1552

Transplantation of the Liver

Ronald W. Busuttil, M.D., Ph.D.

Professor of Surgery
Director, Liver Transplantation Program
University of California, Los Angeles
School of Medicine
Los Angeles, California

Goran B. Klintmalm, M.D., Ph.D.

Professor of Surgery
Director of Transplantation
Department of Surgery
Baylor University Medical Center
Dallas, Texas

W.B. Saunders Company
A Division of Harcourt Brace & Company
Philadelphia London Toronto Montreal Sydney Tokyo

1

History of Liver and Other Splanchnic Organ Transplantation

Thomas E. Starzl, MD, PhD

The history of whole organ engraftment has been told largely by those working with the kidney.[1] Many of these investigators and others in their laboratories began to fill the extrarenal vacuum in the late 1950s. The consequence was the rapid development of canine transplant models with which to study all of the intra-abdominal (Fig 1-1) and thoracic organs. The most fruitful of these efforts involved the liver, which joined the kidney in the mid-1960s as the lead organ in the search for improved immunosuppression. The secondary gains from research in liver transplantation included (1) new information about the metabolic interrelations of the intra-abdominal viscera in disease and health; (2) a more profound understanding of the means by which all whole organ grafts are accepted; and (3) the addition of nontransplant as well as transplant procedures to the treatment armamentarium for gastrointestinal diseases. The way in which the liver was specifically involved in this complex chain of events is summarized and annotated in Table 1-1.

EARLY ANIMAL MODELS

The Liver

Auxiliary Transplantation. The concept of liver transplantation first appeared in the medical literature in 1955 when C. Stuart Welch of Albany, New York, described the insertion of an extra (auxiliary) canine liver into the pelvis or right paravertebral gutter of nonimmunosuppressed recipients.[2] The allograft hepatic artery was revascularized from the aorta or iliac artery, and the portal flow was restored by rerouting the high-volume systemic venous return of the host inferior vena cava into the graft portal vein (Fig 1-2). It was not discovered until a decade later that factors other than rejection contributed to the rapid destruction of the auxiliary transplant (see later section, Eck's Fistula and Hepatotrophic Physiology).

Orthotopic Liver Transplantation. Liver replacement (orthotopic transplantation) (Fig 1-3) was first mentioned by Jack Cannon of the University of California, Los Angeles, who speculated that because the liver played an important role in rejection, it might refrain from contributing to its own repudiation. Although none of Cannon's dogs survived operation, his "Brief report"[3] was included with two articles by Welch and colleagues[2, 4] on the subject of the liver in Woodruff's massive compendium of the entire transplantation field to 1959.[5] By the time Woodruff's book was published in the following year, important independent investigations of liver replacement (orthotopic transplantation) in dogs were completed; these had been started in the summer of 1958 at the Peter Bent Brigham Hospital in Boston[6-8] and at Northwestern University in Chicago.[9, 10] The Boston effort, which was under the direction of Francis D. Moore, was a natural extension of an immunologically oriented institutional commitment to organ transplantation that was initially preoccupied with the kidney.[11]

In contrast, the Northwestern initiative stemmed from questions about the mutually regulatory interrelationship of insulin and the liver[12-14] that ultimately led to a new field called hepatotrophic physiology.[15, 16] For these metabolic investigations, a new technique of total hepatectomy was developed[17] and followed, in July 1958, by the second step of inserting an allograft into the vacated hepatic fossa. From the outset, the premise was strongly supported that portal venous blood had superior liver-supporting qualities compared with systemic venous blood.[9] However, almost 20 years passed before the nature of the principal portal venous factors was clarified.

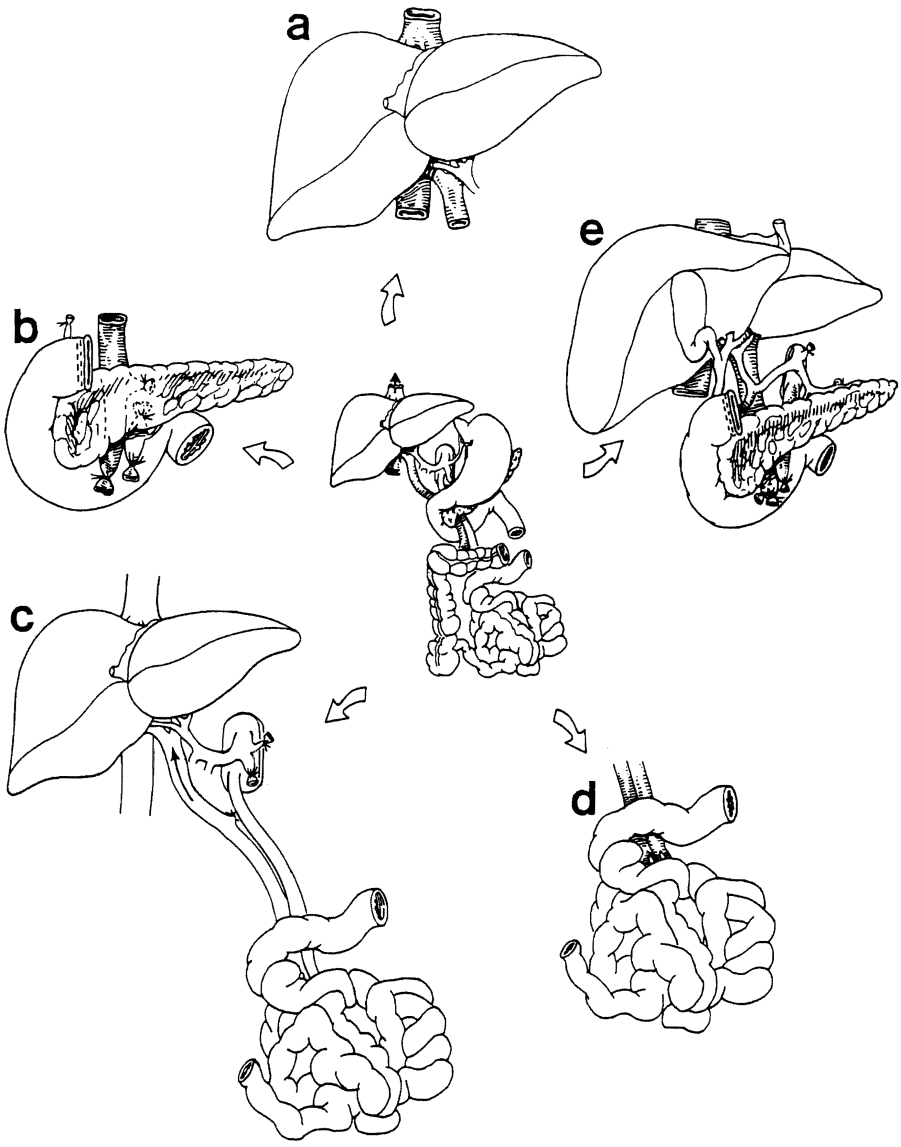

Figure 1-1 The complex of intra-abdominal viscera that have been transplanted as a unit (*center*) or as separate components: *a*, liver; *b*, pancreas; *c*, liver and intestine; *d*, intestine; and *e*, liver and pancreas. (From Starzl TE, Todo S, Tzakis A, Fung J. The transplantation of gastrointestinal organs. Gastroenterology 104:673-679, 1993.)

Despite the absence of effective immunosuppression at that time, a solid basis for future work with orthotopic liver transplantation was laid throughout 1958 and 1959. At the April 1960 meeting of the American Surgical Association, Moore reported on 31 canine experiments with 7 survivors of 4-12 days. In discussing his paper,[18] I described an experience[9] with more than 80 dogs of whom 18 had lived 4-20½ days. Rejection was present after 5-6 days in both series and was usually the principal explanation for death. A few years later, Groth et al[19] demonstrated that drastic reductions in hepatic blood flow were an integral part of the rejection process and explained the infections to which the consequent ischemia made the liver prone.[20, 21]

Aside from elucidating the need to revascularize the hepatic graft to supply splanchnic venous blood, these early investigations clarified the other requirements for successful liver replacement. Preservation of the transplanted liver was accomplished with intraportal infusion of chilled electrolyte solutions in much the same way as is practiced clinically today.[9] Improved infusates in the succeeding years[22, 23] eventually replaced the lactated Ringer's and saline solutions that were used originally. Until 1987, however, the safe preservation time was only 5-6 hours. Since then, the University of Wisconsin solution[24] has permitted reliable and safe refrigeration of human livers for 18-24 hours.[25, 26]

The final requirement for success in dogs was the use of plastic external venous bypasses that passively redirected blood from the occluded splanchnic and systemic venous beds to the superior vena cava during the anhepatic stage while recipient hepatectomy was performed and the new liver was installed.[7, 9] Such venous decompression was later shown to be expendable in dogs submitted to common bile duct ligation several weeks in advance of transplantation. The safety factor was the development in the interim of decompressing venous collaterals.[27]

Similarly, venous bypasses were shown to be nonessential in most clinical cases, if the operations were performed by highly experienced surgeons.[28, 29] Nevertheless, the introduction of pump-driven venovenous bypasses in the 1980s, first with[29, 30] and then without[31-33] anticoagulation, made the operation less stressful in humans and placed it well within the grasp of most competent general

TABLE 1-1 **History of liver transplantation**

Year	Description	Reference
1955	First article in the literature on auxiliary liver transplantation (C. Stuart Welch)	2
1956	First article on orthotopic liver transplantation (Jack Cannon)	3
1958-1960	Formal research programs on liver replacement at Harvard and Northwestern	7, 9
1960	Multivisceral transplantation described, the forerunner of composite grafts	44, 45, 46
1963	Development of the azathioprine-prednisone cocktail (kidneys first, then livers)	99, 100, 104
1963	First human liver transplantation trial (University of Colorado)	115
1964	Confirmation of the portal venous blood hepatotrophic effect; defined the problem of auxiliary liver transplantation	65, 66
1963-1966	Improvements in preservation, in situ and ex vivo	120, 129
1966	Introduction of antilymphocyte globulin (kidneys, then livers)	107
1966	First trial xenotransplantation (chimpanzee)	160
1967	First long survivals of human liver recipients (1967-1968), treated with azathioprine, prednisone, and antilymphocyte globulin	28
1973-1976	Principal portal hepatotrophic substance identified as insulin	15, 74
1976	Improved liver preservation (5-8 hr) permitting long-distance procurement	22, 23
1979d	Systematic use of arterial and venous grafts for vascular reconstruction	137
1979	Cyclosporine introduced for kidneys and liver	111
1980	Cyclosporine-steroid cocktail introduced for kidneys	112
1980	Cyclosporine-steroid cocktail for livers	29, 124
1983	Pump-driven venovenous bypass without anticoagulation	31-33
1984	Standardization of multiple organ procurement techniques	133, 134
1987	University of Wisconsin (UW) solution for improved preservation	24-26
1989	FK506-steroid immunosuppression	114
1992	Discovery of chimerism as explanation of hepatic tolerogenicity	153-156
1992	Baboon to human xenotransplantation	162

and vascular surgeons, allowing the systematic training of a new generation of liver transplant surgeons (Fig 1-4). The way in which these refinements occurred has been reviewed elsewhere.[34]

Multivisceral and Intestinal Transplantation

Isolated Intestine. More than 90 years ago, Alexis Carrel (later working with C.C. Guthrie) performed canine intestinal transplantations.[35] Little more was added until Richard Lillehei and his co-workers replaced almost the entire small intestine in unmodified dogs, after immersing it in iced saline for preservation.[36] The blood vessels were anastomosed to companion recipient structures in an anatomically normal way (Fig 1-5).

Unlike liver transplantation, which progressed steadily from the laboratory to the bedside, the clinical application of intestinal transplantation languished; this was so even after it was demonstrated in Toronto,[37] London (Ontario),[38] Pittsburgh,[39] Kiel,[40] and Paris[41] that the gut could be successfully replaced and long-term survival achieved in large animals under immunosuppression. The first clinical successes with cadaver donors did not come until the late 1980s.[42, 43]

Multivisceral Transplantation. At the time that isolated liver transplantation was being perfected in 1959, the more radical procedure of multiple organ engraftment (including the liver) was shown to be feasible.[44] This transplant was envisioned as a grape cluster with a double arterial stem consisting of the celiac axis and superior mesenteric artery (Fig 1-6, left; and see Fig 1-1, center). In variations of the operation used clinically nearly 30 years later, the grapes, or individual organs, could be removed or retained according to the surgical objectives (Fig 1-6, right; and see Fig 1-1, periphery), but both sources of the arterial supply were preserved.[45] The venous outflow was kept intact up to or beyond the liver.

Two questions raised by the very earliest canine multivisceral experiments have remained clinically relevant since then. First, rejection of the organs making up the composite graft was less severe than expected on the basis of transplantation of the organs individually.[46] Using different models, Calne and colleagues[47] confirmed and

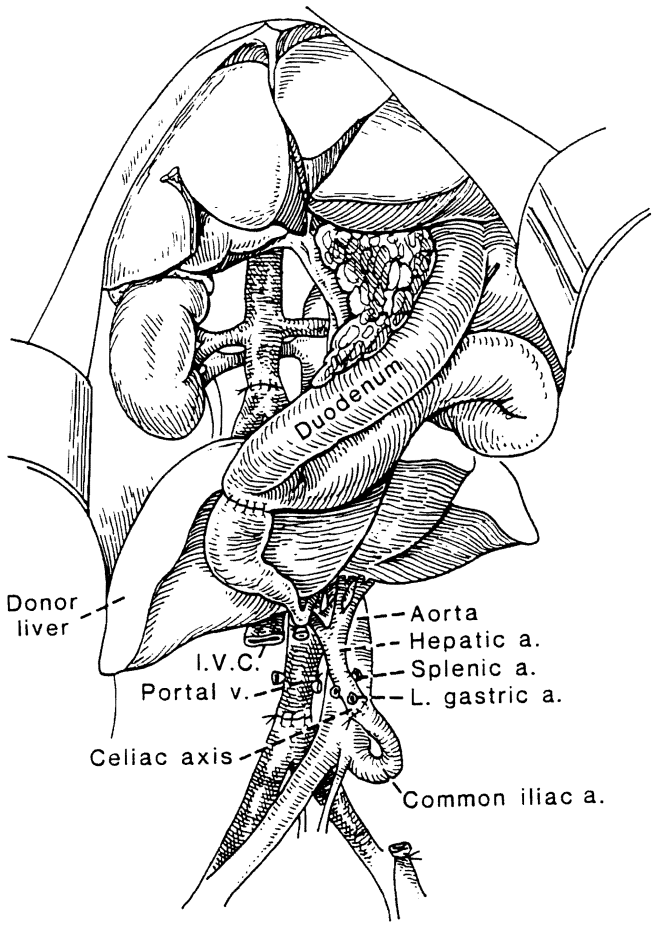

Figure 1–2 Auxiliary liver transplantation in dogs by a modification of Welch's original technique. Note that the reconstituted portal blood supply is from the distal inferior vena cava. I.V.C. = inferior vena cava. Marchioro TL, Rowlands DT Jr, et al. Immunosuppression after experimental and clinical homotransplantation of the liver. Ann Surg 160:411–439, 1964.)

