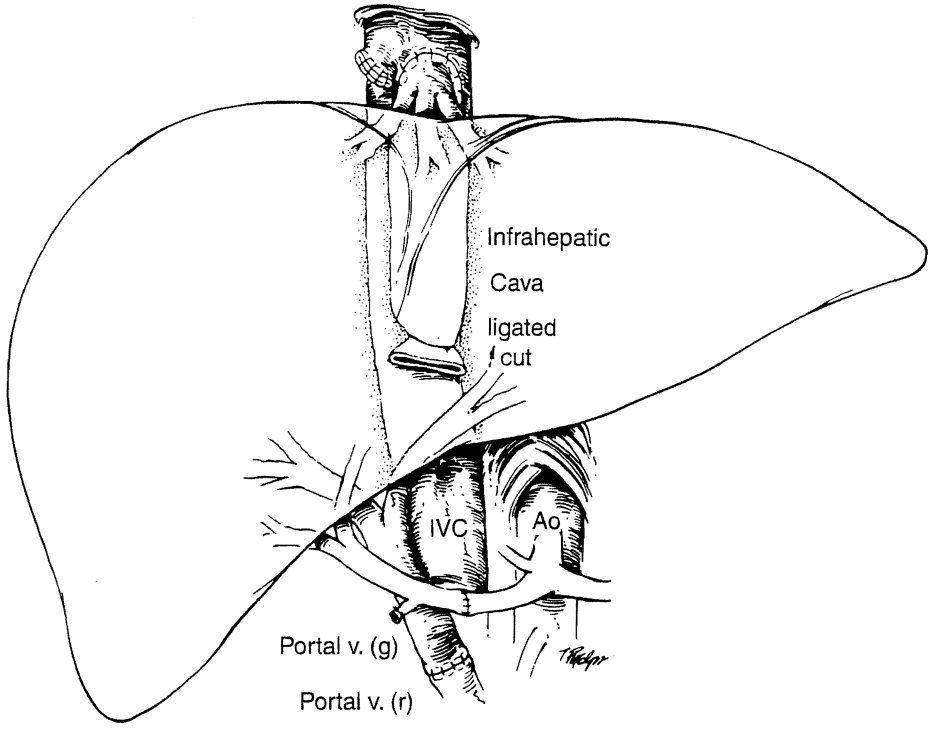

FIGURE 1–13

Transplantation of a liver piggybacked onto an inferior vena cava, which is preserved through its length. Note that the suprahepatic vena cava of the homograft is anastomosed to the anterior wall of the recipient vena cava. The retrohepatic vena cava of the homograft is sutured or ligated, leaving a blind sac into which empty numerous hepatic veins. (From Tzakis A, Todo S, Starzl TE: Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg 210:649-652, 1989.) Ao, aorta; IVC, inferior vena cava.

to beat. By 1987, multiple organ procurement techniques had become so standardized that they were interchangeable not only from city to city but also from country to country. After the chilled organs are removed, subsequent preservation usually is performed by simple refrigeration rather than by sophisticated methods of continuous perfusion that were developed in the 1960s.

Recipient Operation

The incidence of biliary duct complications (obstruction, fistula, and cholangitis), which had been more than 30%, was reduced by the use of choledochocholedochostomy with a T-tube stent or, if this was not feasible, by choledochojejunostomy to a Roux limb.[119] The systematic use of venovenous bypasses without anticoagulation in adult recipients greatly diminished the occurrence of hemorrhages of nightmare proportions that were common at one time. Management of coagulopathies continued to be facilitated by the use of the thromboelastogram to follow the minute-to-minute clotting changes in the operating room.[120] With better control of bleeding, scarring from multiple upper abdominal operations, as well as prior portosystemic shunts, were eliminated as serious adverse factors in major centers. The systematic use of arterial and venous grafts that was introduced in the 1970s[24] eliminated extensive thrombosis of the portal and superior mesenteric veins as a contraindication to liver transplantation[121] and has facilitated arterialization in complex cases.

The shortage of appropriate-sized donors for very small pediatric recipients was greatly ameliorated by the use of partial livers. The introduction of such operations followed the development of sophisticated techniques of hepatic resection for neoplasms.[122,123] The first known reduced liver transplant graft operation was performed in Denver in 1975.[124] This case was not reported, however, until long after the description of the technique by Bismuth and Houssin in Paris[35] and by Broelsch and Pichlmayr and colleagues in Hanover.[36] Implantation of liver fragments has been facilitated by use of the piggyback principle,[49] by which the recipient retrohepatic vena cava is kept intact and the venous outflow of the graft is anastomosed to cuffs of the host hepatic veins (Fig. 1–13). The piggyback modification was first used as early as 1968 in Cambridge, England[69] and in Denver[70] for the transplantation of pediatric livers, but the operation was rarely used for full-sized adult livers until its popularization by Tzakis and colleagues.[45]

Indications for Liver Transplantation

By the early 1990s, liver transplantation had become the accepted court of last appeal for essentially all non-neoplastic end-stage liver diseases and for selected patients with otherwise nonresectable hepatic malignancies.

