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SMALL BOWEL TRANSPLANTATION

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Role of the liver and the portal circulation in intestinal grafting

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Introduction

Until recently, the intestine has been considered a forbidden organ in clinical transplantation. In the 25 years preceding 1989, more than 15 such attempts were performed worldwide, but only with a few encouraging notations.[1] Most of the recipients died or lost their graft to refractory rejection, or to technical failures and infection. With the advent of FK 506, a potent immunosuppressive agent, we have shown that intestinal transplantation in humans alone or in combination with other viscera has become a practical reality.[2,3,4,5] From May 1990 to September 1992, 30 intestinal transplantations were performed in 29 patients at our centre (Table 10.1). Of these 29 recipients, 24 are currently alive, and 21 are completely free from total parenteral nutrition (TPN) from 2 to 25 postoperative months.

Our clinical experience, along with our experimental studies, has generated many questions about previously accepted assumptions regarding intestinal transplantation. These include the procurement and preservation of the intestinal graft, the monitoring and treatment of graft rejection, the occurrence of graft-versus-host disease (GVHD), and the long-term graft function. In addition, two important technical questions will be addressed: first, what method of venous outflow from the graft should be used, and second, what is the role of simultaneous liver transplantation in intestinal grafting?

Methods of clinical intestinal transplantation

The methods of intestinal transplantation are classified into three categories: isolated small bowel grafting, combined intestine and liver transplantation, and abdominal multivisceral transplantation. The isolated graft consists of the entire small bowel (except for a short segment distal to the ligament of Treiz and a segment proximal to the ileocecal valve) on a vascular pedicle of the superior mesenteric artery and the superior mesenteric vein (or skeletonized portal vein). Combined grafts contain both the liver and small bowel in continuity with the portal vein and central arteries (the celiac axis and the superior mesenteric artery). Multivisceral grafts include the liver, stomach, pancreas, duodenum and small intestine (with optional proximal colon) with two nourishing arteries and the entire splanchnic venous system. The principles, steps, and the indications for each procedure in our clinical series are described elsewhere.[2,5,6]

Portal circulation in intestinal grafting

Drainage of the intestinal venous effluent is problematic only with isolated intestinal transplantation, where the venous outflow is either emptied

into the systemic system (mesocaval shunt) or transhepatically via an anastomosis to the native portal or superior mesenteric vein. A systemic shunt, by which the intestinal venous blood flow is drained into the inferior vena cava (bypassing the portal vein and the liver), has been used frequently for experimental and clinical intestinal transplantations because of technical ease and safety. Several studies, however, have indicated that delivery of the venous outflow from the graft into the host superior mesenteric vein or portal vein, with consequent perfusion of the host liver, is superior for metabolic and immunologic reasons.

Basic considerations

Metabolic changes caused by splanchnic venous diversion

Metabolic changes that are caused by shunting intestinal venous blood in intestinal transplantation are similar to those seen after Eck's fistula but less pronounced[7] because with Eck's fistula there is a total diversion of the portal blood, as opposed to the partial diversion of intestinal effluent only. Under normal conditions, the portal vein constitutes a vital link for the enterohepatic circulation by which substances such as cholesterol, bile acids, bilirubin, urea, phospholipids, and lipid-soluble vitamins recirculate from the intestine to the liver to maintain homeostasis. For example, more than 95 per cent of the bile acid pool in the body (2–4 g/adult) is recirculated six times a day.[8] Of the 1 g/day of cholesterol that is secreted into bile from the liver, half is absorbed by the enterocytes and returned to the liver via the thoracic duct or the portal vein, along with an additional 0.5 g/day of cholesterol synthesized by the intestine.[9] Of the 4–6 g/day of urea synthesized by the liver, about one-fifth is degraded into ammonia in the intestine, and about 3.5 g/day of ammonia is re-absorbed and carried back through the portal vein to the liver.[10] As shown by many experiments and reviewed elsewhere,[7] if this enterohepatic circulation is interrupted by a portacaval shunt, significant metabolic abnormalities are induced or aggravated, including elevation of plasma ammonia level and appearance of hepatic encephalopathy.