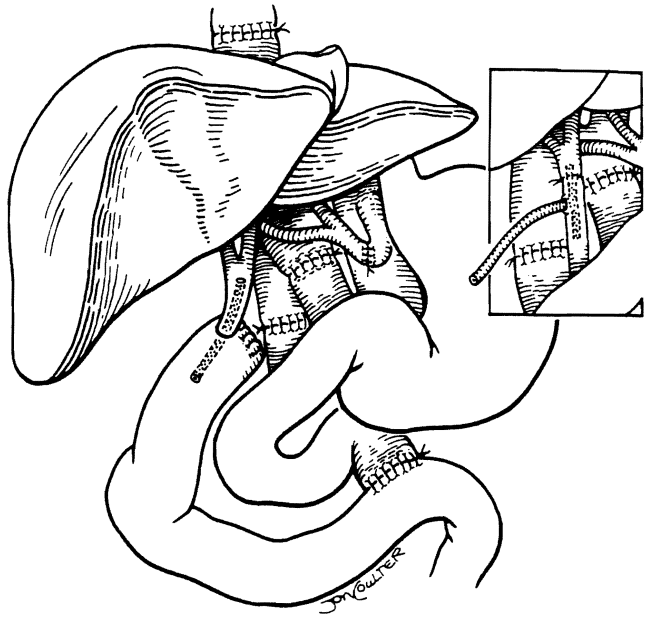

Figure 1–3 Orthotopic liver transplantation (liver replacement). Biliary tract reconstruction is usually with choledochojejunostomy (to a Roux limb) or (*inset*) with a choledochocholedochostomy, which is stented with a T-tube. (From Starzl TE, Demetris AJ, Van Thiel DH. Medical progress: Liver transplantation, Part I. Reprinted with permission from *The New England Journal of Medicine*, 321, 1014–1022, 1989.)

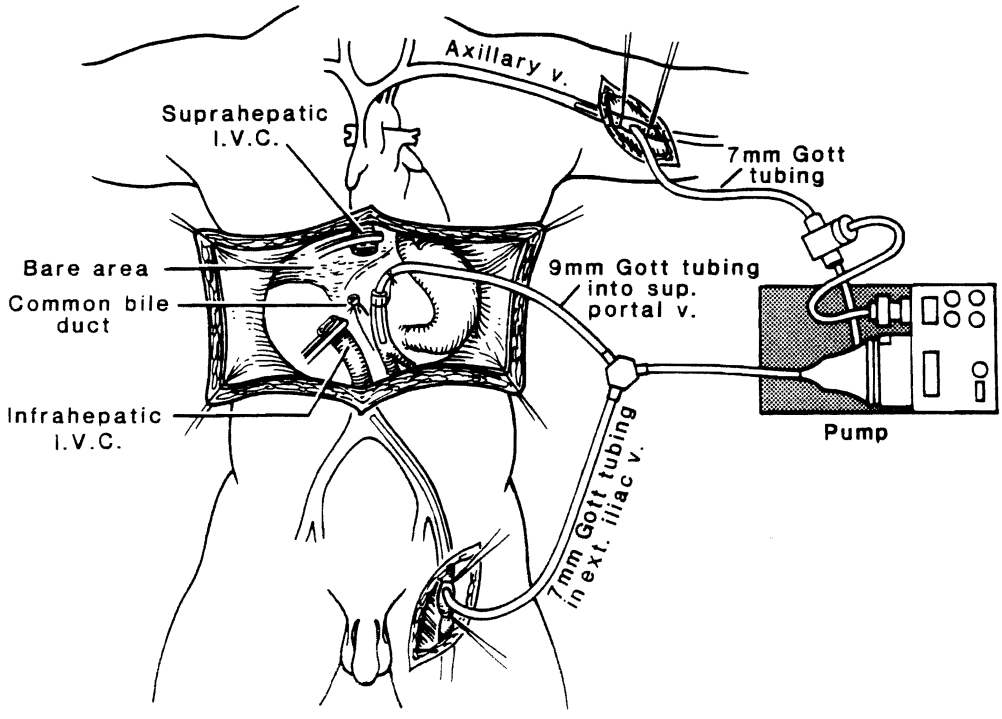

Figure 1–4 Pump-driven venovenous bypass, which allows decompression of the splanchnic and systemic venous beds without the need for heparinization.

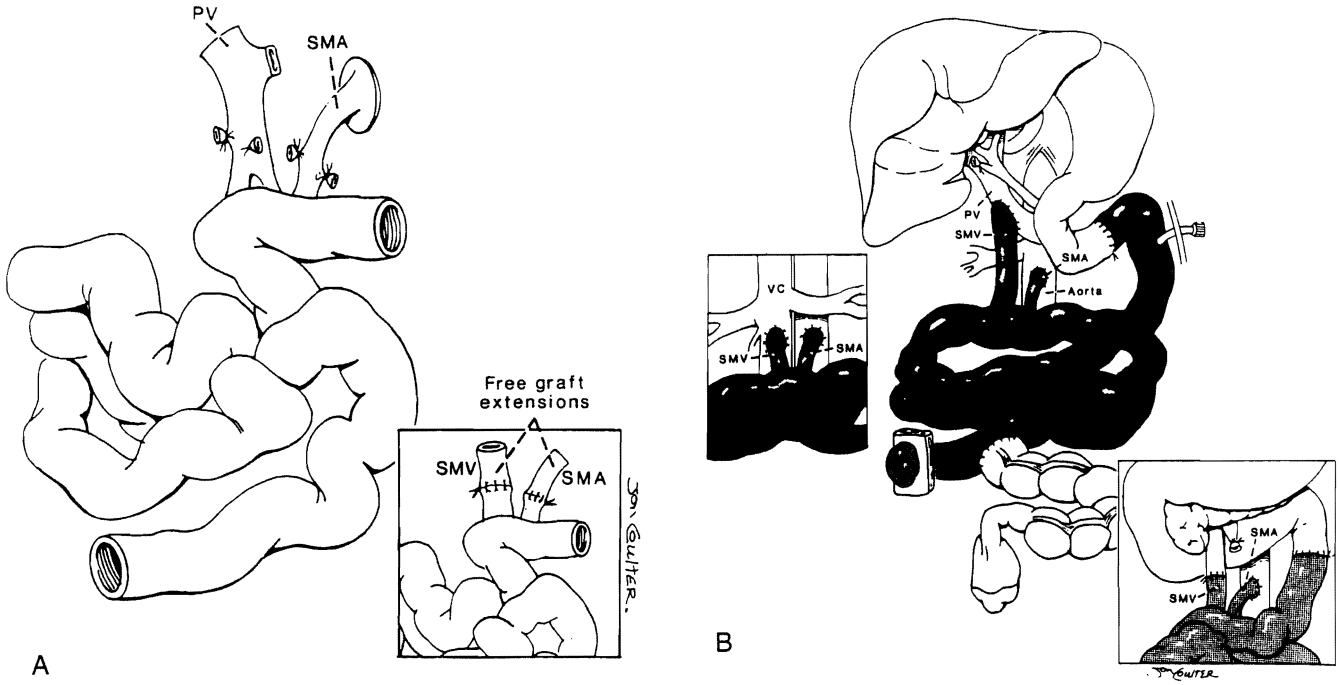

Figure 1-5 Isolated small bowel transplantation. *A*, Donor operation; full-length vascular pedicle of the superior mesenteric artery (SMA) with a Carrel patch of aorta and the superior mesenteric vein (SMV). If both vessels are divided more distally, they can be lengthened on the back table with arterial and venous grafts (*inset*). PV = portal vein. *B*, Recipient operations. Anastomosis of the full-length SMA to the aorta and the angled end of the SMV to the portal vein. With an alternative method (*lower inset*), the SMV is anastomosed to the recipient SMV inferior to the pancreas. Another option (*upper inset*) is to direct the SMV drainage into the inferior vena cava. (*A* and *B* from Todo S, Tzakis AG, Abu-Elmagd K, et al. Intestinal transplantation in composite visceral grafts or alone. Ann Surg 216:223-234, 1992.)

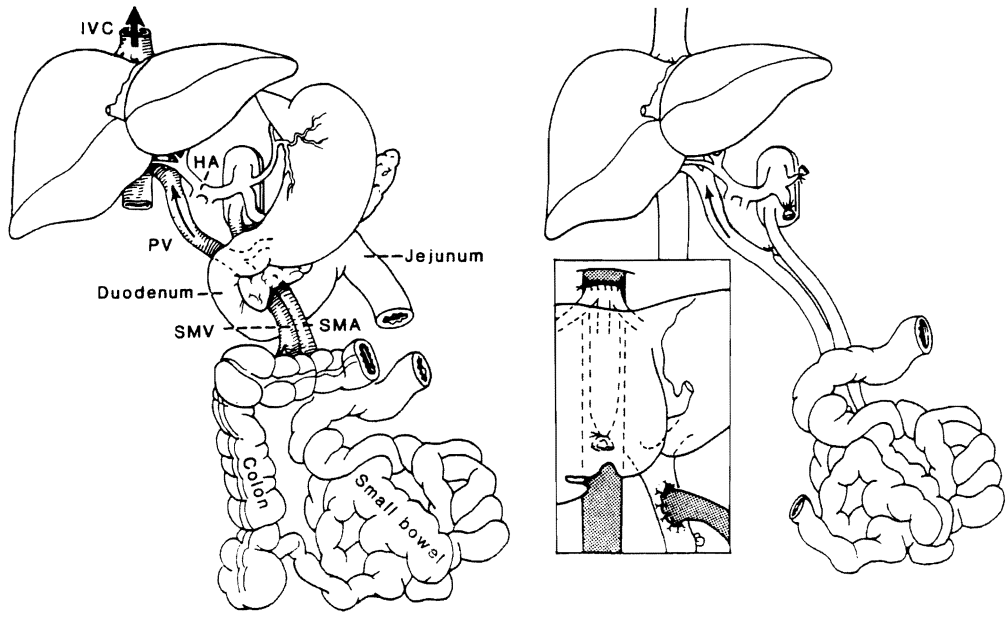

Figure 1-6 The multivisceral transplantation originally developed in dogs (*left*) and a common variant (*right*) in which the central organs (pancreas and duodenum) are removed, leaving the liver and bowel. These two procedures have been performed successfully in humans and provided the first examples of functioning bowel allografts. HA = hepatic artery. (From Starzl TE, Todo S, Tzakis A, Fung J. The transplantation of gastrointestinal organs. Gastroenterology 104:673-679, 1993.)

greatly extended this principle in 1969, when they described the protection of kidney and skin grafts from the hepatic donor in pig liver recipients. These experiments identified the liver as the protective or tolerogenic organ. The hepatic protective effect has been confirmed by the Japanese surgeon Naoshi Kamada, whose experiments were performed in rats,[48] and by many others. Most recently, Valdivia et al[49] demonstrated the cross-species protection of hamster heart and skin xenografts in rats by simultaneous or prior xenotransplantation of a hamster liver.

The second fundamental issue raised by the transplantation of a multivisceral graft or its component organs was the specter of graft-versus-host disease (GVHD), which was largely ascribed to the intestine rather than to the liver.[46] GVHD was well known in 1959 and 1960 from the research of Billingham and Brent[50] and Trentin,[51] but their observations had been almost exclusively based on bone marrow or splenocyte (not whole organ) transplantation. Histopathological evidence of GVHD was found in our canine multivisceral recipients,[46] and GVHD was blamed for the quickly developing multiple organ failure in these animals.

By 1965, it was realized that GVHD could also be caused by the liver when a humoral variety manifested by hemolysis was occurring in canine liver recipients[52] in much the same way as later observed in humans after liver replacement.[53] Finally, GVHD was defined after transplantation of the intestine alone by Monchik and Russell,[54] who used the parent to defenseless offspring first filial generation (F_1) hybrid model. However, these last studies greatly overestimated the GVHD threat after intestinal and multivisceral organ transplantation for reasons explained in Chapter 27.

The multivisceral operation is not often indicated clinically; aside from spawning many variations,[45] however, it was itself the procedure with which the first long survival (>6 months) of a functioning human intestinal graft was accomplished.[55]

Pancreas Transplantation. Transplantation of the pancreas alone will not be considered in these historical notes because this procedure is performed only for endocrine objectives. However, the effect of pancreatic insulin secretion on the liver is a vital concern with all liver engraftments and other splanchnic transplantation procedures (see next section). Even the transplantation of the whole pancreas alone implies the concomitant engraftment of a segment of duodenum that receives exocrine pancreatic secretions and shares its blood supply with the pancreas in humans and animals (see Fig 1-1*b*). Thus, it was not surprising that pancreaticoduodenal grafts were used in the first reported acute experiments on pancreas transplantation.[56, 57] When immunosuppression became available, essentially the same composite graft was used in dogs[58] and, eventually, in humans.[59]

ECK'S FISTULA AND HEPATOTROPHIC PHYSIOLOGY

An erroneous concept about liver physiology was responsible for Welch's belief that rejection was the sole explanation for the rapid destruction of his auxiliary canine liver grafts.[2, 4] The dogma had evolved from nearly 80 years of research with the experimental procedure of Eck's fistula (portacaval shunt) in dogs. In this procedure, blood returning from the pancreas, intestines, and other splanchnic viscera via the portal vein was diverted around the liver. The liver shrinkage that occurred in dogs (and in rats, baboons, and humans)[16, 60] and the consequent wasting, hair loss, and brain damage were generally ascribed, until the mid-1960s, to the diminution of total hepatic blood flow rather than to the loss of exposure of the liver to any specific portal blood constituents.[61-64] This explanation was called the flow hypothesis of portal physiology. Because Welch accepted this dogma and provided a high-volume systemic venous flow for his auxiliary grafts, his belief that rejection was the sole reason for the rapid destruction of the auxiliary canine liver grafts was rational within the incorrect frame of reference of the time.

