

21

The Contribution of Transplantation to Gastroenterologic Knowledge

THOMAS E. STARZL

How whole-organ transplantation came to be a clinical discipline has been told elsewhere by many of the persons directly involved (1). Although the history of the field through 1959 was dominated by the kidney (2), the extrarenal vacuum rapidly filled in the late 1950s with the development in several laboratories of canine transplant models with which to study all of the intra-abdominal (Fig. 21-1) and thoracic organs.

EARLY ANIMAL MODELS

The Liver

Auxiliary Transplantation

In 1955, 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 (3). 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. 21-2). It was not discovered until a decade later that factors other than rejection were involved in the rapid destruction of the auxiliary transplant (see subsequent section on hepatotrophic physiology).

Orthotopic Liver Transplantation

The first mention of liver replacement (orthotopic transplantation) (Fig. 21-3) was by

Dr. Jack Cannon of the University of California, Los Angeles, who cited Welch's article as the stimulus for his own "several successful" operations in dogs "without survival of the patient" (4). Assuming that the liver played an important role in rejection, Cannon speculated that the graft would not contribute to its own repudiation. No details were given about the operation, which remained virtually unknown until its independent investigation in dogs beginning in the summer of 1958 at the Peter Bent Brigham Hospital (Boston) (5-7) and at Northwestern University (Chicago) (8,9). The Boston effort under the direction of Francis D. Moore was part of an immunologically oriented institutional commitment to organ transplantation that initially was preoccupied with the kidney (10).

In contrast, the Northwestern initiative stemmed from a conviction that the liver was a modulator of endogenous insulin, or instead was governed by this hormone (11-13). Such metabolic questions and their investigation ultimately led to the development of a new field called "hepatotrophic physiology" (14,15). To pursue them, a new technique of total hepatectomy (the first half of a transplant operation) was developed (16). The second step of inserting an allograft into the vacated hepatic fossa soon followed; from the outset, the superior liver-supporting qualities of portal versus systemic venous blood were obvious (8).

Although there was no effective way to prevent rejection, an astonishing amount of

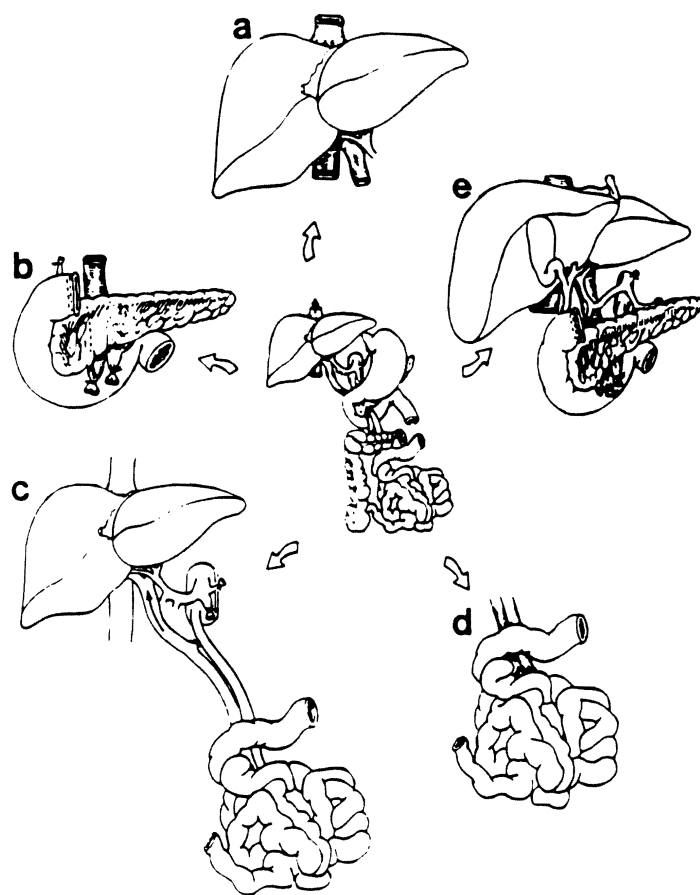


Fig. 21-1. The complex of intra-abdominal viscera which has been transplanted as a unit (center) or as separate components. Counterclockwise: *a*, liver; *b*, pancreas; *c*, liver-intestine; *d*, intestine; *e*, liver-pancreas.

information about orthotopic liver transplantation was compiled in 1958 and 1959. At the April 1960 meeting of the American Surgical Association, Moore reported on 31 canine experiments with 7 survivors of 4 to 12 days. In discussing his paper (17), I described an experience that was in press elsewhere (8) with more than 80 dogs, of which 18 had lived for 4 to 20-1/2 days. Rejection was always present after 5 or 6 days and usually was the cause of death thereafter.

Beyond demonstrating the need to revascularize the hepatic graft with splanchnic venous blood, the work in Boston and Chicago 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 practiced clinically today (8). Improved infusates in the succeeding years (18,19)

eventually replaced the originally used lactated Ringer's and saline solutions. Until 1987, the safe preservation time was only 5 or 6 hours, but since then, the University of Wisconsin (UW) solution (20) has permitted reliable safe refrigeration of human livers for 18 to 24 hours (21,22).

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 so-called anhepatic stage while recipient hepatectomy was performed and the new liver was installed (6,8). Such venous decompression was later shown to be expendable in dogs submitted several weeks in advance of transplantation to common bile duct ligation, because of the development in the interim of decompressing venous collaterals (23). Similarly, venous bypasses

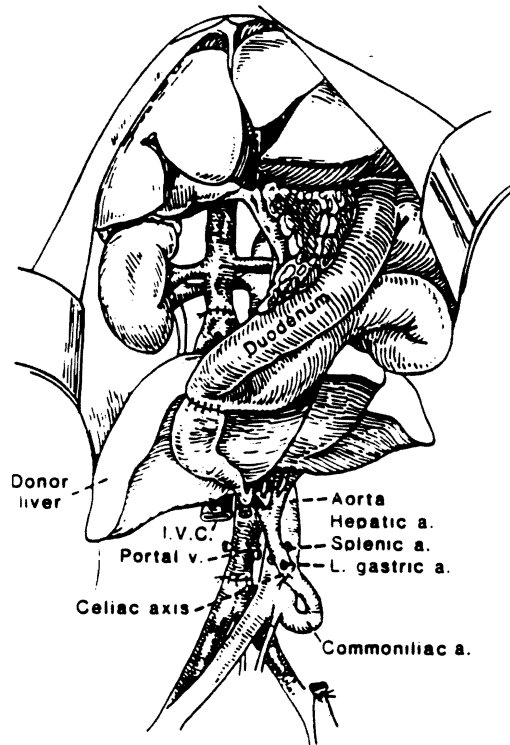


Fig. 21-2. Auxiliary liver transplantation in a dog by a modification of Welch's original technique. Note that the reconstituted portal blood supply is from the distal inferior vena cava. Redrawn with permission from Starzl TE, et al.: Immunosuppression after experimental and clinical homotransplantation of the liver. *Ann Surg* 160:411, 1964.