Benign Disease

Parenchymal and Cholestatic Disorder

By the end of the 1980s, diagnoses that had precluded liver transplantation, such as the diagnosis of alcoholic cirrhosis, were no longer absolute contraindications. The list of benign diseases treatable by transplantation had become so long (nearly 100) that it was being divided into broad categories (Table 1–5) (e.g., cholestatic and parenchymal diseases).[125,126]

Inborn Errors of Metabolism

Products of hepatic synthesis permanently retain the original metabolic specificity of the donor after transplantation. Consequently, the correction of inborn errors by liver transplantation can be expected to endure for the life of the graft. By 1989, 16 liver-based or liver-influenced inborn errors of metabolism had been compiled (Table 1–6). Many others have been added since.

Table 1–5. GENERIC LISTING OF LIVER DISEASE TREATABLE BY LIVER TRANSPLANTATION

Disease Category
PARENCHYMAL
Postnecrotic cirrhosis
Alcoholic cirrhosis
Acute liver failure
Budd-Chiari syndrome
Congenital hepatic fibrosis
Cystic fibrosis
Neonatal hepatitis
Hepatic trauma
Others
CHOLESTATIC
Biliary atresia
Primary biliary cirrhosis
Sclerosing cholangitis
Secondary biliary cirrhosis
Familial cholestasis
Others
Inborn Errors of Metabolism
TUMORS
Benign
Primary malignant
Metastatic

Neoplastic Diseases

The early use of conventional liver transplantation to treat otherwise nonresectable primary or metastatic hepatic cancers resulted in a high rate of recurrence.[8,119,127] Nevertheless, the use of liver transplantation to treat less-advanced cancers has continued, almost invariably in combination with adjuvant chemotherapy or other protocols. Certain kinds of neoplasms have a better prognosis than others. In an attempt to increase the perimeter of resectability, upper abdominal exenteration (i.e., en bloc removal of the liver, pancreas, spleen, stomach, duodenum, proximal jejunum, and ascending colon) has been used to treat extensive sarcomas, carcinoid tumors, and other malignancies that are still regionally confined.[76,128] The excised organs are replaced with hepatopancreaticoduodenal grafts (see Fig. 1–6, top) or, in some cases, by the liver alone.

Organ Shortage

By the late 1980s, there were enough liver transplant teams to use the available supply of deceased-donor organs. Efforts to equitably allocate livers to competing teams began officially in November 1987, when the United Network of Organ Sharing (UNOS) attempted to apply at a national level a *point system* based on urgency of need, size match, and logistic considerations that had been in effect in western Pennsylvania for most of the 1980s.[44] Neither the system nor its many modifications has satisfied all of the caregivers, patient advocacy groups, and other stakeholders. However, all interested groups, including surgeons, have tried to increase the pool of available organs.

Use of Marginal Donors

As early as 1986, Makowka and colleagues[42] identified the impending organ shortage and reported the feasibility of systematically using livers from older donors, donors with biochemical or histopathological evidence of liver injury, and those whose terminal course was characterized by management errors, physiological abnormalities, or the administration of potentially damaging pharmacological agents. At first criticized, this means of expanding the donor pool became widely

Table 1-6. INBORN ERRORS OF METABOLISM TREATED WITH LIVER TRANSPLANTATION*

Disease	Explanation of Disease	Survival	Disease
α_1-Antitrypsin deficiency	Structural abnormality of the protease inhibitor synthesized in the liver	13 yr	Cirrhosis
Wilson's disease	Abnormal biliary copper excretion, decreased copper binding to ceruloplasmin, and copper accumulation in tissues; autosomal recessive gene mapped to chromosome 13	16.5 yr	Cirrhosis
Tyrosinemia	Fumaroylacetoacetate hydrolase deficiency	7.5 yr	Cirrhosis, hepatoma
Type I glycogen storage disease	Glucose-6-phosphatase deficiency	7 yr	Glycogen storage, fibrosis, tumors
Type IV glycogen storage disease	Amylo-1:4,1:6-transglucosidase (branching enzyme) defect	4.5 yr	Cirrhosis
Cystic fibrosis	Unknown; pancellular disease, liver often affected	4.5 yr	Cirrhosis
Niemann-Pick disease	Sphingomyelinase deficiency, sphingomyelin storage	2 yr (died)	None
Sea-blue histiocyte syndrome	Unknown, neurovisceral lipochrome	7 yr	Cirrhosis
Erythropoietic protoporphyria	Hepatic ferrochelatase deficiency, ?overproduction of protoporphyrin by erythropoietic tissues	1.5 yr	Cirrhosis
Crigler-Najjer syndrome	Glucuronyl transferase deficiency	4 yr	None
Type I hyperoxaluria	Peroxisomal alanine: glyoxylate aminotransferase deficiency	8 mo	None
Urea cycle enzyme deficiency (three types)	Ornithine carbamoyltransferase	8 mo	None
C protein deficiency	Defective C protein synthesis	2.5 yr	None
Familial hypercholesterolemia	Low-density lipoprotein receptor deficiency, low-density lipoprotein overproduction	6 yr	None
Hemophilia A	Factor VIII deficiency	4 yr	Cirrhosis, a complication of blood component therapy
Hemophilia B	Factor IX deficiency	6 mo	Cirrhosis, a complication of blood component therapy

*Most of the patients were in the University of Colorado–University of Pittsburgh series. This is a follow-up to January 1989. More inborn errors have been added since 1989.