Although he was wrong, Welch unwittingly created an experimental model of great power. The principle of the model was the coexistence in the same animal of two livers with similar conditions except for the different content of the blood delivered to the respective portal veins. When we repeated Welch's experiments in 1963 under immunosuppression, auxiliary livers protected from rejection by azathioprine but deprived of splanchnic venous inflow shrank within a few days to a fraction of their original size.[65] This acute atrophy (Fig 1-7) was not seen in normally vascularized orthotopic livers,[65] and it could be prevented in auxiliary livers if they were nourished with normal portal blood. Under these circumstances, the shrinkage afflicted the native liver, which had been deprived of its portal supply.[66]

Nontransplant models were soon developed in which the animal's own liver was divided into two fragments, each of which was vascularized with portal venous inflow from different organs or from different regions of the body[67, 68] (Figs 1-8 and 1-9). It was apparent that the healthy and hypertrophic liver fragment with first access to the portal blood (see Fig 1-8), particularly that returning from the upper abdominal viscera (see Fig 1-9), removed hepatotrophic substances so completely that little was left for the competing fragment, which shriveled up (Fig 1-10). Through the use of these double liver fragment models[68-71] and through organ extirpation experiments,[72, 73] insulin was shown to be the most important, but not the only, liver-supporting portal substance. Finally, it was shown that when infused continuously into the tied-off portal vein after portacaval shunt (Fig 1-11), insulin caused hyperplasia of the shrunken hepatocytes and prevented most of the atrophy and other adverse consequences to the liver caused by the Eck fistula.[74]

As other liver growth factors became available, they were screened and evaluated for potency with the Eck fistula model shown in Figure 1-11.[75, 76] Active test substances that mimic the insulin effect include the immunosuppressive agents cyclosporine[77] and FK506,[78] insulin-like growth factor, transforming growth factor-α, and hepatocyte growth factor.[76] By virtue of these developments, hepatotrophic physiology became a consistent collateral theme of all research on the transplantation of the liver and other splanchnic organs and the common ground shared by liver transplantation, clinical portal

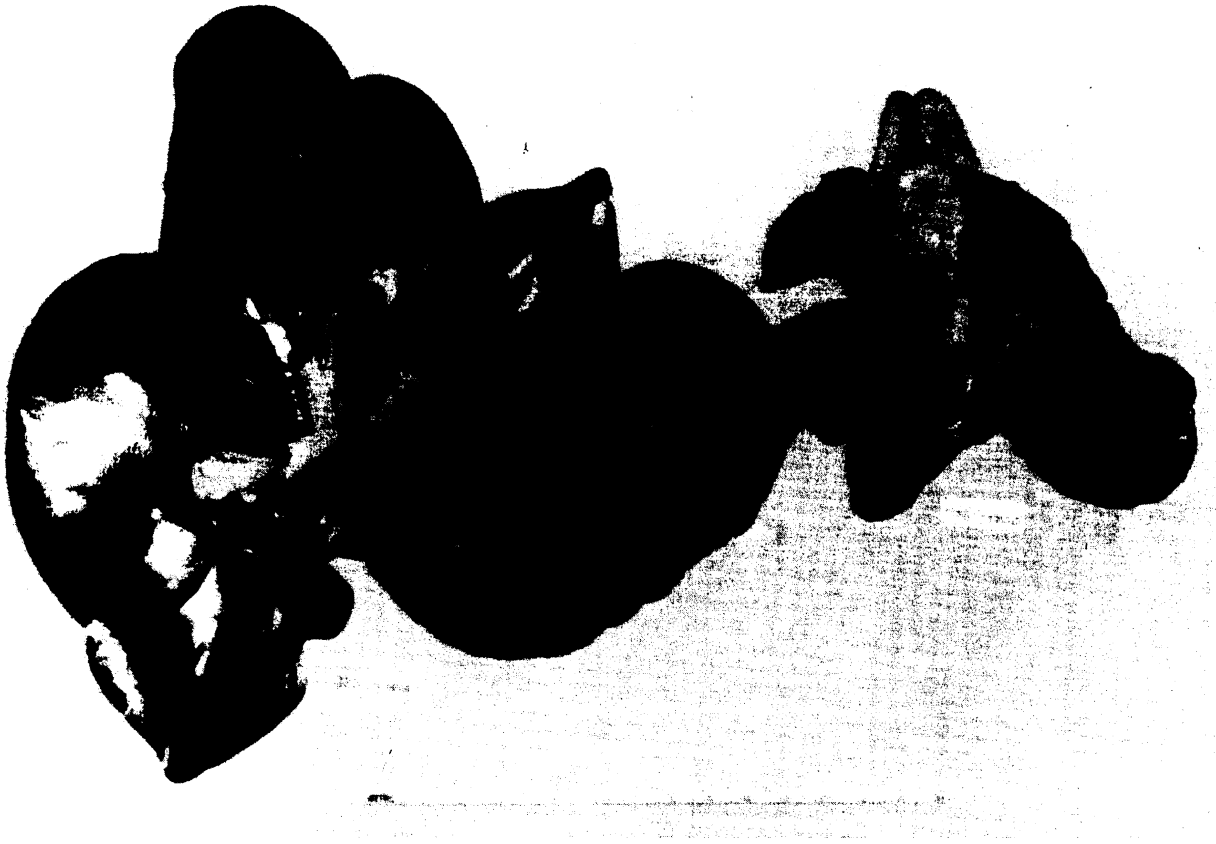

Figure 1-7 An auxiliary homograft (*right*) and the recipient dog's own liver (*left*) 45 days after transplantation. Note the well-preserved but dimensionally reduced general structure of the allograft. At the time of transplantation, both the host organ and the transplant were about the same size. (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.)

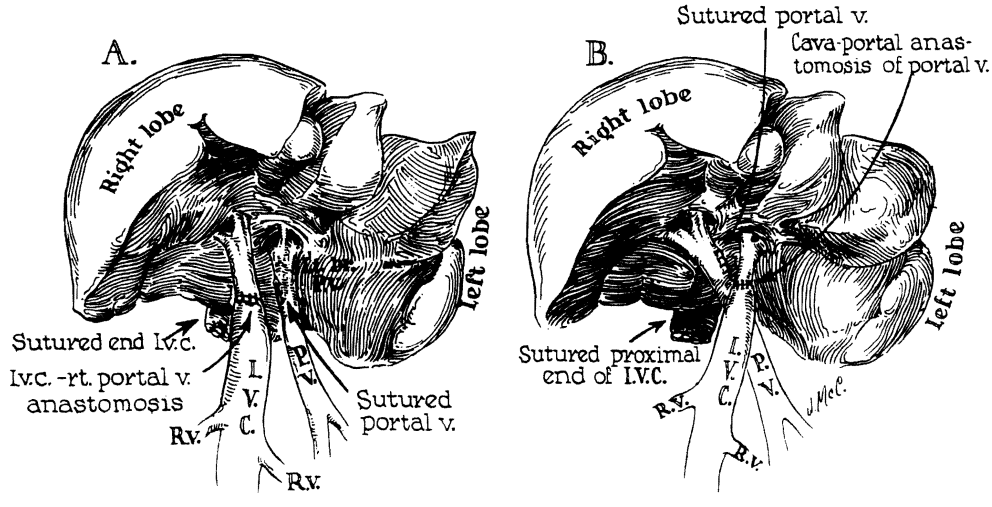

Figure 1-8 The operation of partial (split) transposition in dogs. Note that one of the main portal veins (*left in A, right in B*) retains the natural splanchnic flow and that the other one receives the total input of the suprarenal inferior vena cava. R.V. = renal vein. (*A* and *B* from Marchioro TL, Porter KA, Brown BI, et al. The effect of partial portacaval transposition on the canine liver. Surgery 61:723-732, 1967.)

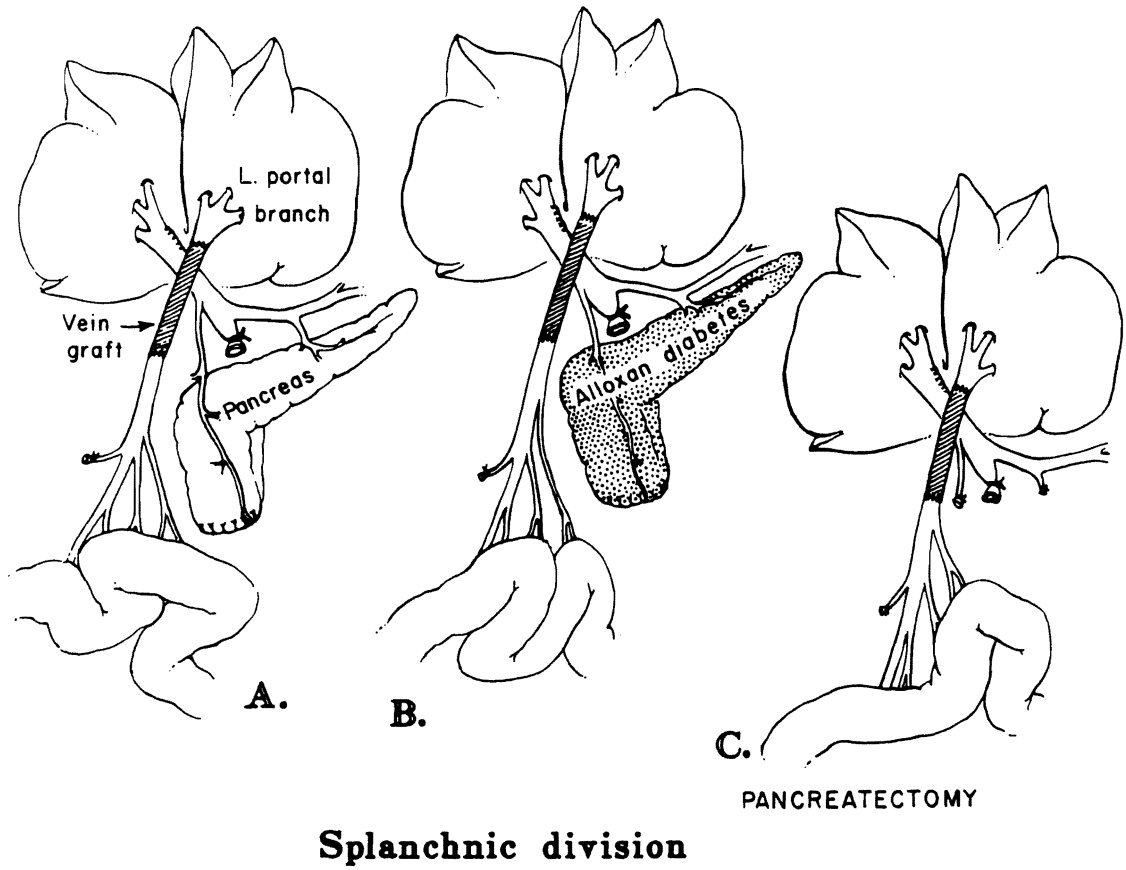

Figure 1-9 Splanchnic division experiments. In these dogs, the right liver lobes received venous return from the pancreaticogastroduodenosplenic region, and the left liver lobes received venous blood from the intestines. *A*, Nondiabetic dogs. *B*, Alloxan-induced diabetic dogs. *C*, Dogs with total pancreatectomy. (*A* to *C* from Starzl TE, Porter KA, Kashiwagi N, et al. The effect of diabetes mellitus on portal blood hepatotrophic factors in dogs. Surg Gynecol Obstet 140:549-562, 1975. By permission of Surgery, Gynecology and Obstetrics.)

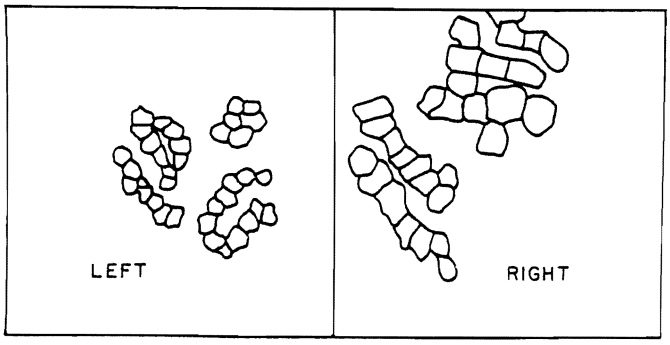

Figure 1-10 Hepatocyte shadows traced during histopathological examination of liver biopsy specimens from the experiments shown in Fig 1-9*A*. These tracings were later cut out on standard paper and weighed as an index of hepatocyte size. The right lobes, with the large hepatic cells, received venous blood from the pancreas, stomach, duodenum, and spleen. The relatively shrunken left lobes, with the small hepatocytes, received intestinal blood. (From Starzl TE, Francavilla A, Halgrimson CG, et al. The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. Surg Gynecol Obstet 137:179-199, 1973. By permission of Surgery, Gynecology and Obstetrics.)

shunt operations (all are variations of Eck's fistula), and the regeneration that follows hepatic resection.[16, 79]

IMMUNOSUPPRESSION

After the demonstration by Medawar in 1944 that rejection is an immunological event,[80, 81] the deliberate weakening of the immune system was shown to ameliorate the rejection of skin grafts in rodents and renal grafts in dogs. This weakening was first accomplished with total body irradiation,[82] corticosteroid therapy,[83, 84] and much later, the thiopurine compounds 6-mercaptopurine and azathioprine.[85-89] In these animal trials, however, complete control of rejection with a single modality was rarely achieved without lethal side effects. The same pessimistic conclusion was made from the early clinical trials of renal transplantation[90-97] using total body irradiation, 6-mercaptopurine, or azathioprine.