Hepatic abnormality by portal diversion

Diversion of the portal blood by portacaval shunt has been shown to cause functional and structural abnormalities of the liver.[7] Marchioro and his associates, using a split (or partial) transposition model in dogs, showed hypertrophy in liver tissue perfused with splanchnic blood, and atrophy of the other tissues perfused by systemic blood.[11] The venous effluent from the nonhepatic splanchnic organs that contains intestinal nutrients and so-called hepatotrophic substances, especially endogenous insulin,[7,12] are essential for hepatocytes to maintain normal metabolism, architecture, and regenerative capacity. Besides insulin, these hepatotrophic factors include other hormones and growth factors that originate in visceral organs other than the pancreas.[7] These are now being studied systematically.[13]

Immunologic modulation after antigen infusion into portal vein

The liver, located between the gastrointestinal tract and the systemic circulation, serves as a filter to eliminate bacteria, endotoxins, carcinogens, and toxic substances absorbed into the portal system. Similarly, this filtration has been postulated to modulate transplantation antigen to offer immunologic protection to a variety of homografts.[14] When the venous return from the grafts is drained into the portal vein rather than into the systemic vein, or the antigen is injected into the portal vein before transplant, significant prolongation of graft survival has been claimed with hearts,[15] kidneys,[16] parathyroid,[17] and pancreas islets.[18] However, when this effect is compared among different species and strains, striking immunologic amelioration by antigen inoculation into the portal system has been restricted principally to mice and rats of low-responder strain combinations.[19,20] Mazzoni et al., who compared the two venous drainage methods, systemic versus portal, could not demonstrate any prolongation of graft survival after kidney transplantation in dogs and pigs,[21] contrary to his earlier observations[16] in the same porcine model.

Experimental findings with intestinal transplantation

Rat experiments

Results on the influence by different venous diversions (systemic circulation versus portal circulation) in intestinal transplantation have been conflicting. In an isograft model, which eliminates

Table 10.1 Clinical features of intestinal transplant recipients at the University of Pittsburgh

Pt.	Age	Sex	Indication	Transplantation Date	Graft†	Patient survival*	Graft survival*	TPN status	Current location
1	31.1	M	Gun shot wound	5/2/90	SB	776	684	Graft removed	
				3/16/92	SB		71	Retransplanted and died	
2	3.2	F	Necrotizing enterocolitis	7/24/90	SB/L	>820	>820	Free	Home
3	26.7	F	SMA thrombosis	8/3/90	SB/L	>810	>810	Free	Home
4	4.3	M	Gastroschisis	11/24/90	SB/L	>697	>697	Free	Home
5	2.8	M	Intestinal atresia	3/24/91	SB/L	385	385	Died	
6	0.6	F	Intestinal atresia	8/9/91	SB/L	23	23	Died	
7	1.1	F	Volvulus	8/10/91	SB/L	>438	>438	Free	Home
8	1.7	F	Volvulus	8/12/91	SB/L	>436	>436	Free	Home
9	21	M	Traffic accident	8/21/91	SB/L	>427	>427	Partial	Home
10	32	M	CA & SMA thrombosis	10/14/91	MV	>373	>373	Partial	Home
11	2.5	F	Microvillus inclusion disease	10/31/91	SB	>356	>356	Free	Home
12	1.3	M	Intestinal atresia	12/25/91	SB	>301	>301	Free	Hospital
13	50	F	Crohn's disease	12/28/91	SB	>298	>298	Free	Home
14	34	F	Desmoid tumor	2/3/92	SB	>261	239	Graft removed	
15	38	M	Crohn's disease	3/4/92	SB	>231	>231	Free	Home
16	10.2	F	Pseudo-obstruction	3/6/92	SB	>229	>229	Free	Home
17	22	F	Crohn's disease	3/12/92	SB	>223	>223	Free	Home
18	25	M	Crohn's disease	3/28/92	SB/L	>207	>207	Free	Home
19	1.5	M	Necrotizing enterocolitis	4/30/92	SB/L	70	70	Died, Multiorgan failure and sepsis	
20	29	F	Desmoid tumor	5/25/92	SB/L	>149	>149	Free	Home
21	24	M	CA & SMA thrombosis	5/28/92	MV	>146	>146	Free	Home
22	20	F	Traffic accident	6/7/92	SB	>136	>136	Free	Home
23	4.2	F	Gastroschisis	6/10/92	SB/L	>133	>133	Free	Home
24	1.4	M	Gastroschisis	7/14/92	SB/L	29	29	Died	
25	0.75	M	Microvillus inclusion disease	7/21/92	SB/L	>92	>92	Free	Home
26	0.5	M	Gastroschisis	7/27/92	SB/L	>86	>86	Free	Home
27	31.5	F	CA & SMA thrombosis	8/12/92	MV	>70	>70	Free	Hospital
28	19.1	M	Traffic accident	8/14/92	SB/L	>68	>68	Free	Home
29	44	F	SMA thrombosis	9/7/92	SB/L	>44	>44	Free	Hospital