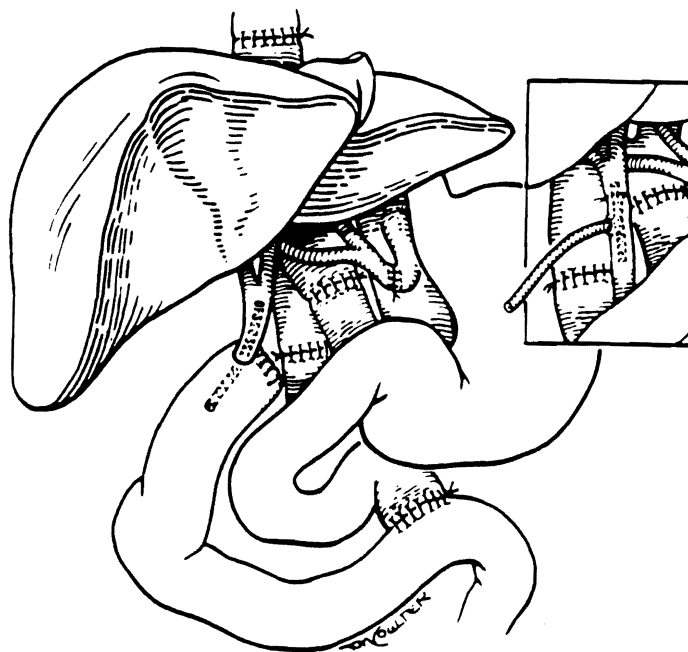


Fig. 21-3. Orthotopic liver transplantation (liver replacement). Biliary tract reconstruction is usually with choledochojejunostomy (to a Roux limb) or (inset) with a choledochocholedochoostomy, which is stented with a T tube. Reproduced with permission from Starzl TE et al.: Medical progress: Liver transplantation. *N Engl J Med* 327:1014, 1989.

were shown to be nonessential in most clinical cases if the operation was performed by highly experienced surgeons (24,25). Nevertheless, the introduction of pump-driven venovenous bypasses in the 1980s, first with (25) and then without anticoagulation (26-28), made the operation less stressful in humans, placed it well within the grasp of most competent general and vascular surgeons, and allowed the systematic training of a new generation of liver transplant surgeons.

Multivisceral and Intestinal Transplantation

Isolated Intestine

Nearly 90 years ago, Alexis Carrel and C.C. Gunthrie performed canine intestinal transplantations. Little more was added until the similar studies of small bowel transplantation in dogs by Richard Lillehei of the University of Minnesota (29), who replaced the entire small intestine in unmodified recipients except for short segments of jejunum and ileum. The graft was preserved by immersing it in iced saline, and the blood vessels were anastomosed to companion recipient structures in an anatomically normal way. Although it was later demonstrated in Toronto (30), London (Ontario) (31), Pittsburgh (32), Kiel (33), and Paris (34) that the gut could be successfully replaced with long survival in large animals under immunosuppression, the clinical application of this procedure languished. The first clinical successes did not come until the late 1980s (35,36).

Multivisceral Transplantation

The multiple organ allograft in this versatile operation (37) was envisioned as a grape cluster with a double central stem consisting of the celiac axis and superior mesenteric artery (Fig. 21-1, 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. 21-1, periphery), but both arterial stem structures were preserved (38). The venous outflow was kept intact up to or beyond the liver.

Two observations were made in the unmodified canine multivisceral recipients of

1959 that have dominated the field of gastroenterologic transplantation since then. First, rejection of the organs making up the composite graft was less severe than that seen when the organs were transplanted individually (39). This finding was confirmed and greatly extended in 1969 by Calne et al. (40), who described in pig liver recipients the protection of kidney and skin grafts from the hepatic donor; these experiments identified the liver as the "protective" organ. Calne's conclusion about hepatic tolerogenicity has been confirmed by the Japanese surgeon Naoshi Kamada, whose experiments were performed in rats (41), and by many others. Most recently, Valdivia et al. (42) demonstrated the similar protection of hamster heart and skin xenografts in rats by simultaneous or prior xenotransplantation of a hamster liver.

The second fundamental issue raised at the outset was the specter of graft-versus-host disease (GVHD) with the multivisceral procedure. GVHD was well known in 1960 from the prior work of Billingham and Brent (43) and Trentin (44), but this was associated almost exclusively with bone marrow or splenocyte (not whole organ) transplantation. Histopathologic evidence of GVHD was found in recipient tissues of our multivisceral canine recipients (39), who quickly developed multiple organ failure. Later experiments by Monchik and Russell (45) confirmed the potential threat of GVHD, using the F₁ hybrid model in which the parent and F₁ hybrid offspring were donor and recipient respectively. However, these studies vastly overestimated the GVHD threat after splanchnic organ transplantation for reasons explained in the subsequent section on "Mechanisms of Graft Acceptance."

The multivisceral operation is not often indicated clinically, but it has spawned many variations (38) and was itself the procedure with which the first long survival (>6 months) of a functioning human intestinal graft was accomplished (46).