This discouraging picture changed dramatically during 1962 and 1963 in Colorado, when the synergism of azathioprine and prednisone was discovered from animal in-

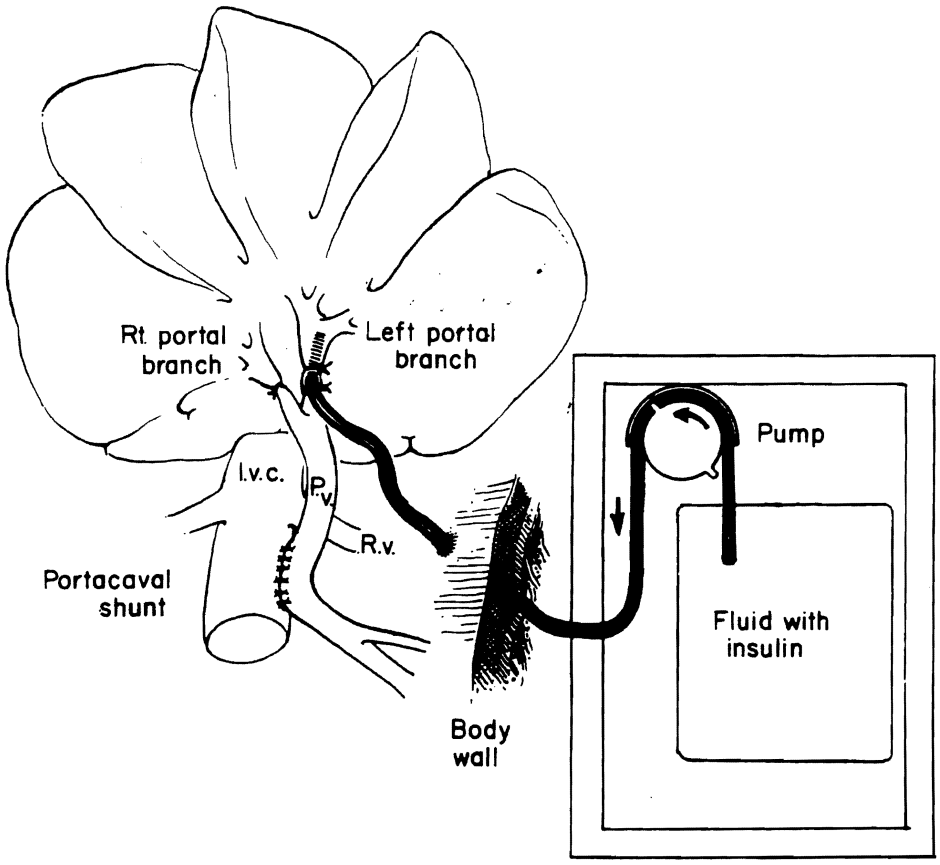

Figure 1-11 Experiments in which postoperative infusions of hormones are made into the left portal vein after performance of Eck's fistula. (From Starzl TE, Watanabe K, Porter KA, Putnam CW. Effects of insulin, glucagon, and insulin/glucagon infusions on liver morphology and cell division after complete portacaval shunt in dogs. Lancet 1:821-825, © by The Lancet Ltd, 1976.)

vestigations.[98] When these two drugs were used together in human kidney transplant recipients,[99, 100] the results precipitated a revolution in clinical transplantation. Rejection could usually be reversed with prednisone, and then the amount of drugs required often lessened with time.[99-102]

The reversibility of rejection and an apparent but unexplained change in host-graft relationship were eventually verified with all other transplanted organs, beginning with the liver.[52, 103] Although immunosuppression has improved, the central therapeutic strategy for whole organ transplantation that had emerged by 1963[99, 100] has changed very little in over 30 years. The dogma calls for daily treatment with one or two baseline drugs, and further immunomodulation with the highly dose-maneuverable adrenocortical steroids to whatever level is required to maintain stable graft function (Table 1-2). Every organ recipient goes through a trial and potential error experience as drug dosages are lowered to achieve maintenance levels.

The principal regimens used clinically within this format for the ensuing 30 years are summarized in Table 1-3.[100-114] Aside from the simplicity and the consequent ease with which the therapeutic formula could be taught, it proved applicable to each new drug regimen or immune-modulating technique used clinically for the next 30 years and to each new organ, of which the liver was the first after the kidney and the intestine is the most recent.

CLINICAL TRIALS OF LIVER TRANSPLANTATION

Phase I: The Failed First Cases

Once the effectiveness of the azathioprine-prednisone cocktail for kidney grafting had been established, a decision was taken at the University of Colorado to move on to the liver.[115, 116] The first recipient was a 3-year-old boy with biliary atresia who had had multiple previous operations. The transplantation could not be completed because of a fatal hemorrhage from venous collaterals and an

TABLE 1-2 **Central therapeutic dogma of immunosuppression**

Strategy	Baseline Agents	Sites of Inhibition
1. Baseline therapy with one or two drugs	1. Azathioprine	DNA synthesis
2. Secondary adjustments with steroids or antilymphoid agents	2. Cyclophosphamide	DNA synthesis
3. Case to case trial (and potential error) of weaning	3. Cyclosporine	Interleukin-2 production
	4. FK506	Interleukin-2 production

TABLE 1-3 **Principal immunosuppressive drug regimens and adjuncts used clinically***

Agents	Year Described and Reported	Place	Deficiencies	Used for Gastrointestinal Organs
Total body irradiation	1960[90]	Boston	Ineffective, dangerous	no
Azathioprine	1962[91]	Boston	Ineffective, dangerous	no
Azathioprine plus steroids	1963[99]	Denver	Suboptimal	yes, liver
Thoracic duct drainage as adjunct	1963[105]	Stockholm	Nuisance: requires 20-30 days pretreatment	yes,† liver
Thymectomy as adjunct	1963[106]	Denver	Unproven value	yes, rarely in 1963
Splenectomy as adjunct	1963[106]	Denver	No longer necessary	yes, once commonly for liver
Antilymphocyte globulin as adjunct	1967[107]	Denver	Suboptimal	yes
Cyclophosphamide substitute for azathioprine	1971[108]	Denver	No advantage except for patients with azathioprine toxicity	yes,‡ liver
Total lymphoid irradiation	1979[109] 1982[110]	Palo Alto, Minneapolis	Dangerous, extensive preparation, not quickly reversible	yes,§ for liver
Cyclosporine	1978-1979[111]	Cambridge	Suboptimal	yes
Cyclosporine plus steroids	1980[112]	Denver	Nephrotoxicity; rejection not always controlled	yes
FK506 plus steroids	1989[114]	Pittsburgh	Nephrotoxicity; rejection not always controlled	yes

*Before 1966, these were developed with kidney transplantation and applied for livers; from 1966 on, the liver increasingly became the dominant test organ.
†It was not realized until much later that pretreatment for 3 to 4 weeks before transplantation was a necessary condition for effective use of thoracic duct drainage.[113]
‡These trials were summarized many years later with at least 10 years of follow-up for surviving patients.[29]
§By Professor J.A. Myburgh of Johannesburg.

uncontrollable coagulopathy (prothrombin time infinity, platelet count $<10{,}000/mm^3$). Even for a team that had been fully prepared for technical vicissitudes by hundreds of animal operations, the exsanguination of this child was a terrible shock.

Two more liver transplantations were carried out in the next 4 months. In both, the procedures seemed satisfactory, but the recipients died after 22 and 7½ days, respectively.[115, 116] The strategy of coagulation control (fresh blood or blood products, and ϵ-aminocaproic acid for fibrinolysis) introduced after the death of the first patient had a delayed backfire in the next recipients in whom it was used. During the time when the livers were sewn in, the plastic external bypasses were used to reroute venous blood around the area of the liver in the same way as had been worked out in dogs. In the humans who were given coagulation-promoting therapy, clots formed in the bypass tubing and passed to the lungs. There they caused abscesses and other lung damage that contributed to or caused delayed death in the first four patients who survived the intraoperative period.[65, 115] A pall settled over the liver program, and a self-imposed moratorium followed that lasted more than 3 years. By this time, isolated attempts made in Boston[117] and Paris[118] had also been unsuccessful.

When these first seven liver transplantations failed in three different centers (Table 1-4), pessimism prevailed worldwide. The operation seemed too difficult to allow practical application. In addition, the methods of preservation were assumed to be inadequate for an organ so seemingly sensitive to ischemic damage. Researchers began to ask whether the available immunosuppression was too primitive to permit success. This possibility was reinforced by the fact that long-term survival after liver replacement had not yet been achieved in experimental animals.

Phase 2: Feasible but Impractical Therapy

By the summer of 1967, these deficiencies had been at least partially rectified by 3 more years of laboratory effort. Many long-term canine survivors had been obtained,[52] and some dogs had passed the 3-year postoperative mark (Fig 1-12). Better immunosuppression with the so-called triple drug therapy was available since the development and first clinical trials of antilymphocyte globulin, which was prepared from sensitized horses[107] and used to supplement azathioprine and prednisone. Finally, techniques of organ preservation for as long as a day had been developed.[119, 120]

TABLE 1-4 **The first seven attempts of clinical orthotopic liver transplantation**

Number	Location (Reference)	Age (Years)	Disease	Survival (Days)	Main Cause of Death
1	Denver[115]	3	Extrahepatic biliary atresia	0	Hemorrhage
2	Denver[115]	48	Hepatocellular cancer, cirrhosis	22	Pulmonary emboli, sepsis
3	Denver[115]	68	Duct cell carcinoma	7½	Sepsis, pulmonary emboli, gastrointestinal bleeding
4	Denver[68]	52	Hepatocellular cancer, cirrhosis	6½	Pulmonary emboli, hepatic failure, pulmonary edema
5	Boston[117]	58	Metastatic colon carcinoma	11	Pneumonitis, liver abscesses, hepatic failure
6	Denver[65]	29	Hepatocellular cancer, cirrhosis	23	Sepsis, bile peritonitis, hepatic failure
7	Paris[118]	75	Metastatic colon carcinoma	0	Hemorrhage

On July 23, 1967, a 1½-year-old child with a huge hepatoma was restored almost immediately from a moribund state to seemingly good health after liver replacement. More cases followed. Most of the attempts made in 1967 and 1968 were initially successful, but all of the patients eventually died; in addition, the first long-term survivor succumbed to recurrent cancer after 400 days. The maximum survival of the other six long-surviving liver recipients treated between July 1967 and March 1968 was 2½ years.[28, 29, 121] For the next 12 years, the 1-year mortality rate after liver transplantation never fell below 50% in cases that were accrued at the University of Colorado at the rate of about one per month. The losses were concentrated in the first postoperative months; after this initial period, the life survival curve flattened, leaving a residual group of stable and remarkably healthy survivors. Thirty (18%) of the first 170 patients in the consecutive series that started March 1, 1963 and ended in December 1979 lived more than ten years; 23 remained alive after 13-23 years. All were treated with azathioprine (or the anti-cancer agent, cyclophosphamide), prednisone, and polyclonal antilymphocyte globulin.[29]

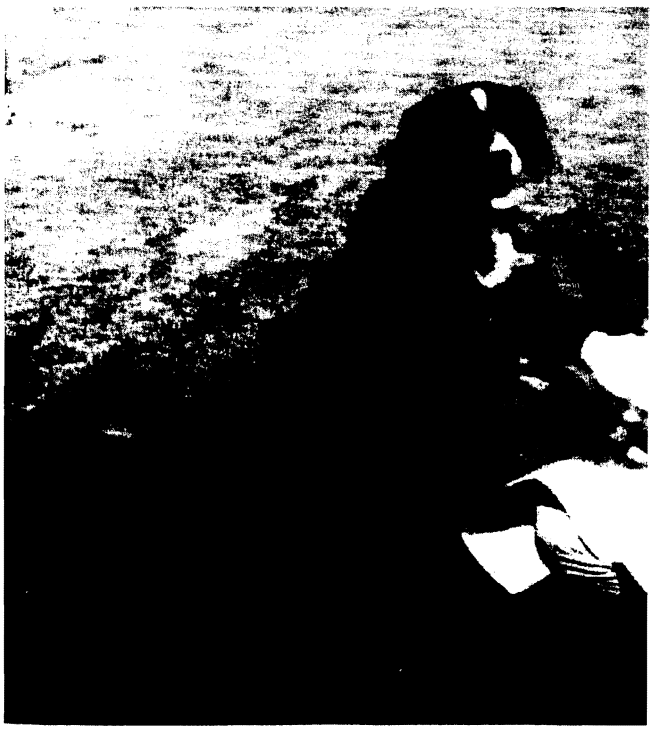

Figure 1-12 Photograph (1968) of a dog whose orthotopic liver transplantation had been carried out in the spring of 1964. The animal died of old age after 11⅔ postoperative years.

In the meantime, Roy Calne of Cambridge University in England began clinical trials of liver transplantation on May 23, 1967. As had been our experience earlier, his first patient exsanguinated.[122] A few months later, Calne formed a collaboration that endured for more than 2 decades with the hepatologist Roger Williams at King's College Hospital in London. The extended survival of patients in both the Colorado and Cambridge-London series was a testimonial for liver transplantation. It was asked increasingly on both sides of the Atlantic, however, if such a small dividend could justify the prodigious effort that had brought liver transplantation this far.[123]

Other teams organized in Hanover (Rudolf Pichlmayr, 1972) and Paris (Henri Bismuth, 1974) also reported the nearly miraculous benefits of liver transplantation when this treatment was successful, but always with the notation that the mortality rate was too high to allow its practical use. Liver transplantation remained a feasible but impractical operation.

Phase 3: The Cyclosporine and FK506 Era

The frustration ended when cyclosporine became available for clinical use in 1979[111] and was combined with prednisone or lymphoid depletion in the first of the cyclosporine-based cocktails.[112] Of our first 12 liver recipients treated with cyclosporine and prednisone in the first 8 months of 1980, 11 lived for more than a year,[124] and 7 were still alive over 12 years later. As the news was confirmed that a 1-year patient survival rate of at least 70% was readily achievable, new liver programs proliferated worldwide.

When FK506 was substituted for cyclosporine in 1989,[114] the 1-year patient and liver graft survival rate rose

again in the Pittsburgh experience,[125] an improvement similar to that in a multicenter European trial. By this time, liver transplantation had become the accepted court of last appeal for almost all non-neoplastic liver disease and even for selected patients with otherwise nonresectable hepatic malignancies. The principal limitation of the technology quickly became the small supply of organs to meet the burgeoning need.