*Survival in days as of 10/21/92

†SB = Small bowel; SB/L = Small bowel – liver; MN = Multivisceral

the participation of immunologic components in transplantation. Schraut et al.[22] and Koltun et al.[23] found that rats receiving an intestinal graft with a systemic shunt had reduced body weight, moderate liver atrophy, increased ammonia levels, and abnormal amino acid profiles. Shaffer et al., however, could not see any difference in these measures during 6 weeks of pair-feeding.[24]

Using a heterotopic allotransplantation model from (LEW/BN)/F1 donors to LEW recipients, Schraut et al. and others studied the difference in immunologic responses between the two drainage methods.[25,26,27] Without immunosuppression, mean survival with a mesenteric-systemic shunt was 10.5 days, while it was significantly prolonged to 22.9 days in animals with portal intestinal drainage. Portal drainage appeared to suppress the early onset of acute rejection, but enhanced the development of chronic rejection. Although these findings supported the theory that transhepatic drainage of venous outflow mitigates the immune response to the intestinal graft, they were not confirmed in the experiment by Shaffer et al., using the same strain combination and surgical technique.[24] Neither group could find any immunologic benefit by transhepatic portal drainage when the intestinal transplantation was performed with a GVHD strain combination, LEW to (LEW/BN) F1, or with a bi-directional strain combination of BN to LEW.[24,27]

However, because animal survival is determined by the function of the recipient's own small bowel in the heterotopic intestinal transplantation model used by these investigators, we used an orthotopic transplantation technique with the BN to LEW strain combination.[28] When no immunosuppression was given, both group animals died of intestinal rejection with median survival time of 12.0 days in portal drainage animals and 10.5 days in systemic shunt animals (not significant). When a moderate dose of FK 506 was administered for two weeks postoperatively, all of the animals except for one in each group survived for more than 100 days. Although long-surviving animals from both groups showed similar histopathologic changes of chronic graft rejection, postoperative weight gain was superior when the venous drainage was transportal. These findings suggested that portal drainage of the intestinal graft offers better metabolic conditions, but provides little immunologic benefit.

Large animal experiments

Conflicting results also have been reported in large animal experiments. Using an autotransplantation model in dogs, Raju et al. studied the nutritional status, body weight, nitrogen balance, d-xylose and fat absorption, serum iron, and serum albumin for as long as one year.[29] Most of these measures except for body weight and nitrogen balance were abnormal with both portal and systemic venous drainage methods, but more severely so in the animals reconstructed with a mesenteric-systemic shunt. However, no such metabolic distinction was seen between the two drainage methods in the pig experiments of Kaneko et al.[30] In addition, the latter authors could not prove any prolongation of animal survival of portal drainage in allotransplantation experiments under treatment with cyclosporin.

Clinical experience

Historical cases

Detailed descriptions of operative procedures and postoperative courses of 11 patients receiving isolated intestinal grafts under azathioprine or cyclosporin have been reported by others in the literature (Table 10.2).[31–41] The arterial reconstruction in these cases was made by using three vessels: the infrarenal abdominal aorta, the iliac artery, and the superior mesenteric artery. The preferred outflow sites for intestinal venous drainage were the iliac vein and the inferior vena cava, but the left renal vein, the superior mesenteric vein and the portal vein were also used in three cases. In the selection of the recipient vein for these reconstructions, technical feasibility was the single most determining factor. For example, Alican anastomosed the graft vein to the left renal vein of the recipient since both the inferior vena cava and the iliac vein were completely thrombosed by his patient's underlying disease.