Pancreas Transplantation

Transplantation of the pancreas alone has not been considered in these historical notes because this procedure is done only for endocrine objectives. However, the effect of pancreatic insulin secretion on the liver is a

vital concern with all gastroenterologic transplant procedures (see next section). Furthermore, even the transplantation of the whole pancreas "alone" implies the concomitant engraftment of a segment of duodenum which receives exocrine pancreatic secretions and with which the pancreas shares its blood supply in humans and animals (Fig. 21-1b). Thus, it was not surprising that pancreaticoduodenal grafts were used in the first reported acute experiments on pancreas transplantation (47,48). When immunosuppression became available, essentially the same pancreaticoduodenal graft was used in dogs (49) and eventually in humans (50).

HEPATOTROPHIC PHYSIOLOGY: LIVER ATROPHY AND REGENERATION

The Eck Fistula and Liver Transplantation

C. S. Welch's conclusion that rejection was solely responsible for the rapid destruction of the auxiliary liver graft (3,51) was based on an erroneous concept about liver physiology that had evolved from nearly 80 years of research with the experimental procedure of Eck's fistula (portacaval shunt) in dogs. The operation of canine Eck fistula is well known to gastroenterologists. When it is performed, blood returning from the pancreas, intestines, and other splanchnic viscera by way of the portal vein is diverted around the liver instead of through it. Thus, the liver, which now is supplied only by the hepatic artery, loses much of its total blood flow. The liver shrinkage that occurs in dogs (and also in rats, baboons, and humans [15,52]) and the wasting, hair loss, and brain damage that follow were ascribed until the mid 1960s to the diminution of flow rather than the loss of exposure to the liver of any specific substance(s) in the portal blood (53-56). This became known as the flow hypothesis of portal physiology.

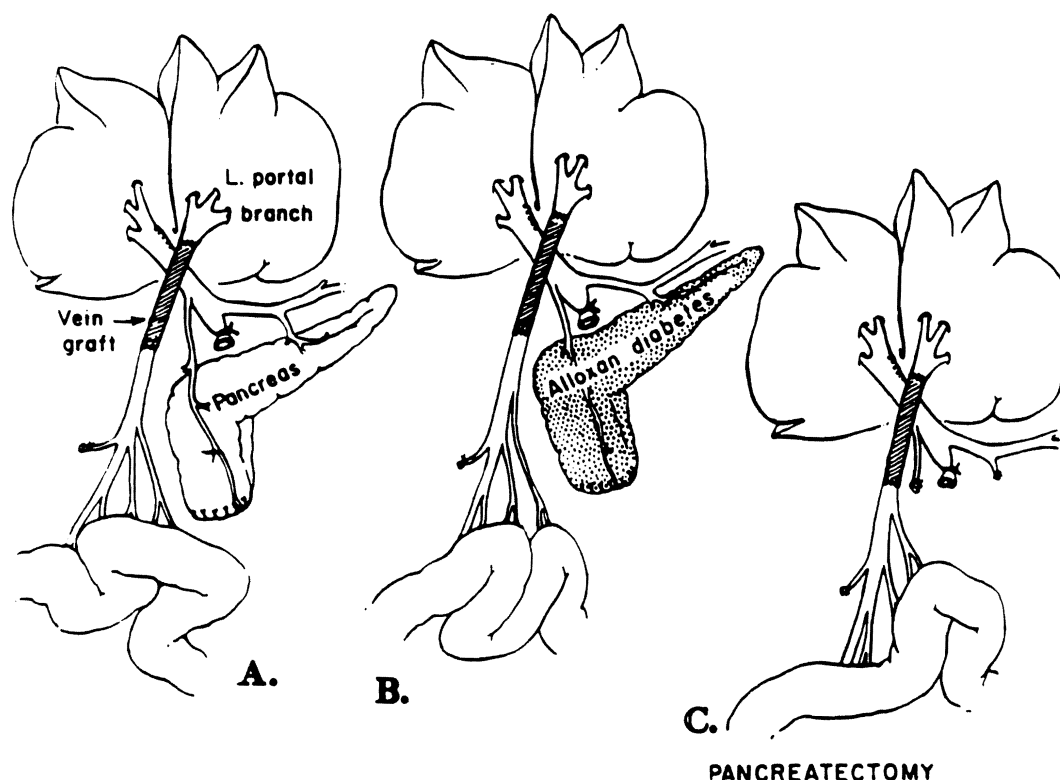
Although Welch accepted this false dogma and attributed auxiliary graft destruction to rejection alone, he unwittingly had created an experimental model of great power. The principle of the model was the coexistence of two livers in the same animal

with similar conditions except for the content of the blood delivered to the graft and native 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 (57). This acute atrophy was not seen in normally vascularized orthotopic livers. The atrophy could be prevented in auxiliary livers if they were nourished with normal portal blood; then, it afflicted the native liver that was deprived of its portal supply (58).

Soon, nontransplant models were developed in which the animal's own liver was divided into two parts, each of which could be given the venous blood that came from different organs or different parts of the body (59,60) (Fig. 21-4). It was apparent that the healthy and hypertrophic liver fragment with first access to the portal blood, particularly that returning from the upper abdominal viscera, was able to remove substance(s) so completely that little was left for the competing fragment which shriveled up (Fig. 21-5). From the outset, it was postulated that insulin was the most important, although not the only, liver-supporting substance (60-63). This conclusion was supported by later experiments in which the effect on the liver of removing the nonhepatic visceral organs was tested (64,65).

Meanwhile, infusion experiments had been performed showing that insulin, when injected alone into the tied-off central vein after portacaval shunt (Fig. 21-6), could prevent most of the consequences to the liver that were caused by the Eck fistula (66). As other liver growth factors of pancreatic, enteric, and nonsplanchnic origin have become available in recent years, they have been screened and evaluated for potency with the Eck fistula model (67,68). In this preparation, an active test substance prevents in the infused liver lobes the expected acute hepatocyte atrophy, organelle disruption, and fatty infiltration caused by depriving the liver of portal venous blood—the comparison of protected versus nonprotected hepatic tissue being similar to that in Figure 21-5.