Although the ascension of liver transplantation was dominated by improvements in immunosuppression, there were other significant developments also, including modifications in the details of the operation itself. The incidence of biliary duct complications (obstruction, fistula, and cholangitis), which had been more than 30%,[126] was reduced by the use of choledochocholedochostomy with a T-tube stent or, if this was not feasible, by choledochojejunostomy to a Roux limb.[29] Management of coagulopathies was facilitated by the use of the thromboelastogram to follow the minute-to-minute clotting changes in the operating room.[115, 127] The systematic use of venovenous bypasses without anticoagulation also greatly diminished the occurrence of hemorrhages of nightmare proportions common at one time.

ORGAN PROCUREMENT: HYPOTHERMIA AND CORE COOLING

Although few in number, steps in the development of liver graft procurement and preservation established principles that could be applied to other whole organs. The first was core cooling by infusion of chilled, lactated Ringer's solution into the portal vein,[9] a laboratory technique soon modified for use in clinical kidney transplantation[128] and subsequently for other organs.

Today, core cooling is the initial stage in the preservation of all whole organs. However, in contrast to the original method of skeletonization and removal of the individual grafts before infusion of chilled fluids, core cooling is performed by variations of the in situ technique originally developed before the acceptance of brain death conditions. This technique involved continuous hypothermic perfusion of cadaveric kidney and liver donors[129, 130] (Fig 1-13). Ackerman and Snell[131] and Merkel and colleagues[132] simplified the in situ cooling of cadaveric kidneys with cold electrolyte solutions infused into the distal aorta, without continuous perfusion.

Eventually, in situ cold infusion techniques were perfected that allowed removal of all thoracic and abdominal organs, including the liver, without jeopardizing any of the individual organs[133] (Fig 1-14). Modifications of this procedure were made for unstable donors and even for donors whose hearts had ceased to beat.[134] By 1987, multiple organ procurement techniques were interchangeable not only from city to city but from country to country and had become standardized in all parts of the world. Today, after the chilled organs have been removed, subsequent preservation may be by simple refrigeration or by sophisticated methods of continuous perfusion.

INDICATIONS FOR LIVER TRANSPLANTATION

Benign Disease Categories

By 1989, 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) such as cholestatic disorders and those involving the parenchyma.[135, 135a] Because products of hepatic synthesis permanently retain

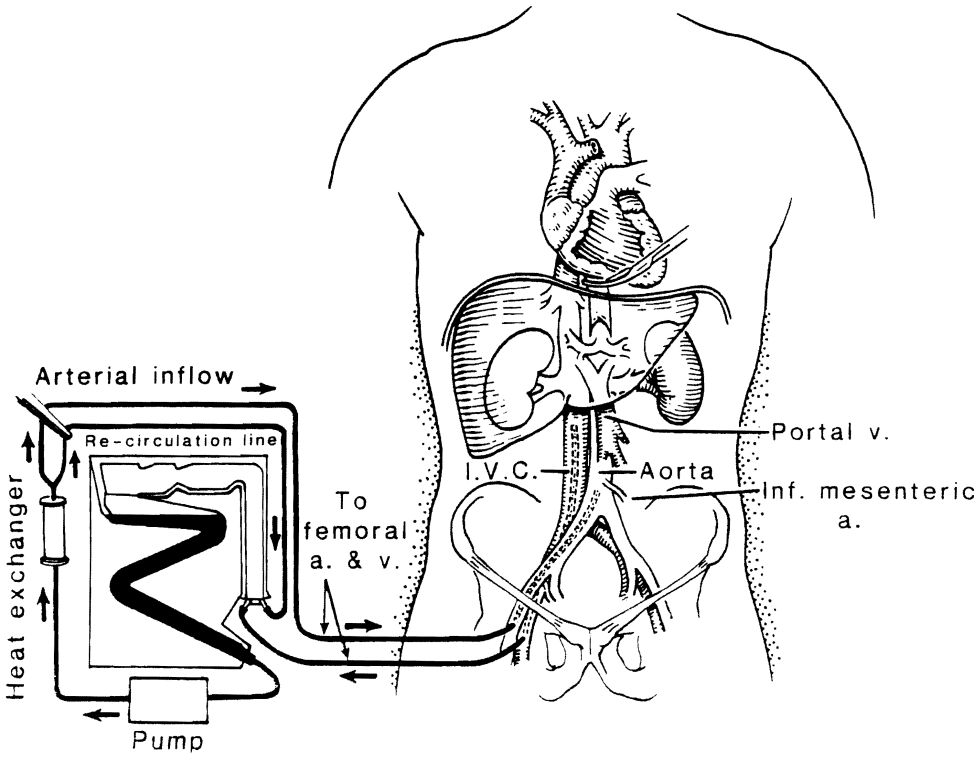

Figure 1-13 The first technique of in situ cooling by extracorporeal hypothermic perfusion. The catheters were inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. Temperature control was provided with a heat exchanger. Crossclamping of the thoracic aorta limited perfusion to the lower part of the body. This method of cadaveric organ procurement was used from 1962 to 1969, before the acceptance of brain death. The preliminary stages of this approach provided the basis for subsequent in situ infusion techniques. (From Starzl TE. Experience in Renal Transplantation. Philadelphia, WB Saunders, 1964, p 56.)

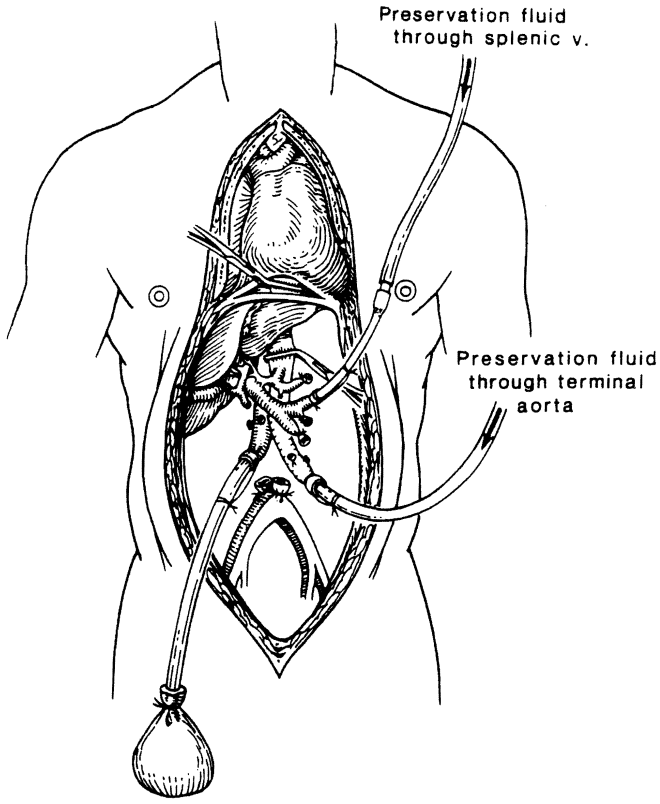

Figure 1-14 Principle of in situ cooling used for multiple organ procurement. With limited preliminary dissection of the aorta and great splanchnic veins (in this case the splenic vein), cold infusates can be used to chill organs in situ. In this case, the kidneys and liver were to be removed. Note the aortic crossclamp above the celiac axis. (Redrawn from Starzl TE, Hakala TR, Shaw BW Jr, et al. A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet 158:223–230, 1984. By permission of Surgery, Gynecology and Obstetrics.)

TABLE 1-5 **Generic listing of liver diseases treatable by liver transplantation**

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

the original metabolic specificity of the donor after transplantation,[135, 136] the correction of inborn errors by liver transplantation can be expected to endure for the life of the graft. Sixteen liver-based or liver-influenced inborn errors of metabolism have been compiled under the inborn error category of indications (Table 1-6).

Trimming the Contraindication List

A number of diseases that precluded transplantation 5-10 years ago, such as alcoholic cirrhosis, are no longer absolute contraindications. Scarring from multiple upper abdominal operations and prior portosystemic shunts have been eliminated as serious adverse factors in major centers. Extensive thrombosis of the portal and superior mesenteric veins, which previously made liver transplantation difficult or impossible, has been almost eliminated as a deterrent to transplantation by the use of vein grafts[137-141] (Fig 1-15). The systematic use of arterial and venous grafts was introduced at the University of Colorado in the 1970s.[137] Harvesting these life-saving conduits was made an integral component of the cadaveric organ procurement procedure thereafter.[133] A particularly useful technique has been the antepancreatic venous jump graft first described by Sheil et al[139] of Sydney (Fig 1-16).

Similarly, inflexible age proscriptions at either the upper or lower range were dropped by the mid-1980s. The shortage of appropriate-sized donors for very small pediatric recipients was greatly ameliorated by the use of liver fragments. The first known reduced liver graft operation was performed in Denver in 1975,[142] but it was not reported until long after the landmark descriptions of this technique by Henri Bismuth and Didier Houssin of Paris[143] and by the team of Rudolf Pichlmayr and Christoph Broelsch et al of Hanover.[144] In 1989, Lynch and Strong successfully transplanted a portion of the left lobe from a living related donor,[145] a procedure further refined and popularized by Broelsch during a stint at the University of Chicago.[146] These liver reduction procedures were facilitated by the use of the *piggyback* principle by which the recipient retrohepatic vena cava is kept intact and the suprahepatic venous outflow of the graft is anastomosed to cuffs of the hepatic veins (Fig 1-17). The piggyback modification was first described by Calne[122] for the transplantation of pediatric livers into adults; it was used sporadically for many years and ultimately popularized by Tzakis et al.[147]

Neoplastic Diseases

The use of conventional liver transplantation to treat otherwise nonresectable primary or metastatic hepatic cancers has resulted in a very high rate of recurrence.[135] Nevertheless, the use of liver transplantation to treat cancer is still being investigated by many transplantation teams, almost invariably in combination with adjuvant

TABLE 1-6 **Inborn errors of metabolism treated with liver transplantation.***

Disease	Explanation of Disease	Longest Survival	Associated Liver 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	16½ yr	Cirrhosis
Tyrosinemia	Fumaroylacetoacetate hydrolase deficiency	7½ 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	4½ yr	Cirrhosis
Cystic fibrosis	Unknown; pancellular disease, liver often affected	4½ yr	Cirrhosis
Niemann-Pick disease	Sphingomyelinase deficiency, sphingomyelin storage	2 yr (died)	None
Sea-blue histiocyte syndrome	Unknown, neurovisceral lipochrome storage	7 yr	Cirrhosis
Erythropoietic protoporphyria	Hepatic ferrochelatase deficiency, ?overproductive of protoporphyrin by erythropoietic tissues	1½ yr	Cirrhosis
Crigler-Najjar syndrome	Glucuronyl transferase deficiency	4 yr	None
Type 1 hyperoxaluria	Peroxisomal alanine:glyoxylate aminotransferase deficiency	8 mo	None
Urea cycle enzyme deficiency (three types)	Ornithine carbamoyltransferase deficiency	8 mo	None
C protein deficiency	Defective C protein synthesis	2¼ 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

From Starzl TE, Demetris AJ, Van Thiel DH. Medical progress: Liver transplantation. Part I, N Engl J Med 321:1014-1022; Part II, 321:1092-1099. Reprinted by permission of *The New England Journal of Medicine*, 1989. Copyright 1989, Massachusetts Medical Society.
*Most of the patients were in the University of Colorado-University of Pittsburgh series. Follow-up to January 1989.

chemotherapy or other experimental treatment protocols. Certain kinds of neoplasms have a better prognosis than others (Chapter 12). A radical extension of this attempt to increase the perimeter of resectability is the removal of upper abdominal organs en bloc (liver, pancreas, spleen, stomach, duodenum, proximal jejunum, and right colon) (Fig 1-18) to treat extensive sarcomas and carcinoid tumors that are still regionally confined.[148] The excised organs are replaced with hepatopancreaticoduodenal grafts (Fig 1-19) or, in some cases, by the liver alone.

CLINICAL TRIALS OF INTESTINAL TRANSPLANTATION WITH THE LIVER IN COMPOSITE VISCERAL GRAFTS OR ALONE

Composite Grafts

Function of a cadaveric intestine for more than 6 months was not accomplished until 1987. In November of that year, a recipient of a multivisceral graft who was treated with cyclosporine, prednisone, and the antilymphoid agent OKT3 survived for 192 days before dying of a B cell

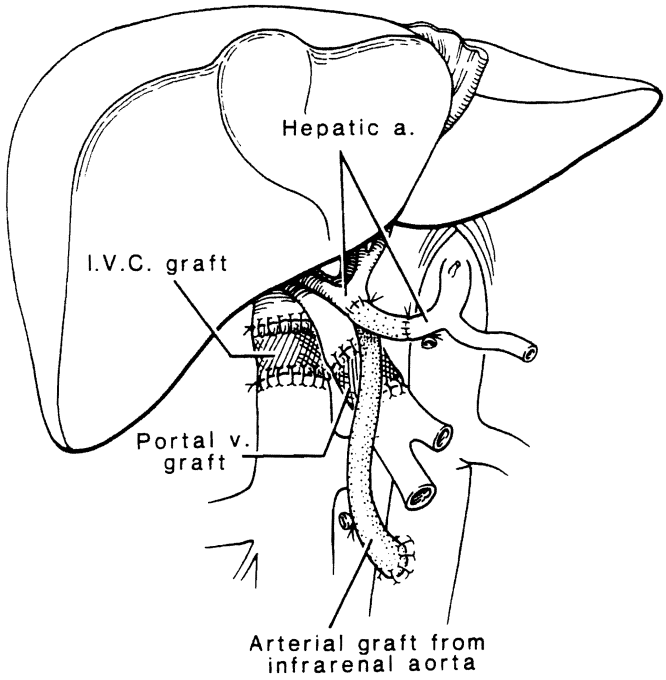

Figure 1-15 By 1979, all of the demonstrated grafts had been used clinically. The use of vascular grafts has been life saving; liver transplantation should never be attempted without an emergency assortment of these grafts. (Redrawn from Starzl TE, Halgrimson CG, Koep LJ, et al. Vascular homografts from cadaveric organ donors. Surg Gynecol Obstet 149:76-77, 1979. By permission of Surgery, Gynecology and Obstetrics.)

