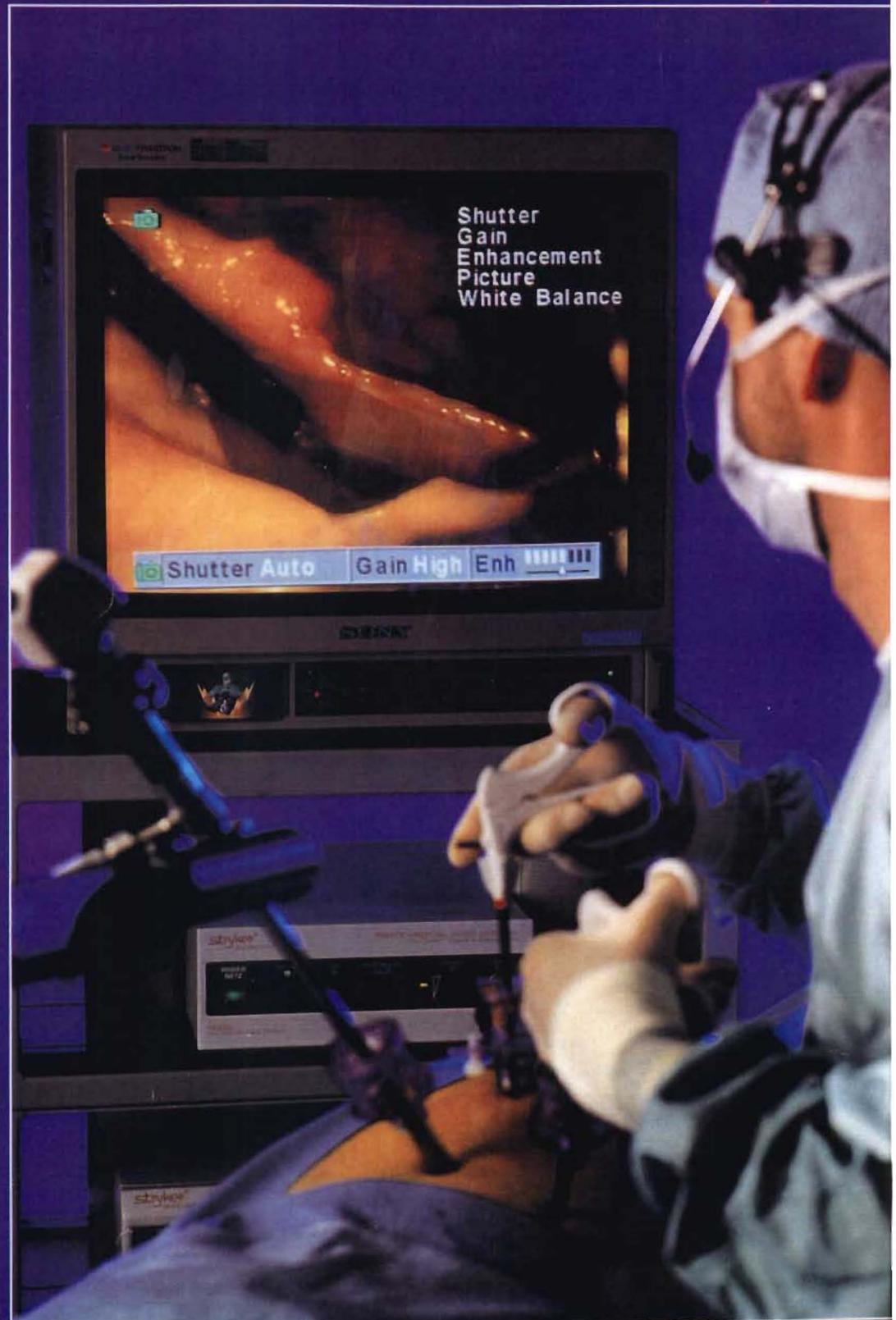


# SURGICAL TECHNOLOGY

INTERNATIONAL VIII

International  
Developments  
in Surgery and  
Surgical  
Research



Edited by Zoltán Szabó, PhD, FICS, James E. Lewis, MD, FACOG,  
Gary A. Fantini, MD, FACS and Raghu S. Savalgi, MD, PhD(surg), FRCS