In addition to affecting the size of hepatocytes, the most potent factors tested in the model shown in Figure 21-6 also promote



Splanchnic division

Fig. 21-4. Splanchnic division experiments. In these dogs, the right liver lobes received venous return from the pancreaticogastrroduodenosplenic 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. Reproduced with permission from Starzl TE et al.: The effect of diabetes mellitus on portal blood hepatotrophic factors in dogs. *Surg Gynecol Obstet* 140:549, 1975.

proliferation—beginning with insulin (66) but also including the immunosuppressive agents cyclosporine (69) and FK 506 (70) and the growth factors, insulin-like growth factor (IGF-II), transforming growth factor- α (TGF α) and hepatocyte growth factor (HGF) (68). By virtue of these developments, hepatotrophic physiology has become a consistent countertheme of all research on the transplantation of splanchnic organs as well as a common ground shared by liver transplantation, clinical portal shunt operations (all are variations of Eck's fistula), and the regeneration that follows hepatic resection (15,71). In the portal shunt field, the new insight into portal hepatotrophic physiology provided an incentive to use portal flow-sparing procedures such as the Warren shunt in reference to complete

portal diversion for the treatment of portal hypertension (15).

In contrast, the completely diverting portacaval shunt has been used preferentially to palliate several inborn errors of metabolism (15). The principle was to create with complete portal diversion a subtle kind of liver disease that inhibited the synthesis and accumulation of abnormal glycogen in patients with certain glycogen storage diseases (72), or α -1-antitrypsin in patients with α -1-antitrypsin deficiency (73,74). Because portal diversion reduces the production of cholesterol that cannot be normally catabolized in the disease of familial hypercholesterolemia, portacaval shunt lowered serum cholesterol in patients with this diagnosis (75,76). The manufacture in the liver of many other substances also is

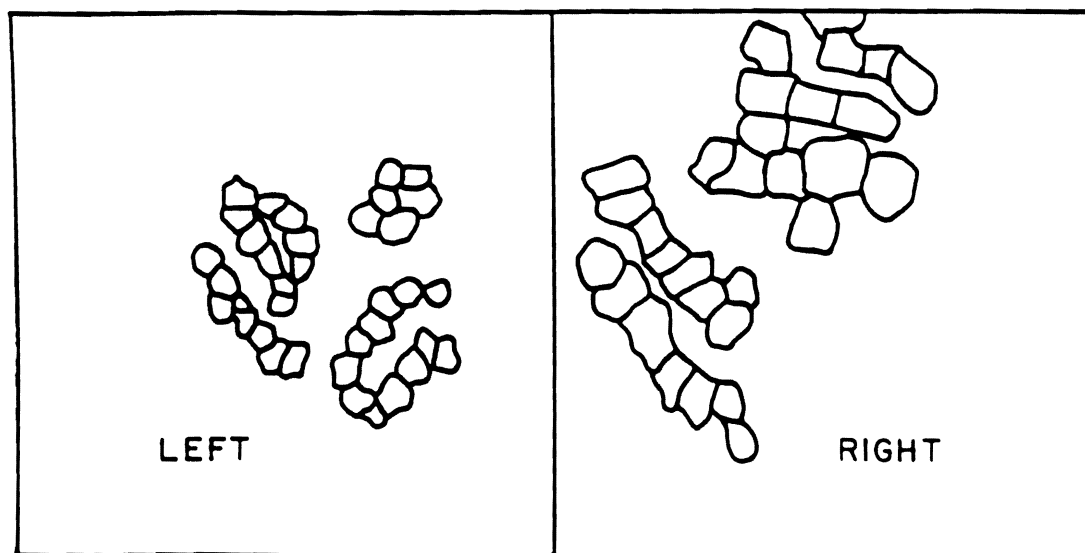


Fig. 21-5. Hepatocyte shadows traced during histopathologic examination of liver biopsies from experiments shown in Figure 21-4A. These were later cut out on standard paper and weighed as an index of hepatocyte size. The right lobes with the large hepatic cells received venous blood from the pancreas, stomach, duodenum, and spleen. The relatively shrunken left lobes with the small hepatocytes received intestinal blood. Reproduced with permission from Starzl TE et al.: *Surg Gynecol Obstet* 137:179, 1973. The origin, hormonal nature, and action of hepatotrophic substances in portal venous blood.

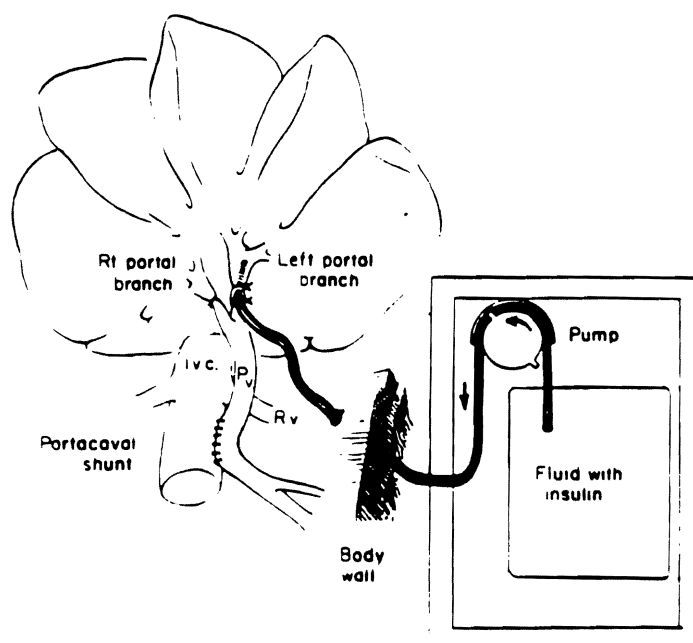


Fig. 21-6. Experiments in which postoperative infusions of hormones are made into the left portal vein after performance of Eck fistula. Reproduced with permission from Starzl TE et al.: *Lancet* 7:821, 1976. Effects of insulin, glucagon, and insulin:glucagon infusions on liver morphology and cell division after complete portacaval shunt in dogs.

curtailed by portal diversion, but the consequent adverse effects in patients with the metabolic diseases were superseded in significance by the gain in control of the abnormal or runaway metabolites. Eventually, it was shown that all three of the cited inborn errors, as well as many others, could be corrected definitively by liver replacement (see subsequent section). When this occurred, the use of portal diversion for metabolic purposes became obsolete.