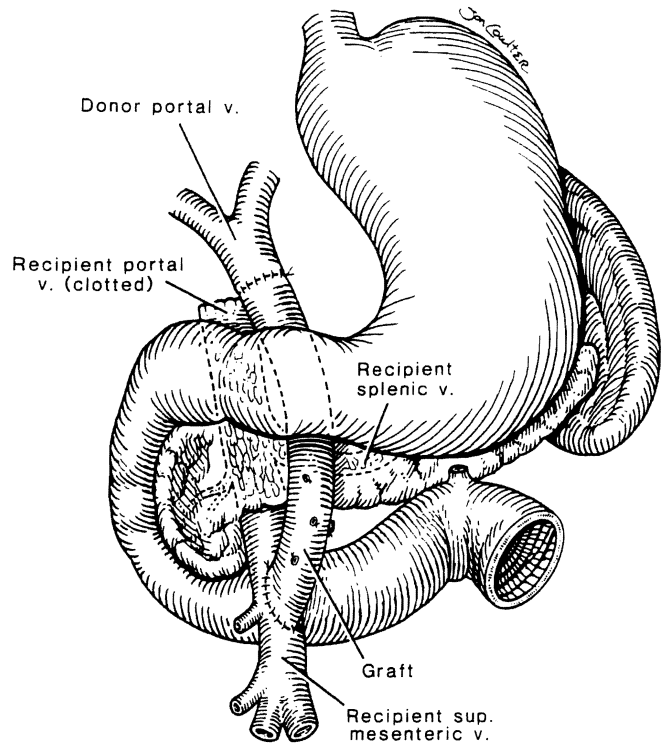

Figure 1-16 An antepancreatic route for a vascular graft placed onto the infrarenal abdominal aorta, as originally described by Sheil.[139] The graft is brought to the right or left of the middle colic vessels, anterior to the pancreas and beneath the pylorus. (From Tzakis A, Todo S, Steiber A, Starzl TE. Venous jump grafts for liver transplantation in patients with portal vein thrombosis. Transplantation 48:530-531, 1989.)

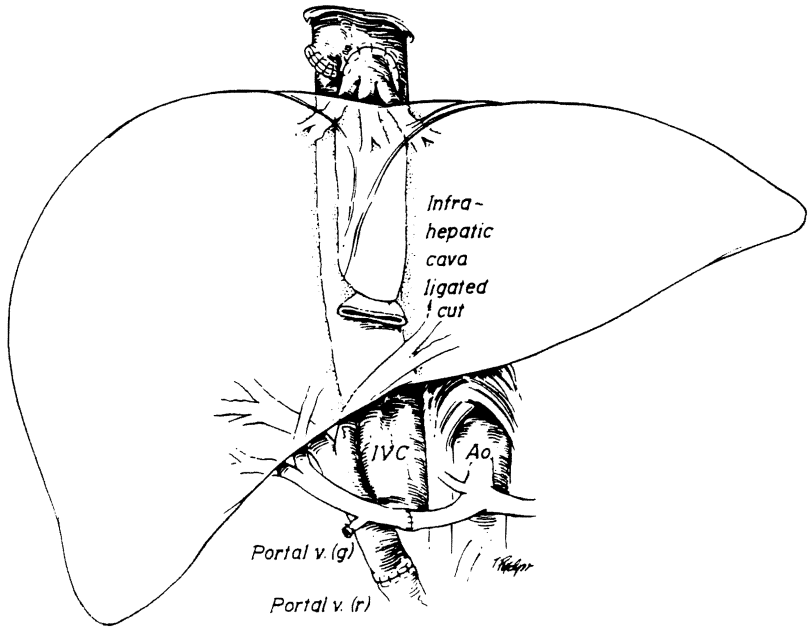

Figure 1-17 Transplantation of a liver piggybacked onto an inferior vena cava, which is preserved through its length. Note that the suprahepatic vena cava of the homograft is anastomosed to the anterior wall of the recipient vena cava. The retrohepatic vena cava of the homograft is sutured or ligated, 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.)

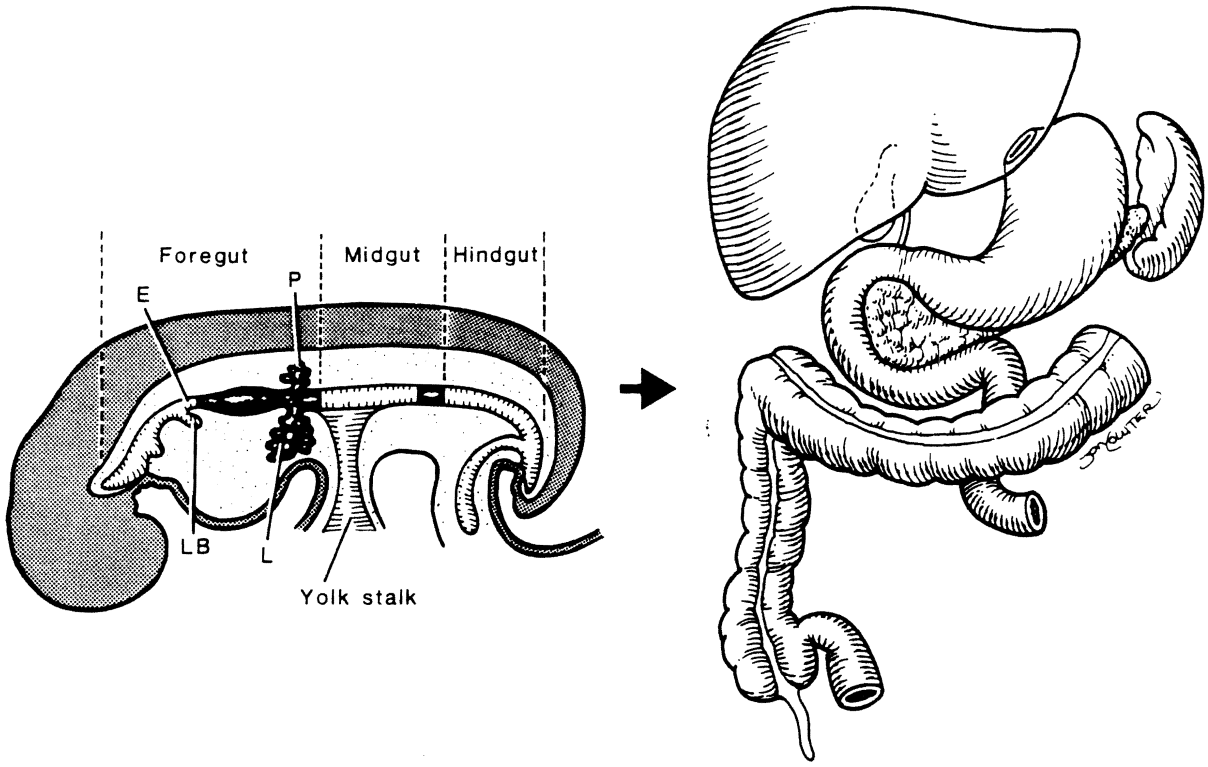

Figure 1-18 Delineation in embryonal life (*left*) of that region of the gastrointestinal tract (darkly shaded) that was resected in an organ cluster operation (E = esophagus; LB = lung bud; L = liver; P = pancreas). The adult organs (*right*) deriving from the shaded primitive analog are shown. (From Starzl TE, Todo S, Tzakis A. Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 210:374-386, 1989.)

lymphoma.[55] Several subsequent recipients of the full multivisceral graft (see Fig 1-6, *left*) are alive after as long as 17 months under treatment with FK506.[149]

A variant procedure in which only the liver and small bowel are retained (see Fig 1-1*c* and Fig 1-6, *right*) was first described and used successfully by Grant and coworkers[150] of London, Ontario (Canada). This operation has been particularly useful in patients with the short gut syndrome who developed liver failure after prolonged hyperalimentation.[43] With the use of FK506, 13 (76.5%) of 17 patients treated by Starzl and colleagues[149] in the Pittsburgh series of liver-intestine grafts were alive after 5-31 months, and all but one had been liberated from total parenteral nutrition.

Intestinal Transplantation Alone

As recently as late 1991, some workers in the field believed that the protection to the intestine afforded by the concomitant transplantation of the liver from the same donor (see earlier) was sufficiently great to justify combined liver and intestinal transplantation even when only a technically simpler intestinal transplant was needed. Enthusiasm for this draconian strategy began to fade with the successful transplantation in March 1989 of a cadaveric small intestine by Goulet and colleagues[42] of Paris, and of an ileal segment from a living related donor by Deltz et al of Kiel, Germany.[151]

These were isolated straws in the wind. In Pittsburgh, the routine survival of cadaveric intestinal recipients then became possible under immunosuppression with FK506; the results have been better with isolated intestinal transplantation than with either the multivisceral operation or its liver-intestine variant.[43, 149, 152] Eight of nine such recipients are alive, several after 1-2 years, and all but one are free from total parenteral nutrition. The expected release of FK506 for general use in the near future is certain to stimulate rapid further development of the intestinal transplantation field.

Metabolic Interactions

Normally, the venous effluent from all nonhepatic splanchnic organs contributes to the portal blood supply, assuring the liver first-pass exposure to the intestinal nutrients and to the so-called portal hepatotrophic substances of which insulin is the most important. This factor, which is operational for native livers and transplanted ones, should be considered in any intra-abdominal visceral transplantation, whether it be of the liver or intestine alone or one of the multivisceral procedures that alter the portal circulation.

For example, when partial multivisceral grafts such as that of the liver and intestine are used in recipients whose pancreas and other upper abdominal organs are retained, it is preferable to direct the venous effluent from the resid-

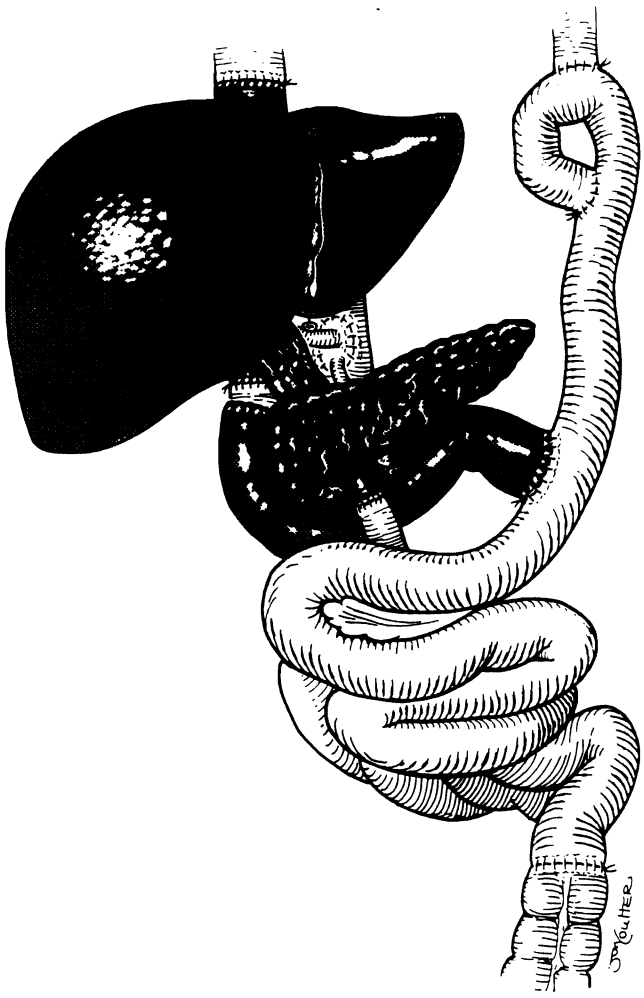

Figure 1-19 Completed reconstruction in the recipient after a cluster resection (upper abdominal exenteration). (From Starzl TE, Todo S, Tzakis A. Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 210:374-386, 1989.)

ual host organs into the portal circulation of the new liver (see Fig 5*B*). If this is not done, injury to the liver that is typical of, although less severe than, that caused by Eck's fistula can occur. Similarly, when the intestine is transplanted alone, the ideal route of graft venous return is through the native liver. However, the inability to drain intestinal return into the host liver for technical reasons has not caused severe hepatic complications in a small number of human recipients.[43]

MECHANISM OF GRAFT ACCEPTANCE

Throughout the modern history of transplantation, it was not known how grafts were able, with the aid of immunosuppression, to resist the onslaught of rejection and later merge half forgotten into the host. In 1992, the study of liver, kidney, and other organ recipients who had survived for as long as 3 decades provided unique insights into this process (Chapter 27). In all successful cases, donor leukocytes (principally dendritic cells) could be demonstrated in the skin lymph nodes, heart, and other tissues of the long-surviving hosts.

These chimeric cells that had emigrated from the grafts and then perpetuated themselves for many years were present in larger numbers at any given peripheral site in liver recipients than in patients carrying other transplanted organs, such as the kidney.[153-156] The heavy endowment of the liver with these potentially migratory cells is now thought to be the basis for hepatic tolerogenicity, which allows the liver to induce its own acceptance more readily than other organs can. In some experimental models, graft acceptance has occurred without immunosuppression. This mechanism of acceptance is postulated to be the basis by which donor livers shield concomitantly transplanted organs from rejection and even resist the attack of preformed antibodies. These discoveries have necessitated a paradigm shift in many aspects of transplantation immunology, as discussed in Chapter 27.

WHOLE ORGAN XENOTRANSPLANTATION

When organs are transplanted from a significantly disparate species, the first immunologic hurdle is that of preformed xenospecific antibodies that quickly devascularize the graft and exclude it from recipient circulation by damaging its blood vessels.[157] The liver is subject to this humoral (hyperacute) rejection, but it was demonstrated more than 20 years ago to be unusually resistant to the injury caused by antigraft antibodies.[158] When the antibody barrier is surmounted, as has been possible with the adjuvant use of antimetabolite drugs such as cyclophosphamide,[159] the subsequent events of xenograft acceptance involve the same cell migration and consequent systemic chimerism as with allotransplantation.[157]

Human liver xenotransplantation using chimpanzee donors[160] was attempted three times between 1966 and 1973 with deaths after 0, 9, and 14 days.[161] The clinical evolution and histopathological findings were indistinguishable from those after allotransplantation. Two additional hepatic xenotransplantations were attempted, in June 1992 and January 1993, with the phylogenetically more distant baboon donor. Survival was 70 and 26 days.[162, 163] Neither antibody nor cell-mediated rejection could be indicted as the cause of death of these patients; both of them had systemic chimerism in life and at autopsy. However, neither xenograft functioned optimally, and both developed findings of intrahepatic cholestasis within the first postoperative week. The dichotomy of histopathological findings and clinical course has raised suspicions that synthetic products of the baboon liver may have been incompatible with the human metabolic environment. If so, the main importance of this experience may have been as a forerunner to xenotransplantation of metabolically less complex organs such as the kidney and heart.