# Intestinal Transplantation: Current Status and Latest Developments

CATALDO DORIA, M.D., ASSISTANT PROFESSOR OF SURGERY<sup>1</sup>  
MAURICIO GIRALDO, M.D., CLINICAL FELLOW<sup>1</sup>  
JAVIER R. BUENO, M.D., CLINICAL FELLOW<sup>1</sup>  
GEORGE MAZARIEGOS, M.D., F.A.C.S., ASSISTANT PROFESSOR OF SURGERY<sup>2</sup>  
HUGO VARGAS, M.D., ASSISTANT PROFESSOR MEDICINE<sup>3</sup>  
SAMUEL KOCOSHIS, M.D., PROFESSOR OF PEDIATRICS<sup>4</sup>  
IGNAZIO R. MARINO, M.D., F.A.C.S., PROFESSOR OF SURGERY<sup>1</sup>  
ANTHONY DEMETRIS, M.D., PROFESSOR OF PATHOLOGY<sup>5</sup>  
JOHN J. FUNG, MD, PH.D., F.A.C.S., PROFESSOR OF SURGERY, CHIEF, TRANSPLANTATION SURGERY<sup>1</sup>  
THOMAS E. STARZL, M.D., PH.D., F.A.C.S., DISTINGUISHED SERVICE PROFESSOR OF SURGERY, DIRECTOR<sup>1</sup>  
JORGE REYES, M.D., F.A.C.S., ASSOCIATE PROFESSOR OF SURGERY<sup>2</sup>  
KAREEM ABU-ELMAGD, M.D., F.A.C.S., ASSOCIATE PROFESSOR OF SURGERY<sup>1</sup>

<sup>1</sup>DEPARTMENT OF SURGERY, THOMAS E. STARZL TRANSPLANTATION INSTITUTE  
UNIVERSITY OF PITTSBURGH AND THE NATIONAL LIVER TRANSPLANT CENTER OF THE DEPARTMENT OF VETERANS AFFAIRS;

<sup>2</sup>DEPARTMENT OF TRANSPLANT SURGERY, CHILDREN'S HOSPITAL OF PITTSBURGH

<sup>3</sup>DIVISION OF GASTROENTEROLOGY AND HEPATOLOGY, UNIVERSITY OF PITTSBURGH

<sup>4</sup>DIVISION OF GASTROENTEROLOGY AND HEPATOLOGY, CHILDREN'S HOSPITAL OF PITTSBURGH

<sup>5</sup>DIVISION OF TRANSPLANT PATHOLOGY, UNIVERSITY OF PITTSBURGH

PITTSBURGH, PA

Intestinal transplantation is no longer an experimental procedure and is the treatment of choice for patients with irreversible intestinal failure that cannot be maintained on total parenteral nutrition (TPN). The intestine was a forbidden organ to be transplanted in humans until the 1980s due to its rich lymphoid content that precipitates either host-versus-graft or graft-versus-host alloreactivity.

These immunologic barriers were initially recognized and appreciated in the dog models studied by Lillehei<sup>1</sup> and Starzl.<sup>2</sup> The evolution of intestinal transplantation has distantly paralleled that for kidney and liver transplantation. Despite the availability of

cyclosporin A (CyA) since the beginning of the last decade, the delay in the clinical success of intestinal transplantation was mainly due to refractory allograft rejection, host infection and complexity of the operation. Although the intestine was one of the first organs

to be transplanted experimentally, it has been the last to be successfully transplanted in humans. Before the clinical introduction of CyA, intestinal transplantation was successfully performed in seven patients and despite the use of azathioprine, steroid, anti-

lymphocyte globulin, or thoracic duct drainage, all died of rejection and/or sepsis within the first 10 weeks after transplantation.<sup>3</sup> With the clinical introduction and proven therapeutic benefits of CyA, the Toronto group performed the first intestinal transplantation using CyA in 1986, but the patient died during the early post-operative period. Before the clinical introduction of tacrolimus (FK506) several other patients had been transplanted under CyA based immunosuppression and all of them except one succumbed to rejection and/or sepsis. The only survivor is a French girl who received an isolated small bowel transplant more than 11 years ago.<sup>4</sup> She was recently switched from CyA to tacrolimus based immunosuppression and has been off TPN for many years with full nutritional autonomy.

Clinical introduction of tacrolimus during the second half of 1989 triggered a new interest in intestinal transplantation. Based upon the International Transplant Registry<sup>5</sup> database more than 33 centers worldwide are currently performing intestinal transplantation. Up to February of 1997, more than 280 intestinal transplants were performed in Europe and in North America.