An additional ripple effect of research in transplantation was stimulated by the referral for liver replacement of patients with large but still localized liver neoplasms that were thought to be unresectable. As an alternative to transplantation, we standardized and popularized the previously dangerous operation of right trisegmentectomy (77) and introduced the new operation of left trisegmentectomy (extended left hepatic lobectomy) (78).

IMMUNOSUPPRESSION

While the gastroenterologic transplant operations were being perfected, other developments had raised hopes of their potential clinical application. The literature on these developments, which has been summarized elsewhere (79), began with the demonstration by Medawar in 1944 that rejection is an immunologic event (80,81). The deliberate weakening of the immune system with total body irradiation (82), and corticosteroid therapy (83,84), and (much later) the thiopurine compounds, 6-mercaptopurine and azathioprine (85-89) ameliorated the rejection of skin grafts in rodents and renal grafts in dogs. However, complete control of rejection with a single agent was rarely

achieved in animals without lethal side effects. This same thing was seen in discouraging clinical trials of renal transplantation (90-95). In the numerous clinical trials of kidney transplantation from January 1959 through the autumn of 1962, there were only 8 examples of survival for at least 5 months—2 in Boston (90-92) and 6 in Paris (96,97). All except the last of these patients were treated primarily with total body irradiation; the final patient was the first to have long survival with azathioprine (92).

This discouraging picture changed dramatically during 1962 and 1963 in Colorado, where the synergism of azathioprine and prednisone was known from animal investigations (98). When these two drugs were used together from the outset in human kidney transplant recipients, the results exceeded everyone's expectations (99,100) and precipitated a revolution in clinical transplantation. Success hinged, first, on the fact that acute rejection usually could be reversed with prednisone and, second, that the amount of drug treatment required to achieve stability of graft function often became less in time (99-102).

The reversibility of rejection and change in host-graft relationship were eventually verified with all other transplanted organs, beginning with the liver (103,104). Although immunosuppression has improved, the central therapeutic dogma for whole organ transplantation that had emerged by 1963 (99,100) has changed little in nearly 30 years. The dogma calls for daily treatment with one or two baseline drugs with further immune modulation by the highly dose-maneuverable adrenal cortical steroids to whatever level is required to maintain stable graft function (Table 21-1). This means that every organ recipient goes through a trial

Table 21-1
Central Therapeutic Dogma

Strategy	Baseline Agents	Sites of Action
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. Cyclosporine	IL-2 production
3. Case-to-case trial (and potential error) of weaning	4. FK 506	IL-2 production

Table 21-2
Principal Immunosuppressive Drug Regimens and Adjuncts* Used Clinically

Agents	Year Described and Reported (Ref.)	Place	Deficiencies	Used for GI Organs
Total body irradiation	1960 (90)	Boston	Ineffective, dangerous	No
Azathioprine	1962 (91)	Boston	Ineffective, dangerous	No
Azathioprine-steroids	1963 (99)	Denver	Suboptimal	Yes, liver
Thoracic duct drainage as adjunct	1963 (105)	Stockholm	Nuisance: requires 20 to 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
ALG as adjunct	1966 (107)	Denver	Suboptimal	Yes
Cyclophosphamide substitute for azathioprine	1970 (108)	Denver	No advantage except for patients with azathioprine toxicity	Yes‡, liver
Total lymphoid irradiation	1979 (109, 110)	Palo Alto, Minneapolis	Dangerous, extensive preparation, not quickly reversible	Yes§, for liver
Cyclosporine	1978-1979 (111)	Cambridge	Suboptimal	Yes
Cyclosporine-steroids	1980 (112)	Denver	Nephrotoxicity; rejection not always controlled	Yes
FK506-steroids	1989 (114)	Pittsburgh	Nephrotoxicity; rejection not always controlled	Yes

* Until 1966, these were developed with kidney transplantation and applied for livers. From 1966 onward, 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 TDD (113).

‡ These trials were summarized many years later with at least 10 years follow-up for surviving patients (25).

§ By Professor J. A. Myburgh of Johannesburg.

and potential error experience as drugs are weaned to maintenance levels.

The principal regimens used clinically within this format over the ensuing 30 years are summarized in Table 21-2. 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 over the next 30 years

(105-114) and to each new organ, of which the liver was the first after the kidney and the intestine the most recent.

The history of this remarkable phase in transplantation has been told elsewhere (79). Even at the end of 1962, transplantation still seemed like a mirage. One year later, a wild proliferation of kidney transplant centers had begun on both sides of the Atlantic, driven by knowledge of the effi-

cacy of the "drug cocktail" approach, of which the first example was the azathioprine-prednisone combination. Trials with the liver, the next vital organ beyond the kidney, had started (115) and clinical kidney xenotransplantation with chimpanzee (116) and baboon (117) donors had been systematically tried with encouraging, although ultimately unsatisfactory, results.

CLINICAL TRIALS OF LIVER TRANSPLANTATION

Phase 1: The Failed First Cases

The prospect of establishing a forerunner kidney program in Denver in preparation for liver transplantation was the reason for my move from Northwestern to the University of Colorado in late 1961 (118). Now, the effectiveness of azathioprine-prednisone cocktail for kidney grafting having been proved, a decision was taken to move on to the liver (115,119). 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 uncontrollable coagulopathy. 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 7-1/2 days, respectively (115,119). The strategy of coagulation control introduced after the death of the first patient had a delayed backfire in all of the liver transplant 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 being given drugs and blood products to promote clots, these clots formed in the bypass tubing and passed on to the lungs. There, they caused abscesses and other lung damage which contributed to or caused delayed death of all four of the patients who survived the intraoperative period (57,115). A pall settled over the liver

program, with a self-imposed moratorium that lasted more than 3 years. By this time, isolated attempts also were unsuccessful at the Brigham (120) and in France (121).

When these first seven liver transplantations failed in three different centers (Table 21-3), pessimism settled in worldwide. The operation seemed too difficult to allow practical application, the methods of preservation were thought inadequate for an organ so seemingly sensitive to ischemic damage, and it began to be asked if immunosuppression available was considered too primitive to permit success. This last reservation was reinforced by the fact that truly chronic survival after liver replacement had never been achieved to this time 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 (103), some dogs having passed the 3-year postoperative mark. Better immunosuppression with the so-called triple drug therapy was now available, following the development and first clinical trials in the world of antilymphocyte globulin (ALG) prepared from sensitized horses (107) and used to supplement azathioprine and prednisone. Finally, improved techniques of organ preservation had been developed (122,123).