It was not practical to compare the performance of systemic versus portal drainage methods in these clinical cases because most of the grafts failed shortly after intestinal transplantation. However, it is noteworthy that two recipients whose graft venous flow (one from a segment of living donor intestine and the other a cadaver intestine) was drained into the systemic circulation, are currently alive for more than 3.5 and 4 years, respectively, with no evidence of metabolic abnormality.[39,41] One of the patients, a 15 month-

Table 10.2 Historical cases of isolated intestinal transplantation

Year	Investigator	Reference Number	Patient's Age	Indication	Donor	Graft	Reconstruction Artery	Reconstruction Vein
A. Azathioprine era								
1967	Lillehei	31	46	SMV thrombosis	Cadaveric	Whole	Iliac	Iliac
1968	Okumura	32	34	SMA thrombosis	Cadaveric	Partial	Iliac	Iliac
1969	Olivier	33	35	Gardner's syndrome	Cadaveric	Whole	SMA	SMV
1969	Allican	34	8	Volvulus	Living	Partial	Aorta	Left Renal
1970	Fortner	35	37	Gardner's syndrome	Living	Partial	Iliac	Iliac
B. Cyclosporine era								
1985	Cohen	36	26	Gardner's syndrome	Cadaveric	Whole	Aorta	IVC
1987	Goulet	37	9	Volvulus	Cadaveric	Partial	Aorta	IVC
1988	Hansmann	38	5	Volvulus	Living	Partial	Iliac	Iliac
1988	Deltz	39	42	SMV thrombosis	Living	Partial	Iliac	Iliac
1988	Grant	40	8	Neuromyopathy	Cadaveric	Whole	Aorta	Portal
1989	Goulet	41	0.4	Volvulus	Cadaveric	Whole	Aorta	IVC

old girl, who was underdeveloped at the time of transplantation, is now normal for both height and weight.[41] Thus, the problem of venous drainage in clinical intestinal transplantation may have less influence on metabolism and immunology than in animal experiments.

Our experience

We tried to drain the intestine physiologically through the host portal vein in our isolated intestinal recipients. The predicted technical difficulties were minimized by using a mesenteric piggy-back procedure.[42] With this approach, the portal vein is found in the subhepatic triad and dissected to obtain enough length for its side to accept the end of the superior mesenteric vein or the portal vein of the graft. This has been feasible even when the patients have had multiple laparotomies and adhesions. Of the 9 recipients in whom an isolated graft was transplanted, intestinal transplantation was successfully performed with this technique in 7. In the remaining two, the recipient superior mesenteric vein which was dissected out of the scar inferior to the transverse mesocolon was used to receive the graft superior mesenteric vein end-to-end. The inferior vena cava for mesenteric outflow was used on one occasion for retransplantation of a patient who had a gunshot wound at the hepatic hilum and who lost the first graft to chronic rejection. The venous drainage for the first graft had been via an end-to-end anastomosis to the recipient's superior mesenteric vein. There were no technical complications nor metabolic problems in any of these cases.

Liver in intestinal grafting

There are numerous experiments demonstrating that the concomitantly transplanted liver induces immunologic protection, or tolerance, to other organ allografts procured from the same donor. Because of severe graft rejection that develops in experimental and clinical intestinal transplantation, Grant et al. proposed that the liver should be transplanted with the intestinal graft to mitigate graft rejection, even if the recipient has normal liver function.[43] In contrast, patients who have intestinal failure and liver disease, as complication of TPN or inborn errors, require combined intestine and liver transplant. If the intestinal failure is from the thrombotic problems that involve both the celiac axis and the superior mesenteric artery or if the indication is a centrally located tumour, abdominal multivisceral transplantation may be chosen as the method of surgical treatment.