The author's present opinion, however, is that the inadequate graft function was related to the early injury of these organs by inflammatory mediators triggered by preformed xenospecific antibodies (principally immunoglobulin M) and complement activation. This pathogenesis is similar to that defined 25 years ago as the basis for hyperacute rejection of kidney allografts[164, 165] and, more re-

cently, the humoral rejection of liver allografts.[166, 167] The use of a new generation of complement inhibitors[168] may provide the missing piece in the treatment mosaic that will make liver xenotransplantation possible.[169]

References

1. Terasaki PI. History of Transplantation: Thirty-Five Recollections. Los Angeles, UCLA Tissue Typing Laboratory, 1991.
2. Welch CS. A note on transplantation of the whole liver in dogs. Transplant Bull 2:54–55, 1955.
3. Cannon JA. Brief report. Transplant Bull 3:7, 1956.
4. Goodrich EO Jr, Welch HF, Nelson JA, et al. Homotransplantation of the canine liver. Surgery 39:244–251, 1956.
5. Woodruff WMA. The Transplantation of Tissues and Organs. Springfield, IL, Charles C Thomas, 1960.
6. Moore FD, Smith LL, Burnap TK, et al. One-stage homotransplantation of the liver following total hepatectomy in dogs. Transplant Bull 6:103–110, 1959.
7. Moore FD, Wheeler HB, Demissianos HV, et al. Experimental whole organ transplantation of the liver and of the spleen. Ann Surg 152:374–387, 1960.
8. McBride RA, Wheeler HB, Smith LL, et al. Homotransplantation of the canine liver as an orthotopic vascularized graft. Histologic and functional correlations during residence in the new host. Am J Pathol 41:501–520, 1962.
9. 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.
10. 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.
11. Moore FD. Give and Take: The Development of Tissue Transplantation. Philadelphia, WB Saunders, 1964.
12. Meyer WH Jr, Starzl TE. The reverse portacaval shunt. Surgery 45:531–534, 1959.
13. Meyer WH Jr, Starzl TE. The effect of Eck and reverse Eck fistula in dogs with experimental diabetes mellitus. Surgery 45:760–764, 1959.
14. Starzl TE. A trip south. In Starzl TE. Puzzle People: Memoirs of a Transplant Surgeon. Pittsburgh, University of Pittsburgh Press, 1992, pp 47–58.
15. Starzl TE, Francavilla A, Halgrimson CG, et al. The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. Surg Gynecol Obstet 137:179–199, 1973.
16. Starzl TE, Porter KA, Francavilla A. The Eck fistula in animals and humans. Curr Probl Surg 20:687–752, 1983.
17. Starzl TE, Bernhard VM, Benvenuto R, Cortes N. A new method for one-stage hepatectomy in dogs. Surgery 46:880–886, 1959.
18. Starzl TE. In Moore et al (Reference 7) Discussion Ann Surg 152:386–387, 1960.
19. Groth CG, Porter KA, Otte JB, et al. Studies of blood flow and ultrastructural changes in rejecting and nonrejecting canine orthotopic liver homografts. Surgery 63:31–38, 1968.
20. Brettschneider L, Tong JL, Boose DS, et al. Specific bacteriologic problems after orthotopic liver transplantation in dogs and pigs. Arch Surg 97:313–322, 1968.
21. Starzl TE. Infectious complications, excluding partial hepatic gangrene. In Starzl TE, ed. Experience in Hepatic Transplantation. Philadelphia, WB Saunders, 1969, pp 329–347.
22. Wall WJ, Calne RY, Berbertson BM, et al. Simple hypothermic preservation for transporting human livers long distance for transplantation. Transplantation 23:210–216, 1977.
23. Benichou J, Halgrimson CG, Weil R III, et al. Canine and human liver preservation for 6 to 18 hours by cold infusion. Transplantation 24:407–411, 1977.
24. Jamieson NV, Sundberg R, Lindell, S, et al. Successful 24- to 30-hour preservation of the canine liver: A preliminary report. Transplant Proc 20(Suppl 1):945–947, 1988.
25. Kalayoglu M, Sollinger WH, Stratta RJ, et al. Extended preservation of the liver for clinical transplantation. Lancet 1:617–619, 1988.
26. Todo S, Nery J, Yanaga K, et al. Extended preservation of human liver grafts with UW solution. JAMA 261:711–714, 1989.
27. Picache RS, Kapur BML, Starzl TE. The effect of liver disease on the need for venous decompression during the anhepatic phase of canine orthotopic liver transplantation. Surgery 67:319–321, 1970.
28. Starzl TE, Groth CG, Brettschneider L, et al. Orthotopic homotransplantation of the human liver. Ann Surg 168:392–415, 1968.
29. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. Hepatology 2:614–636, 1982.
30. Cutropia F, Coratolo F, Spinetta A, et al. Experimental orthotopic liver transplantation. Rev Esp Enferm Apar Dig 38:553–570, 1972.
31. Denmark SW, Shaw BW, Starzl TE, Griffith BP. Veno-venous bypass without systemic anticoagulation in canine and human liver transplantation. Surg Forum 34:380–382, 1983.
32. Shaw BW, Martin DJ, Marquez JM, et al. Venous bypass in clinical liver transplantation. Ann Surg 200:524–534, 1984.
33. Griffith BP, Shaw BW, Hardesty RL, et al. Veno-venous bypass without systemic anticoagulation for transplantation of the human liver. Surg Gynecol Obstet 160:270–272, 1985.
34. Starzl TE, Groth CG, Makowka L, eds: Clio Chirurgica, Part III, The Human Trials. Austin, TX, Silvergirl, Inc, 1988, pp 164–278.
35. Carrel A. La technique opératoire des anastomoses vasculaires et la transplantation des viscères. Lyon MEO 98:859–864, 1902.
36. Lillehei RC, Goott B, Miller FA. The physiologic response of the small bowel of the dog to ischemia, including prolonged in vitro preservation of the bowel with successful replacement and survival. Ann Surg 150:543–560, 1959.
37. Craddock GN, Nordgren SR, Reznick RD, et al. Small bowel transplantation in the dog using cyclosporine. Transplantation 35:284–288, 1983.
38. Grant D, Duff J, Zhong R, et al. Successful intestinal transplantation in pigs treated with cyclosporine. Transplantation 45:279–284, 1988.
39. Diliz-Perez HS, McClure J, Bedeti C, et al. Successful small bowel allotransplantation in dogs with cyclosporine and prednisone. Transplantation 37:126–129, 1984.
40. Deltz E, Ulrich K, Schach T, et al. Graft-versus-host reaction in small bowel transplantation and possibilities for its circumvention. Am J Surg 151:379–386, 1986.
41. Ricour C, Revillon Y, Arnaud-Battandier F, et al. Successful small bowel allografts in piglets using cyclosporine. Transplant Proc 15:3019–3026, 1983.
42. Goulet O, Revillon Y, Brousse N, et al. Successful small bowel transplantation in an infant. Transplantation 53:940–943, 1992.
43. Todo S, Tzakis AG, Abu-Elmagd K, et al. Intestinal transplantation in composite visceral grafts or alone. Ann Surg 216:223–234, 1992.
44. Starzl TE, Kaupp HA Jr. Mass homotransplantation of abdominal organs in dogs. Surg Forum 11:28–30, 1960.
45. Starzl TE, Todo S, Tzakis A, et al. The many faces of multivisceral transplantation. Surg Gynecol Obstet 172:335–344, 1991.
46. Starzl TE, Kaupp HA Jr, Brock DR, et al. Homotransplantation of multiple visceral organs. Am J Surg 103:219–229, 1962.
47. Calne RY, Sells RA, Pena Jr, et al. Induction of immunological tolerance by porcine liver allografts. Nature 223:472–474, 1969.
48. Kamada N. The immunology of experimental liver transplantation in the rat. Immunology 55:369–389, 1985.
49. Valdivia LA, Demetris AJ, Fung JJ, et al. Successful hamster to rat liver xenotransplantation under FK506 immunosuppression induces unresponsiveness to hamster heart and skin. Transplantation 55:659–661, 1993.
50. Billingham R, Brent L. Quantitative studies on transplantation immunity. IV. Induction of tolerance in newborn mice and studies on the phenomenon of runt disease. Philos Trans R Soc Lond (Biol) 242:439–477, 1956.
51. Trentin JJ. Mortality and skin transplantability in X-irradiated mice receiving isologous or heterologous bone marrow. Proc Soc Exp Biol Med 92:688–693, 1956.
52. Starzl TE, Marchioro TL, Porter KA, et al. Factors determining short- and long-term survival after orthotopic liver homotransplantation in the dog. Surgery 58:131–155, 1965.
53. Ramsey G, Nusbacher J, Starzl TE, Lindsay GD. Isohemagglutinins of graft origin after ABO-unmatched liver transplantation. New Engl J Med 311:1167–1170, 1984.
54. Monchik GJ, Russell PS. Transplantation of the small bowel in the rat: Technical and immunologic considerations. Surgery 70:693–702, 1971.
55. Starzl TE, Rowe M, Todo S, et al. Transplantation of multiple abdominal viscera. JAMA 26:1449–1457, 1989.
56. Houssay BA: Technique de la greffe pancréaticoduodenal au cou. C R Soc Biol 100:138–140, 1929.
57. DeJode LR, Howard JM: Studies in pancreaticoduodenal homotransplantation. Surg Gynecol Obstet 114:553–558, 1962.
58. Idezuki Y, Feemster JA, Dietzman RH, Lillehei RC. Experimental pancreaticoduodenal preservation and transplantation. Surg Gynecol Obstet 126:1002–1014, 1968.
59. Kelly WD, Lillehei RC, Merkel FK, et al. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 61:827–837, 1967.
60. Putnam CW, Porter KA, Starzl TE. Hepatic encephalopathy and light and electron micrographic changes of the baboon liver after portal diversion. Ann Surg 184:155–161, 1976.
61. Mann FC: The William Henry Welch Lectures: II. Restoration and pathologic reactions of the liver. J Mt Sinai Hosp 11:65–74, 1944.
62. Child CG, Barr D, Holswade GR, Harrison CS. Liver regeneration following portacaval transposition in dogs. Ann Surg 138:600–608, 1953.
63. Fisher B, Russ C, Updegraff H, Fisher ER. Effect of increased hepatic blood flow upon liver regeneration. Arch Surg 69:263–272, 1954.
64. Bollman JL. The animal with an Eck fistula. Physiol Rev 41:607–621, 1961.
65. Starzl TE, Marchioro TL, Rowlands DT Jr, et al. Immunosuppression after experimental and clinical homotransplantation of the liver. Ann Surg 160:411–439, 1964.
66. Marchioro TL, Porter KA, Dickinson TC, et al. Physiologic requirements for auxiliary liver homotransplantation. Surg Gynecol Obstet 121:17–31, 1965.