On July 23, 1967, a 1-1/2 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. The ripple effect of successfully transplanting a vital organ other than the kidney was far-reaching (124). If the liver, the most difficult of all organs, could be transplanted, anything seemed possible. The smoldering embers in other specialty centers burst into flames: first, with the heart transplantation in Cape-town by Christiaan Barnard (December 1967), then with attempts at intestinal transplantation by Richard Lillehei and William Kelly (University of Minnesota, 1967), and finally with the first successful lung transplantation on November 14, 1968 (by F. Derom of Louvain, Belgium).

Table 21-3
The First 7 Attempts of Clinical Orthotopic Liver Transplantation

No.	Location (Ref.)	Age (Yr)	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 (57)	52	Hepatocellular cancer, cirrhosis	6½	Pulmonary emboli, hepatic failure, pulmonary edema
5	Boston (120)	58	Metastatic colon carcinoma	11	Pneumonitis, liver abscesses, hepatic failure
6	Denver (57)	29	Hepatocellular cancer, cirrhosis	23	Sepsis, bile peritonitis, hepatic failure
7	Paris (121)	75	Metastatic colon carcinoma	0	Hemorrhage

Most of these attempts failed early, and all of the patients eventually died. For the liver also, it was not a time of triumph. The child who became the first long-term survivor after hepatic replacement died of recurrent cancer after 400 days. The maximum survival of the other six liver recipients treated between July 1967 and March 1968 was 2-1/2 years (25,124). For the next 12 years, the 1-year mortality 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 terrible losses were concentrated in the first postoperative months. After this, the life survival curve flattened, leaving a residual group of stable and remarkably well survivors. Thirty (18%) of the first 170 patients in the consecutive series that started 1 March 1963 and ended in December 1979 lived more than a decade; 23 are still alive after 13 to 23 years. All were treated with azathioprine (or cyclophosphamide), prednisone, and polyclonal ALG (25).

In the meanwhile, Professor Roy Calne at Cambridge University (England) began clinical trials of liver transplantation on May 23, 1967. As in our earlier experience, his first patient exsanguinated (125). A few

months later, Calne formed a collaboration that endured for more than two decades with the hepatologist, Professor Roger Williams, at Kings College Hospital in London. The Colorado and Cambridge-London teams continued their clinical efforts through the years, in spite of frequent disappointments and many tragic failures. The long survival of patients in both series was a testimonial for liver transplantation, but it was asked increasingly on both sides of the Atlantic if such a small dividend could justify the prodigious effort that had brought liver transplantation this far (126). Other teams established subsequently in Hannover (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 was too great to allow its practical use. Liver transplantation was a feasible but impractical operation.

Phase 3: The Cyclosporine/FK 506 Era

The frustration ended when cyclosporine became available clinically in 1979 (111), but only after this drug 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 (127) and 7 are still alive more than 12 years later. As the news was confirmed that 1-year patient survival of at least 70% was readily achievable, new liver programs proliferated worldwide. When FK 506 was substituted for cyclosporine in 1989 (114), the 1-year patient and liver graft survival rose another 15% in the Pittsburgh experience (128). An improvement also was recorded in a multicenter European trial. By now, liver transplantation had become the accepted court of last appeal for almost all non-neoplastic liver diseases, and even for selected patients with otherwise nonresectable hepatic malignancies. The principal limitation of the technology quickly became the supply of organs to meet the burgeoning needs.

Although the ascension of liver transplantation was dominated by improvements in immunosuppression, other significant improvements occurred, including modified details of the operation itself. The incidence of biliary duct complications (obstruction, fistula, and cholangitis), which had been more than 30% (129), was reduced by the use of choledochocholedochostomy with a T-tube stent, or if this was not feasible, by choledochojunostomy to a Roux limb (25). Management of coagulopathies was facilitated by the use of the thromboelastogram to follow the minute-to-minute clotting changes in the operating room (115,130). The systematic use of veno-venous bypasses without anticoagulation also greatly diminished the hemorrhages of nightmare proportions that were common at one time (131).

ORGAN PROCUREMENT

Hypothermia and Core Cooling

Steps in the development of liver graft procurement and preservation have been few. However, these steps have had an importance far beyond their application for liver replacement, because the principles were applied equally to other whole organs. The first step was core cooling by infusion

of chilled lactated Ringer's solution into the portal vein (8) a laboratory technique promptly modified for use in clinical kidney transplantation (132).

Today, core cooling is the first step in the preservation of all whole organ grafts, but in contrast to the original method, this is most often done by some variant of the in-situ technique originally developed at the University of Colorado to cool and continuously perfuse cadaveric liver and kidney donors before the acceptance of brain death conditions (133,134). Ackerman and Snell (135) and Merkel and colleagues (136) simplified the in-situ cooling of cadaveric kidneys with cold electrolyte solutions infused into the distal aorta. Finally, 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 (137). Modifications of this procedure have been made for unstable donors and even for donors whose hearts have ceased to beat (138). In less than 5 years, multiple-organ procurement, using techniques that are interchangeable not only from city to city but from country to country, had become standardized in all parts of the world.

The technique is versatile. A complete midline abdominal and thoracic incision is made. The aorta at the diaphragm is encircled so that it can be crossclamped when the core cooling is begun. The distal aorta is used as an entry site for the fluid infusion. By coordination of the fluid infusion and the crossclamping of the great vessels and by dissection and ligation of appropriate arterial branches, the cold infusate can be made to go selectively to the organs (including the liver) that are to be transplanted. The portal vein of the liver also is infused after a catheter is placed into it through the splenic vein or other major tributary. Core cooling of the thoracic organs is accomplished with the same principles (137). 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

Because the potentially suitable candidates for liver transplantation outnumber

Table 21-4
Generic Listing of Liver Diseases
Treatable by Hepatic 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 available organs by 3 to 1, the selection of appropriate recipients from such a large pool requires highly individualized assessment. By 1989, the list of benign diseases treatable by transplantation had become so long that it was increasingly given in broad categories such as cholestatic or parenchymal disease (Table 21-4). The simplification made it easy to lose sight of the fact that nearly 100 distinct diseases have been treated with liver transplantation, including more than 20 in the broad category of cholestatic disorders. Because products of hepatic synthesis permanently retain the original metabolic specificity of the donor after transplantation (139,140), liver transplantation is a decisive way to treat many liver-based or liver-influenced inborn errors of metabolism (Table 21-5).