Basic considerations

Hepatic tolerogenicity

Evidence of hepatic tolerogenicity for other tissues and organs from the same donor was first noted in our original canine multivisceral experiments.[44] The concept was fully developed by Calne in 1969 who showed indefinite prolongation of kidney and skin graft survival in pigs receiving concomitant liver transplantation.[45] This finding was confirmed later by Kamada and others, using rat liver transplantation with various strain combinations.[46] The mechanism of hepatic tolerogenicity is still unclear, but many explanations have been proposed, such as clonal deletion of cytotoxic T cells, production of antibody to class II MHC, liver enzymes inactivating antigen, antigen alteration by Kuppfer cells, inhibition of immune stimulation, and production of soluble donor class I antigen. However, the recent demonstration that migratory tissue leukocytes from the liver create a state of microchimerism in the recipient has provided an alternative and more likely explanation.[47,48,49]

Microchimerism

We now believe that the development of two-way cell traffic, between the graft and the recipient, leading to long-lasting systemic microchimerism is the reason for hepatic tolerance as well as tolerance induced by other organs including the intestine. During histoimmunologic studies of rats receiving multivisceral transplantation, Murase et al. found that the cells in the lymphoid and non-lymphoid tissues of the grafts were replaced by recipient-derived cells as early as 12 days after transplant,[50] a finding also seen by Arnaud-Battandier in pigs.[51] Not only did recipient spindle-shaped dendritic cells, positive for anti-recipient-Ia monoclonal antibody, repopulate into the graft, but donor dendritic cells migrated from the graft and resided in tissues of the recipient.[52] After intestinal transplantation, donor-derived cells in the spleen, mesenteric lymph nodes and peripheral blood in the recipient accounted approximately for 10–15 per cent of cells at 1 week, 5–10 per cent at 3 weeks and 5 per cent at 4 to 6 weeks.[52] Similarly, Iwaki et al. described two-way cell traffic phenomenon in the patients receiving intestinal transplantation.[53] Ten to 15 per cent of peripheral blood cells in the human recipients were of donor phenotype for several weeks after transplantation, and lymphoid tissues of the intestinal graft were completely repopulated by recipient-derived cells within 45–90 days after transplantation. Although Grant attributed the presence of donor cells in recipient circulation to transient GVHD,[43] no GVHD was seen in Iwaki's cases and we now realize that this occurs in all cases.

The two-way cell traffic phenomenon or microchimerism is not unique to intestinal transplantation, but is also seen after transplantation of other organs in both experimental and clinical settings; donor-derived dendritic cells were demonstrated in the peripheral blood and tissues of patients who underwent hepatic or renal transplantation 10 to 29 years previously. Thus, development of systemic chimerism seems to be an obligatory step for successful transplantation and for graft acceptance or tolerance in all whole organs. These findings suggest that the liver exhibits more pronounced tolerogenicity because it contains abundant lymphoreticular cells and has a greater capacity to induce systemic microchimerism than other organs. Donor-specific soluble class I antigens that are detectable in systemic circulation after liver transplantation have been attributed to hepatocytes,[54] but these antigens undoubtedly are secreted in large part by these peripheralized donor-derived cells of macrophage/monocyte lineage.

Experimental findings with intestinal transplantation

Rat experiments

Protection by the liver of intestinal graft rejection has been studied by Grant's group in Canada and Goulet's group in France.[55,56,57] Grant et al. demonstrated that when the LEW intestine was transplanted into DA rats without immunosuppression, all of the rats developed histologic acute rejection at 7 days, and had full-thickness necrosis of the intestinal wall at 14 days at sacrifice. However, these changes were not observed when they transplanted the intestine and liver simultaneously. Combined graft recipients had suppressed function of both T and B cells. Goulet and his associates tried to induce tolerance of the intestine by transplanting the intestine 14 days after liver transplantation from DA rats to PVD rats.[57] By this method, five of the six combined graft animals lived for more than 150 days without any immunosuppression, whereas all of the iso-

lated intestine recipients died of rejection with median animal survival of 7.6 days.

However, the induction of immunologic protection by the liver appears to be limited to particular strain combinations and to the timing of intestinal grafting after liver transplantation. When the combined grafts from DA rats were transplanted simultaneously,[50] not separately, into PVG recipients (a low responder), the intestine did not become tolerant; rather, the PVG recipients died within 9 days after transplant from lethal GVHD. Neither the liver nor intestine of the combined graft animals showed rejection. Animals receiving an isolated graft of this combination died by rejection with mean survival of 18.6 days. When a BN to LEW combination (a moderate responder) was used, animals that received a combined graft died either of GVHD or liver rejection with mean survival of 12.6 days. Isolated intestinal graft recipients with this combination died of rejection with a mean survival time of 12.8 days. Finally, when an ACI to LEW combination (a high responder) was used, 3 out of the 5 combined graft animals died within 13 days from severe hepatic rejection but with normal intestine. Isolated graft rats in this combination died of rejection with mean survival of 12 days.