From Starzl TE, Demetris AJ, Van Thiel DH: Liver transplantation (1). N Engl J Med 321:1014-1022, 1989. Reprinted by permission of The New England Journal of Medicine, 1989. Copyright 1989. Massachusetts Medical Society.

accepted once the magnitude of the supply problem was appreciated. Serious and frequently contentious efforts are still being made to define what constitutes a *marginal* donor and how to decide who gets the liver.[129]

Living Donor Transplantation

In an extension of the reduced liver graft procedures developed in deceased donors,[35,36] portions of liver ranging from the left lateral segment to the extended right lobe have been removed from volunteer adult donors for transplantation to pediatric recipients. Living donor liver transplantation from an adult liver to a child was first done successfully by Strong and Lynch in Adelaide, Australia.[49] The operation for pediatric recipients was subsequently popularized by Christoph Broelsch and associates at the University of Chicago,[50] who reported their results at the American Surgical Association conference in 1990 along with their experience with reduced-size deceased-donor organs and deceased-donor split livers.

To obtain an adequate liver mass for recipient body weight in adult-to-adult living donor transplantation, the size of the transected liver fragment was first increased from the left lateral segment to a full left lobe. The more common operation today is transplantation of a right lobe. This was first carried out in Japan

when unexpected anatomical findings were encountered in the donor.[54] The first cases and series of right lobe transplantation in the United States were not published until 1998-1999.[55,56] Since then, more than 1500 right lobe transplantations have been performed in more than 40 American centers with patient and graft survival equivalent to that with whole-organ, deceased-donor transplantation or with various kinds of partial liver transplantation, including the predecessor adult-to-child procedure.

Despite its utility, liver donation from a living donor has been used with caution by many liver transplant surgeons because it has had a mortality of approximately 0.5%.

Split-Liver Procedures

More efficient use of deceased-donor organs has been made possible by sharing one liver between two recipients. The split-liver procedure was first reported from Europe by Rudolf Pichlmayr in 1989 and soon thereafter by Bismuth (Paris) and Broelsch (Chicago). The results were inferior at first to those obtained with whole livers.[50] But after a learning curve and incorporation of the lessons learned from living donors, the results with livers split between adult and pediatric recipients have been comparable to standard deceased-donor transplantation of whole organs. This practice may make the use of living donors for pediatric recipients unnecessary.

Moreover, splitting of the adult liver into full left and right lobes for transplantation into two adults (or even the sharing of a pediatric liver by two infants or children) could further relieve the organ shortage. This has been done successfully in a small number of adult cases.[130,131] Full implementation of this technique will require restriction of its use to optimal donors, careful assessment of the donor's physiological status before hepatectomy, careful consideration of the logistics involved, and the intelligent application of allocation rules for recipient selection.[132]

Xenotransplantation

Clinical transplantation of chimpanzee livers[12] was attempted three times between 1966 and 1973, with deaths after 0, 9, and 14 days.[133] The clinical course and pathological findings in the two patients who survived the operation were indistinguishable from those after allotransplantation. Two additional hepatic xenotransplantations were attempted, in June 1992 and January 1993, with more phylogenetically distant baboon donors. Survival was 70 and 26 days.[134,135] Neither humoral nor cell-mediated rejection could be indicted as the cause of failure in these cases. However, there was evidence of continuous complement activation in both. The xenografts did not function optimally, and both developed findings of intrahepatic cholestasis within the first postoperative week. It also was suspected that synthetic products of the baboon liver may have been incompatible with the human metabolic environment.

The anthropomorphic qualities of chimpanzees and baboons and the perception that these animals pose a high risk from zoonotic infections have all but precluded further trials with primate donors. Hopes of using lower mammalian donors have been raised recently by the knockout in cloned pigs of both copies of the α1,3-galactosyltransferase gene.[58] The enzyme product of this gene is required for the synthesis of the sugar chain epitope α-gal, against which humans and other higher primates have preformed antibodies.

Elimination (double knockout) of the α-gal epitope avoids the immediate innate immune response to pig organs (i.e., hyperacute rejection does not occur), but it is almost certain that other genetic modifications will be needed before pig organs will be suitable for clinical use. Even if the immune barrier to livers is controlled, the multiple synthetic products of the porcine liver could make pig-to-human liver xenotransplantation tantamount to endowment of an inborn error (or errors) of metabolism.

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