Diseases that precluded transplantation 5 or 10 years ago, such as alcoholic cirrhosis, are no longer absolute contraindications. In addition, scarring from multiple upper abdominal operations and prior portal-systemic shunts that at one time would have ruled out liver transplantation are no longer overriding deterrents in any major center. Extensive thrombosis of the portal and superior mesenteric veins which previously

made liver transplantation difficult or impossible has been almost eliminated as a contraindication to attempted liver transplantation by the use of vein grafts (141-145).

Inflexible age proscriptions at either the upper or lower range have been dropped. 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 (146) but was not reported until long after the landmark descriptions of this technique by Henri Bismuth and Didier Houssin of Paris (147) and the team of Rudolf Pichlmayr and Christoph Broelsch of Hannover (148).

The use of conventional liver transplantation to treat otherwise nonresectable primary or metastatic hepatic cancers has resulted in a very high rate of recurrence (139). Nevertheless, the use of liver transplantation to treat cancer is still being investigated by many transplantation teams, almost invariably in combination with adjuvant chemotherapy or other experimental treatment protocols. Certain kinds of neoplasms have a better prognosis than others. A crucial condition of candidacy involves ruling out the possibility that the tumor has spread beyond the liver.

A radical extension of this concept is the removal of organ clusters *en bloc* (liver, pancreas, spleen, stomach, duodenum, proximal jejunum, and right colon) to treat extensive sarcomas and carcinoid tumors of the pancreas or duodenum with liver metastases, bile duct carcinomas with liver metastases, and hepatomas that had invaded the duodenum and colon (149). The excised organs have been replaced with hepatopancreaticoduodenal grafts (see Fig. 21-1e), or in some cases by the liver alone.

CLINICAL TRIALS OF INTESTINAL TRANSPLANTATION IN COMPOSITE VISCERAL GRAFTS OR ALONE

Composite Grafts

Function for more than a half year of a cadaveric intestine was not accomplished until 1987 (150,151). In November of that

Table 21-5

Inborn Errors of Metabolism Treated with Liver Transplantation—Most of the Patients Were in University of Colorado—University of Pittsburgh Series. Follow-up to January 1989 (139).

Disease	Explanation of Disease	Longest Survival	Associated Liver Disease
α_1 Antitrypsin deficiency	Structural abnormality of the protease inhibitor synthesized in 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 storage	7 yr	Cirrhosis
Erythropoietic protoporphyria	Hepatic ferrochelatase deficiency, ?overproductive of protoporphyrin by erythropoietic tissues	1.5 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 (3 types)	Ornithine carbamoyltransferase deficiency	8 mo.	None
C protein deficiency	Defective C protein synthesis	2.25 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

year, the 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 lymphoma (46). Several subsequent recipients of the full multivisceral graft (see Fig. 21-1, center) are alive after as long as 17 months under treatment with FK 506 (36,152).

A variant procedure in which only the liver and small bowel are retained (see Fig. 21-1c) was described by Grant et al. (153) of London, Ontario. This operation has been particularly useful in patients with the short gut syndrome who developed liver failure after prolonged hyperalimentation (36). Using FK 506, 13 (76.5%) of 17 patients in the Pittsburgh series of liver-intestinal grafts are alive after 5 to 31 months—all but one liberated from total parenteral hyperalimentation (TPN) (36,152).

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 previous text) 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 et al. (35) of Paris, and of an ileal segment from a living related donor by Deltz of Kiel, Germany (154).

These were isolated straws in the wind. The routine survival of cadaveric intestinal recipients then became possible in Pittsburgh under immunosuppression with FK 506, where the results have been better with isolated intestinal transplantation than with either the multivisceral operation or its liver-intestine variant (36,152). Eight of 9 such recipients are alive, several after 1 to 2 years—all but one being TPN-free. The expected release of FK 506 for general use in the near future is certain to stimulate rapid further development of the intestinal transplantation field.

Metabolic Interactions

Nonimmunologic factors can influence the success or failure of abdominal organ

grafts. Normally, the venous effluent from all of the nonhepatic splanchnic organs contributes to the portal blood supply, ensuring the liver of first-pass exposure to the intestinal nutrients, and the so-called portal hepatotropic substances, of which insulin is the most important.

When partial multivisceral grafts such as the liver-intestine are used in recipients whose pancreas and other upper abdominal organs are retained, it is preferable to direct the venous effluent from the residual host organs into the portal circulation of the new liver. Otherwise, subtle injury of the liver typical of, although less severe than, that caused by Eck fistula, can be produced. Similarly, when the intestine is transplanted alone, the ideal route of venous return is through the liver. However, the inability for technical reasons to drain intestinal return into the host liver has not caused severe hepatic complications in a small number of our human recipients (36).

MECHANISM OF GRAFT ACCEPTANCE

Throughout the modern history of transplantation, it has not been known how grafts were able, with the aid of immunosuppression, to weather the initial attack by the recipient immune system, and later to merge half-forgotten into the host. Study of the gastrointestinal organs and their recipients has provided unique insights into this process (155,156). In 1969, the liver became the first transplanted organ to be recognized as having a composite (chimeric) structure. It was noted that the Kupffer cells and other tissue leukocytes became predominantly recipient-phenotype within 100 days after transplantation while the hepatocytes permanently retained their donor specificity. At the time and long afterward, this transformation was assumed to be unique to the hepatic allograft.

However, 22 years later, first in rat models (157), and then in humans (158), it was realized that the same process occurred in all successfully transplanted intestines. The epithelium of the bowel remained that of the donor, whereas the lymphoid, dendritic and other leukocytes of recipient origin quickly became the dominant cells in the

lamina propria, Peyer's patches, and mesenteric nodes. Subsequent studies of the kidney and thoracic organs made it obvious that all whole-organ grafts underwent a similar transformation that differed only quantitatively from organ to organ. The number of substituted tissue leukocytes ranged from large in the case of the liver to small in organs like the kidney and heart.