Instead of combined intestine and liver grafts, we studied immunologic protection by the liver using a multivisceral transplantation model in BN to LEW strain combination.[50,58] The results of multivisceral transplantation were compared with those with isolated intestine or liver transplantation alone. Without immunosuppression, isolated liver recipients survived indefinitely, whereas animals receiving multiple organs or an isolated intestine lived only for 10 to 13 days. Both groups of animals had severe and similar intestinal rejection by histopathologic study. Thus, immunologic protection by the liver to the companion intestine was not demonstrated in this model. When a 14-day course treatment with low-dose FK 506 was given, most of the animals were able to survive for more than a 100 days in all three transplant groups.[50] However, intestinal rejection detected by histologic analysis of sacrificed animals was worse in animals with an isolated intestine than in animals with a composite of multivisceral grafts. Body weight gain was suppressed in isolated graft animals compared with the multivisceral group. These findings indicate that the liver in the multivisceral graft provides an immunologic advantage to the companion intestine under low-dose FK 506 treatment. However, when immunosuppression was augmented to a high-dose 14-day course therapy, the difference between the multivisceral group and the isolated intestine group decreased. When both groups of animals were treated by high-dose FK 506 for 14 days and with weekly supplementation, there was no difference in body weight gain or histologic severity of intestinal rejection. Hepatic tolerogenicity that is barely seen with low-dose immunosuppression became insignificant when high-dose FK 506 was administered.

Large animal experiments

The multivisceral transplant operation was described in dogs more than 30 years ago.[44] Of the 38 animals submitted to this operation in 1959 without immunosuppression, only 5 lived for 5.5 to 9 days. Histologic studies revealed attenuation of liver graft rejection in these animals compared with animals that underwent liver transplantation alone, suggesting mitigation of the rejection process. There also was little evidence of rejection in the bowel and other organs of the multivisceral graft, prompting the conclusion that here also rejection was attenuated. On the other hand, strong histopathologic evidence of GVH reaction was found in the bone marrow, lungs, and other organs of the animals receiving multivisceral organs than in animals receiving isolated liver grafts.

Clinical experience

Historical cases

In November 1987, a child in Pittsburgh who received a multivisceral graft became the first recipient of an intestine that provided nutritional function. The patient died after 6 months of a B cell lymphoma, but during life there was little or no evidence of rejection – either of the liver or of the other viscera.[59] Immunosuppression was with cyclosporin, low doses of prednisone, and OKT3.

More decisive clinical evidence of amelioration of intestinal rejection by a hepatic graft was subsequently described by Grant et al. in a 41 year-old woman, who lost her small intestine by superior mesenteric artery thrombosis from antithrombin-III deficiency.[43] She received a combined liver and small bowel allograft under immunosuppression with cyclosporin, steroids and azathioprine. The donor was treated by OKT3 before procurement. After surgery, she de-

veloped mild GVHD on the eleventh postoperative day, which subsided spontaneously. During the ninth postoperative week, she developed mild intestinal rejection which was easily treated by steroid tapering and OKT3. There was no other episode of rejection in either of the grafts thereafter. The patient has been doing well for the past 4 years, nutritionally supported by an unlimited oral diet. The benign postoperative course in this historically important case was in clear contrast to this group's previous experiences with clinical intestinal transplantation, suggesting that the coexisting liver graft ameliorated intestinal rejection. However, a patient who received a combined graft in Wisconsin died after 52 days by rejection,[60] and a second patient treated by us with multivisceral transplantation under cyclosporin suffered the same fate as well as a disseminated lymphoma.[61]