67. Marchioro TL, Porter KA, Brown BI, et al. The effect of partial portacaval transposition on the canine liver. Surgery 61:723–732, 1967.
68. Starzl TE, Francavilla A, Halgrimson CG, et al. The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood. Surg Gynecol Obstet 137:179–199, 1973.
69. Starzl TE, Porter KA, Kashiwagi N, et al. The effect of diabetes mellitus on portal blood hepatotrophic factors in dogs. Surg Gynecol Obstet 140:549–562, 1975.
70. Starzl TE, Porter KA, Kashiwagi N, Putnam CW. Portal hepatotrophic factors, diabetes mellitus and acute liver atrophy, hypertrophy and regeneration. Surg Gynecol Obstet 141:843–858, 1975.
71. Starzl TE, Lee IY, Porter KA, Putnam CW. The influence of portal blood upon lipid metabolism in normal and diabetic dogs and baboons. Surg Gynecol Obstet 140:381–396, 1975.
72. Starzl TE, Francavilla A, Porter KA, Benichou J. The effect upon the liver of evisceration with or without hormone replacement. Surg Gynecol Obstet 146:524–531, 1978.
73. Starzl TE, Francavilla A, Porter KA, et al. The effect of splanchnic viscera removal upon canine liver regeneration. Surg Gynecol Obstet 147:193–207, 1978.
74. Starzl TE, Watanabe K, Porter KA, Putnam CW. Effects of insulin, glucagon, and insulin/glucagon infusions on liver morphology and cell division after complete portacaval shunt in dogs. Lancet 1:821–825, 1976.
75. Starzl TE, Jones AF, Terblanche J, et al. Growth-stimulating factor in regenerating canine liver. Lancet 1:127–130, 1979.
76. Francavilla A, Starzl TE, Porter K, et al. Screening for candidate hepatic growth factors by selective portal infusion after canine Eck fistula. Hepatology 14:665–670, 1991.
77. Mazzaferro V, Porter KA, Scotti-Foglieni CL, et al. The hepatotrophic influence of cyclosporine. Surgery 107:533–539, 1990.
78. Starzl TE, Porter KA, Mazzaferro V, et al. Hepatotrophic effects of FK 506 in dogs. Transplantation 51:67–70, 1991.
79. Starzl TE, Terblanche J. Hepatotrophic substances. In Popper H, Schaffner F, eds. Progress in Liver Diseases, Vol 6. New York, Grune & Stratton, 1979, pp 135–152.
80. Medawar PB. The behavior and fate of skin autografts and skin homografts in rabbits. J Anat 78:176–199, 1944.
81. Medawar PB. Second study of behavior and fate of skin homografts in rabbits. J Anat 79:157, 1945.
82. Dempster WJ, Lennox B, Boag JW. Prolongation of survival of skin homotransplants in the rabbit by irradiation of the host. Br J Exp Pathol 31:670–679, 1950.
83. Billingham RE, Krohn PL, Medawar PB. Effect of cortisone on survival of skin homografts in rabbits. Br Med J 1:1157–1163, 1951.
84. Morgan JA. The influence of cortisone on the survival of homografts of skin in the rabbit. Surgery 30:506–515, 1951.
85. Meeker WR, Condie R, Weiner D, et al. Prolongation of skin homograft survival in rabbits by 6-mercaptopurine. Proc Soc Exp Biol Med 102:459–461, 1959.
86. Schwartz R, Dameshek W. The effects of 6-mercaptopurine on homograft reactions. J Clin Invest 39:952–958, 1960.
87. Calne RY. The rejection of renal homografts: Inhibition in dogs by 6-mercaptopurine. Lancet 1:417–418, 1960.
88. Zukoski CF, Lee HM, Hume DM. The prolongation of functional survival of canine renal homografts by 6-mercaptopurine. Surg Forum 11:470–472, 1960.
89. Calne RY, Murray JE. Inhibition of the rejection of renal homografts in dogs by Burroughs Wellcome 57–322. Surg Forum 12:118–120, 1961.
90. Murray JE, Merrill JP, Dammin GJ, et al. Study of transplantation immunity after total body irradiation: Clinical and experimental investigation. Surgery 48:272–284, 1960.
91. Murray JE, Merrill JP, Dammin GJ, et al. Kidney transplantation in modified recipients. Ann Surg 156:337–355, 1962.
92. Murray JE, Merrill JP, Harrison JH, et al. Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. N Engl J Med 268:1315–1323, 1963.
93. Woodruff MFA, Robson JS, Nolan B, et al. Homotransplantation of kidney in patients treated with preoperative administration of antimetabolite (Imuran). Lancet 2:675–682, 1963.
94. Goodwin WE, Martin DC. Transplantation of the kidney. Urol Surv 13:229–248, 1963.
95. Groth CG. Landmarks in clinical renal transplantation. Surg Gynecol Obstet 134:323–328, 1972.
96. Hamburger J, Vaysse J, Crosnier J, et al. Renal homotransplantation in man after radiation of the recipient. Am J Med 32:854–871, 1962.
97. Kuss R, Legrain M, Mathe G, et al. Homologous human kidney transplantation. Experience with six patients. Postgrad Med J 38:528–531, 1962.
98. Marchioro TL, Axtell HK, LaVia MF, et al. The role of adrenocortical steroids in reversing established homograft rejection. Surgery 55:412–417, 1964.
99. Starzl TE, Marchioro TL, Waddell WR. The reversal of rejection in human renal homografts with subsequent development of homograft tolerance. Surg Gynecol Obstet 117:385–395, 1963.
100. Starzl TE. Experience in Renal Transplantation. Philadelphia, WB Saunders, 1964.
101. Starzl TE, Schroter GPJ, Hartmann NJ, et al. Long term (25 year) survival after renal homotransplantation—the world experience. Transplant Proc 22:2361–2365, 1990.
102. Hume DM, Magee JH, Kauffman HM, et al. Renal transplantation in man in modified recipients. Ann Surg 158:608–644, 1963.
103. Starzl TE. Early liver rejection in patients without hepatic gangrene. In Starzl TE, ed. Experience in Hepatic Transplantation. Philadelphia, WB Saunders, 1969, pp 277–307.
104. Starzl TE. Immunosuppression in man. In Starzl TE, ed. Experience in Hepatic Transplantation. Philadelphia, WB Saunders, 1969, pp 242–276.
105. Franksson C. Survival of homografts of skin in rats depleted of lymphocytes by chronic drainage from the thoracic duct. Lancet 1:1331–1332, 1984.
106. Starzl TE, Marchioro TL, Talmage DW, Waddel WR. Splenectomy and thymectomy in human renal transplantation. Proc Soc Exp Biol Med 113:929–932, 1963.
107. Starzl TE, Marchioro TL, Porter KA, et al. The use of heterologous antilymphoid agents in canine renal and liver homotransplantation and in human renal homotransplantation. Surg Gynecol Obstet 124:301–318, 1967.
108. Starzl TE, Putnam CW, Halgrimson CG, et al. Cyclophosphamide and whole organ transplantation in humans. Surg Gynecol Obstet 133:981–991, 1971.
109. Strober S, Slavin S, Fuks Z, et al. Transplantation tolerance after total lymphoid irradiation. Transplant Proc 11:1032–1038, 1979.
110. Najarian JS, Ferguson RM, Sutherland DE, et al. Fractionated total lymphoid irradiation as preparative immunosuppression in high risk renal transplantation. Ann Surg 196:442–452, 1982.
111. Calne RY, Rolles K, White DJG, et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet 2:1033–1036, 1979.
112. Starzl TE, Weil R III, Iwatsuki S, et al. The use of cyclosporin A and prednisone in cadaver kidney transplantation. Surg Gynecol Obstet 151:17–26, 1980.
113. Starzl TE, Weil R III, Koep LJ, et al. Thoracic duct drainage before and after cadaveric kidney transplantation. Surg Gynecol Obstet 149:815–821, 1979.
114. Starzl TE, Todo S, Fung J, et al. FK506 for human liver, kidney, and pancreas transplantation. Lancet 2:1000–1004, 1989.
115. Starzl TE, Marchioro TL, Von Kaulla KN, et al. Homotransplantation of the liver in humans. Surg Gynecol Obstet 117:659–676, 1963.
116. Starzl TE. The failed liver transplantation trials. In Starzl TE. Puzzle People: Memoirs of a Transplant Surgeon. Pittsburgh, University of Pittsburgh Press, 1992, pp 96–105.
117. Moore FD, Birtch AG, Dagher F, et al. Immunosuppression and vascular insufficiency in liver transplantation. Ann N Y Acad Sci 102:729–738, 1964.
118. Demirleau, Noureddine, Vignes, et al. Tentative d'homogreffe hépatique (Attempted hepatic homograft). Mem Acad Chir (Paris) 90:177–179, 1964.
119. Starzl TE. The donors and the organs. In Starzl TE. Puzzle People: Memoirs of a Transplant Surgeon. Pittsburgh, University of Pittsburgh Press, 1992, pp 145–154.
120. 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.
121. Starzl TE. A Pyrrhic victory. In Starzl TE. Puzzle People: Memoirs of a Transplant Surgeon. Pittsburgh, University of Pittsburgh Press, 1992, pp 162–172.
122. Calne RY, Williams R: Liver transplantation in man. I. Observations on technique and organization in five cases. BMJ 4:535–550, 1968.
123. Starzl TE. Icebergs and hammer blows. In Starzl TE. Puzzle People: Memoirs of a Transplant Surgeon. Pittsburgh, University of Pittsburgh Press, 1992, pp 173–196.
124. Starzl TE, Klintmalm GBG, Porter KA, et al. Liver transplantation with the use of cyclosporin A and prednisone. N Engl J Med 305:266–269, 1981.
125. Todo S, Fung JJ, Starzl TE, et al. Liver, kidney, and thoracic organ transplantation under FK506. Ann Surg 212:295–305, 1990.
126. Starzl TE, Putnam CW, Hansbrough JF, et al. Biliary complications after liver transplantation: With special reference to the biliary cast syndrome and techniques of secondary duct repair. Surgery 81:212–221, 1977.
127. Kang YG, Martin DJ, Marquez J, et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 64:888–896, 1985.
128. Starzl TE. Experience in Renal Transplantation. Philadelphia, WB Saunders, 1964, pp 68–71.
129. Marchioro TL, Huntley RT, Waddell WR, Starzl TE. Extracorporeal perfusion for obtaining postmortem homografts. Surgery 54:900–911, 1963.
130. Starzl TE. Experience in Hepatic Transplantation. Philadelphia, WB Saunders, 1969, pp 45–48.
131. Ackerman JR, Snell ME. Cadaveric renal transplantation. Br J Urol 40:515–521, 1968.
132. Merkel FK, Jonasson O, Bergan JJ. Procurement of cadaver donor organs. Evisceration technique. Transplant Proc 4:585–589, 1972.
133. Starzl TE, Hakala TR, Shaw BW Jr, et al. A flexible procedure for multiple cadaveric organ procurement. Surg Gynecol Obstet 158:223–230, 1984.
134. Starzl TE, Miller C, Broznick B, Makowka L. An improved technique for multiple organ harvesting. Surg Gynecol Obstet 165:343–348, 1987.
135. Starzl TE, Demetris AJ, Van Thiel DH. Medical progress: Liver transplantation, Part I. N Engl J Med 321:1014–1022, 1989.

135a. Starzl TE, Demetris AJ, Van Thiel DH. Medical progress: Liver transplantation, Part II. N Engl J Med 321:1092–1099, 1989.
136. Starzl TE. The little drummer girls. In Starzl TE. Puzzle People: Memoirs of a Transplant Surgeon. Pittsburgh, University of Pittsburgh Press, 1992, pp 318–333.
137. Starzl TE, Halgrimson CG, Koep LJ, et al. Vascular homografts from cadaveric organ donors. Surg Gynecol Obstet 149:737, 1979.
138. Shaw BW Jr, Iwatsuki S, Bron K, Starzl TE. Portal vein grafts in hepatic transplantation. Surg Gynecol Obstet 161:66–68, 1985.
139. Sheil AGR, Thompson JF, Stevens MS, et al. Mesoportal graft for thrombosed portal vein in liver transplantation. Clin Transpl 1:18–21, 1987.
140. Tzakis A, Todo S, Stieber A, Starzl TE. Venous jump grafts for liver transplantation in patients with portal vein thrombosis. Transplantation 48:530–531, 1989.
141. Stieber AC, Zetti G, Todo S, et al. The spectrum of portal vein thrombosis. Ann Surg 213:199–206, 1991.
142. Starzl TE, Demetris AJ. Liver Transplantation: A 31-Year Perspective. Chicago, Year Book, 1990, pp 38–41.
143. Bismuth H, Houssin D. Reduced-size orthotopic liver graft in hepatic transplantation in children. Surgery 95:367–370, 1984.
144. Broelsch CE, Neuhaus P, Burdelski M, et al. Orthotope transplantation von Lebesegmenten bei mit Gallengangsatresien. (Orthotopic transplantation of hepatic segments in infants with biliary atresia) In Kolsowski L, ed. Chirurgisches Forum 1984, F Experim U Klimische Forschung Hrsga. Berlin, Springer-Verlag, 1984, pp 105–109.
145. Strong RW, Lynch SV, Ong TH, et al. Successful liver transplantation from a living donor to her son. N Engl J Med 322:1505–1507, 1990.
146. Broelsch CE, Emond JC, Whitington PF, et al. Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts, and living related segmental transplants. Ann Surg 212:368–375, 1990.
147. Tzakis A, Todo S, Starzl TE Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg 210:649–652, 1989.
148. Starzl TE, Todo S, Tzakis A. Abdominal organ cluster transplantation for the treatment of upper abdominal malignancies. Ann Surg 210:374–386, 1989.
149. Starzl TE, Todo S, Tzakis A, Fung J. The transplantation of gastrointestinal organs. Gastroenterology 104:673–679, 1993.
150. Grant D, Wall W, Mimeault R, et al. Successful small bowel/liver transplantation. Lancet 335:181–184, 1990.
151. Deltz E, Schroeder P, Gundlach M, et al. Successful clinical small-bowel transplantation. Transplant Proc 22:2501, 1990.
152. Todo S, Tzakis A, Reyes J, et al. Intestinal transplantation in humans under FK506. Transplant Proc 25:1198–1199, 1993.
153. Starzl TE, Demetris AJ, Murase N, et al. Cell migration, chimerism, and graft acceptance. Lancet 339:1579–1582, 1992.
154. Starzl TE, Demetris AJ, Trucco M, et al. Cell migration and chimerism after whole organ transplantation: The basis of graft acceptance. Hepatology 17:1127–1152, 1993.
155. Starzl TE, Demetris AJ, Murase N, et al. Cell chimerism permitted by immunosuppressive drugs is the basis of organ transplant acceptance and tolerance. Immunol Today, 14:326–332, 1993.
156. Starzl TE, Demetris AJ, Trucco M, et al. Chimerism after liver transplantation for type IV glycogen storage disease and type I Gaucher's disease. N Engl J Med 328:745–749, 1993.
157. Starzl TE, Valdivia LA, Murase N, et al. The biologic basis of and strategies for clinical xenotransplantation. Immunol Rev 141, September 1994.
158. Starzl TE, Ishikawa M, Putnam CW, et al. Progress in and deterrents to orthotopic liver transplantation, with special reference to survival, resistance to hyperacute rejection, and biliary duct reconstruction. Transplant Proc 6:129–139, 1974.
159. Murase N, Starzl TE, Demetris AJ, et al. Hamster to rat heart and liver xenotransplantation with FK506 plus antiproliferative drugs. Transplantation 55:701–708, 1993.
160. Starzl TE: Orthotopic heterotransplantation. In Starzl TE, ed. Experience in Hepatic Transplantation. WB Saunders, Philadelphia, 1969, pp 408–421.
161. Starzl TE. Baboon renal and chimpanzee liver heterotransplantation. In Hardy MA, ed. Xenograft 25. Amsterdam, Excerpta Medica, Elsevier Science (Biomedical Division), 1989, pp 17–28.
162. Starzl TE, Fung J, Tzakis A, et al. Baboon to human liver transplantation. Lancet 341:65–71, 1993.
163. Starzl TE, Tzakis A, Fung JJ, et al. Human liver xenotransplantation. Xeno 1:4–7, 1993.
164. Starzl TE, Lerner RA, Dixon FJ, et al. Shwartzman reaction after human renal transplantation. N Engl J Med 278:642–648, 1968.
165. Starzl TE, Boehmig HJ, Amemiya H, et al. Clotting changes, including disseminated intravascular coagulation, during rapid renal-homograft rejection. N Engl J Med 283:383–390, 1970.
166. Starzl TE, Demetris AJ, Todo S, et al. Evidence for hyperacute rejection of human liver grafts: The case of the canary kidneys. Clin Transpl 3:37–45, 1989.
167. Demetris AJ, Nakamura K, Yagihashi A, et al. A clinicopathologic study of human liver allograft recipients harboring IgG lymphocytotoxic antibodies. Hepatology 16:671–681, 1992.