What remained to be determined was the fate of the leukocytes vacating the grafts. The answers were provided in the spring and summer of 1992 by the longest survivors of kidney and liver transplantation (155, 156, 159, 160). Samples were taken from the transplanted organ as well as from the patient's own skin, lymph nodes, and other tissues. After special staining procedures (immunostaining or sex identification after fluorescence in-situ hybridization), the tissues were examined under the microscope to see if the individual cells that made them up had come from the organ donor, the recipient's own body, or both. Alternatively, the donor and recipient contributions

to any specimen could be separated by polymerase chain reactions ("DNA fingerprinting") techniques.

Within minutes after restoring the blood supply of any whole organ transplant, myriads of sessile but potentially migratory leukocytes that are part of the normal structure of all organs left the graft and migrated all over the recipient while similar recipient cells took their place in the transplant without disturbing the highly specialized donor parenchymal cells (Fig. 21-7). The relocated donor and recipient leukocytes learned to live in harmony, provided they were given sufficient protection during their nesting by immunosuppressive drugs. The same process applied to the intestine and all whole organs. In this new context, the drugs could be viewed as traffic directors, allowing movement of the white cells in both directions (to and from the graft) but preventing the immune destruction that is the normal purpose of this traffic.

It is not known yet how the two sets of white cells—a small population of predomi-

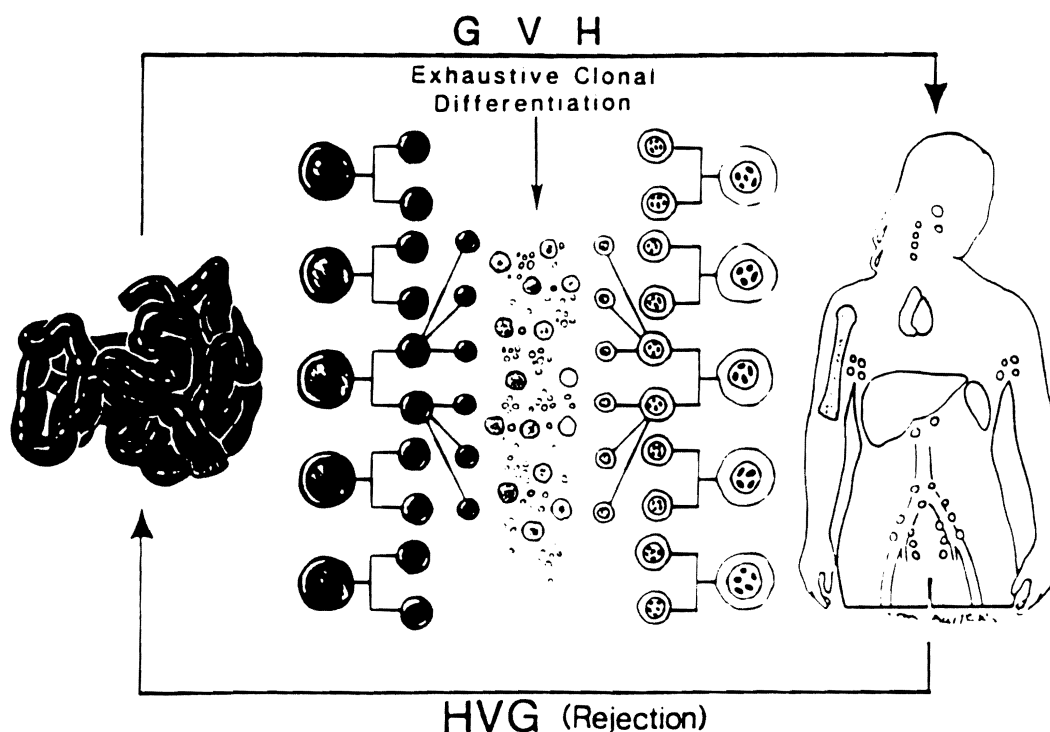


Fig. 21-7. Current understanding of the graft and systemic chimerism that occurs after transplantation, in this case of the intestine. Evolution of this concept has explained how grafts are accepted (see text).

nantly dendritic cells from the donated organ and a large one that is in essence the entire recipient immune system of the patient—reach a "truce." This is so complete in some cases that immunosuppression can be stopped, particularly after liver transplantation and less constantly with other organs. Such a stable biologic state can be induced more easily by the liver than by other transplanted organs because of the liver's higher content of the critical missionary leukocytes. This was thought to be the explanation for the protection afforded the intestine by a concomitantly transplanted liver (38,39).

While still incomplete, this much information already provides a tool with which to shape future strategies (156,159). The migratory cells can be purified from the bone marrow or spleen of a donor and then infused to improve the "acceptability" of various organs from that specific donor including those taken from an animal for use in humans as xenografts. The cell migration and mixed chimerism phenomena make comprehensible the unexpected inability of donor-recipient HLA matching to accurately predict the outcome of whole organ transplantation (161). As a result of the mutual cell engagement, neither the new organ nor its new host remains the same as at the time of the matching tests.

WHOLE-ORGAN XENOTRANSPLANTATION

When organs are transplanted from a significantly disparate species, the first immunologic hurdle is that of preformed xenospecific antibodies, which quickly devascularize the graft and exclude it from recipient circulation by damaging its blood vessels (162). If this barrier can be surmounted, the process of xenograft acceptance involves the same bidirectional cell migration and consequent systemic chimerism as with allotransplantation (163). This means that successful clinical xenotransplantation must be visualized along the same lines of donor-recipient cellular migration and repopulation as with allograft acceptance.

SUMMARY

Over a period of 38 years, it has become possible to successfully transplant individual intra-abdominal viscera or combinations of these organs. The consequences have been, first, the acquisition of new information about the metabolic interrelations that the visceral organs have in disease or health; second, the addition of several transplant and nontransplant procedures to the treatment armamentarium for GI diseases; and third, the development of a more profound understanding of the means by which all whole organ grafts are "accepted."

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