Our experience

We only perform a combined intestine and liver transplant on patients who have end-stage organ failure in both the intestine and liver. Of the 17 recipients receiving combined grafts at our centre under FK 506-based immunosuppression, all had cholestatic liver disease related to long-term hyperalimentation, with a median preoperative serum bilirubin level of 18.5 mg/dl, ranging from 2.3 mg/dl to 50.5 mg/dl. Most of these patients had evident portal hypertension and hypersplenism. Nine patients who had intestinal failure with normal liver function were transplanted with the intestine alone. Twelve out of the 17 combined graft recipients and all of the isolated graft recipients were operated on between May 1990 and June 1992. The survival, postoperative course, and the incidence and severity of graft rejection with a minimum follow-up for three months were computed and compared to determine the performance of respective surgical procedures (Table 10.3).[62,63]

Nine of the 12 combined graft recipients are currently alive. There were 3 deaths: 2 from septic complications related to technical problems and 1 from postoperative lymphoproliferative disease. Patient and graft survival was 75 per cent (9/12). Of the 9 isolated graft recipients, one patient died from sepsis 71 days after retransplantation and removal of the primary graft which had been destroyed by chronic rejection after 23 months. Another patient required graft removal and re-

Table 10.3 Comparison of intestinal graft performance

	Isolated small bowel	Combined small bowel and liver
Number		
Patient	9	12
Graft	10	12
Survival*		
Patient	8 (90%)	9 (75%)
Graft	7 (70%)	9 (75%)
ICU Stay, days	6 (4–14)	3 (3–300)
Hospital Stay, days	79 (33–159)	82 (23–320)
Readmission, times	1 (1–7)	2.5 (0–9)
Stop TPN, days	30 (19–113)	83.5 (44–330)
Rejection Episodes		
Intestine	10 (90%)	10 (83%)
Current Status		
TPN, Free	7	8
TPN, Partial	1	1
Hospital	2	0
Home	6	8

*Follow-up till 30 September 1992

turned to hyperalimentation after discontinuation of immunosuppression because of viral encephalitis. Patient and graft survival was 88.9 per cent (8/9) and 70 per cent (7/10), respectively.

The postoperative courses, including Intensive Care Unit (ICU) stay, hospital stay, start of enteral feeding, and discontinuation of TPN, were more favourable for isolated graft recipients than those with the combined grafts. Methods of monitoring and treating graft rejection have been described elsewhere.[2–5,64] Of the 22 grafts, 19 experienced intestinal rejection. This occurred at a 90 per cent incidence (9/10) in the isolated grafts and at an incidence of 83 per cent (10/12) when the intestine was part of a combination graft (differences not significant). Of the 12 combined grafts, acute rejection was more frequent with the intestine (83 per cent, 10/12) than in the liver (42 per cent, 5/12). The incidence of liver rejection in the combined graft was not different from that seen after liver transplantation alone. Synchronous graft rejection in the combined grafts (diagnosed by biopsy samples) of the small intestine and liver was seen on 8 occasions: this accounted for 17 per cent of 48 episodes of intestinal rejection versus 31 per cent of 26 episodes

of hepatic rejection. In contrast, 83 per cent (40/48) and 69 per cent (18/26) of the total episodes of acute rejection developed independently in intestine and in liver, respectively.

Conclusions

Our experience has shown that clinical transplantation of the intestine alone or with other abdominal viscera is feasible under the improved immunosuppression that has been made possible with FK 506. How much these procedures can improve the quality of life for patients who are destined to remain on TPN for life, or save patients from lethal TPN-related complications, will have to be determined by more cases and longer follow-up periods. Venous outflow from isolated intestinal grafts can be drained into the portal system and then through the native liver using a mesenteric piggy-back method. If the mesenteric piggy-back method is not possible, a mesenteric-systemic shunt can be used, probably without serious metabolic consequences. Although hepatic tolerogenicity is a well-established concept, simultaneous liver transplantation is not necessary for successful intestinal transplantation in humans and it adds to the risk and magnitude of the treatment if the patient does not have hepatic failure. Thus, isolated intestinal transplantation should be chosen for patients who are destined to be on TPN for life, but who still have normal liver function. Combined intestine and liver transplantation is reserved for those patients who need an intestine and have liver failure as a complication of TPN or inborn hepatic disorders. Multivisceral transplantation is reserved for special indications.

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