### CAUSES OF INTESTINAL FAILURE

Maintenance of normal gastrointestinal function includes the coordination of a series of complex interactions. Despite the essential regulatory role of the central nervous system, impairment of the digestive, absorptive, neuroendocrine, and motor functions of the gastrointestinal system are the primary causes of gastroenteric failure. Intestinal insufficiency can be defined as the loss of the absorptive capacity of the native intestinal mucosa<sup>6</sup> with the inability to maintain adequate nutrition and proper homeostasis of body fluids and electrolytes. The most common cause of intestinal failure is the development of short gut syndrome due to either the anatomical loss of the intestine or its congenital absence. Under these circumstances, the remaining intestine undergoes a series of adaptive changes which consist of increase in the diameter of the remaining bowel, and the length of the villi. This adaptation phenomenon is probably stimulated by the intraluminal nutrients, pancreatico-

biliary secretions, gut hormones and other enterotropic factors. The adaptation process includes three phases: phase I (7 to 10 days), when diarrhea is severe and patients require massive fluid and electrolyte replacement; phase II (1 to 3 months), when diarrhea stabilizes and patients still need TPN and other medical treatment; and phase III (3 to 12 months), when diarrhea is controlled enough to allow enteral feeding and weaning from TPN.<sup>7</sup> If TPN cannot be discontinued 12 to 24 months after the initial insult, intestinal failure approaches an irreversible state, necessitating permanent TPN therapy.

At the time of the surgical resection of the small bowel, it is very difficult to predict the risk of intestinal failure. However, the length of the remaining small bowel, the location of the resection, the presence of the colon, and the preservation of the ileocecal valve are important factors that determine reversibility of the gut failure.<sup>8,9</sup> In general, resection of more than 70% of the total length of the small bowel with loss of the right colon, including the ileocecal valve, is associated with a high incidence of irreversible intestinal failure.

### INDICATION FOR TRANSPLANTATION

Irreversible (chronic) intestinal failure and the permanent need for TPN is currently an absolute requirement for intestinal transplantation. Irreversibility is based upon length/pathophysiologic status of the remaining native bowel and failure of medical management during the three phases of adaptation. The current indications for intestinal transplantation are primarily short gut syndrome, gastrointestinal dysmotility (pseudo-obstruction), premalignant gastrointestinal tumors, and impaired enterocyte absorptive capacity. The individual causes of these syndromes are the following:

1. short gut syndrome: necrotizing enterocolitis, intestinal atresia, midgut volvulus, complicated gastroschisis, abdominal trauma, Crohn's disease, surgical adhesions, Gardener's syndrome, desmoid tumor, and/or mesenteric vascular thrombosis.
2. Defective intestinal motility: hollow visceral myopathy, neuropathy, and/or total intestinal aganglionosis.
3. Impaired enterocyte absorptive

capacity: microvillus inclusion disease, selective autoimmune enteropathy, radiation enteritis, extensive inflammatory bowel disease and/or massive intestinal polyposis.

Combined liver and small bowel transplantation is considered the only therapeutic option available for patients with irreversible failure of both the liver and the intestine. Liver failure in these unique patients is usually cholestatic and is primarily related to the prolonged use of TPN. In some patients, genetic and metabolic errors of the hepatocytes, including hypercoagulability with thrombosis of the portomesenteric and visceral arterial system, are the leading causes of abdominal organ failure. The manifestations of liver failure in these patients include ascites, refractory variceal bleeding, spontaneous bacterial peritonitis, chronic hepatic encephalopathy, hepatorenal syndrome, and failure to thrive.

Multivisceral transplantation is usually offered for patients with irreversible failure of three or more of the abdominal visceral organs, including the small bowel and for those with extensive low-grade malignant tumors of the gastrointestinal tract. The individual causes are extensive thrombosis of the splanchnic venous system, massive gastrointestinal polyposis, and generalized hollow visceral myopathy or neuropathy.

### PRE-TRANSPLANT WORK-UP

Patients who are candidates for intestinal transplantation usually require a clinical guided work-up. A thorough evaluation, which includes a complete history and physical examination with full assessment of the nutritional, hepatic, renal, cardiopulmonary, hematologic, and immunologic status, is needed for each potential recipient.

Other specific tests should be individualized based upon the nature, severity, and extent of the primary disease. In a patient with short gut syndrome, it is necessary to assess the residual function of the remaining native small bowel, particularly those with diffuse intestinal diseases. This can be achieved by full radiologic, endoscopic, and pathologic examinations of the remaining intestine.

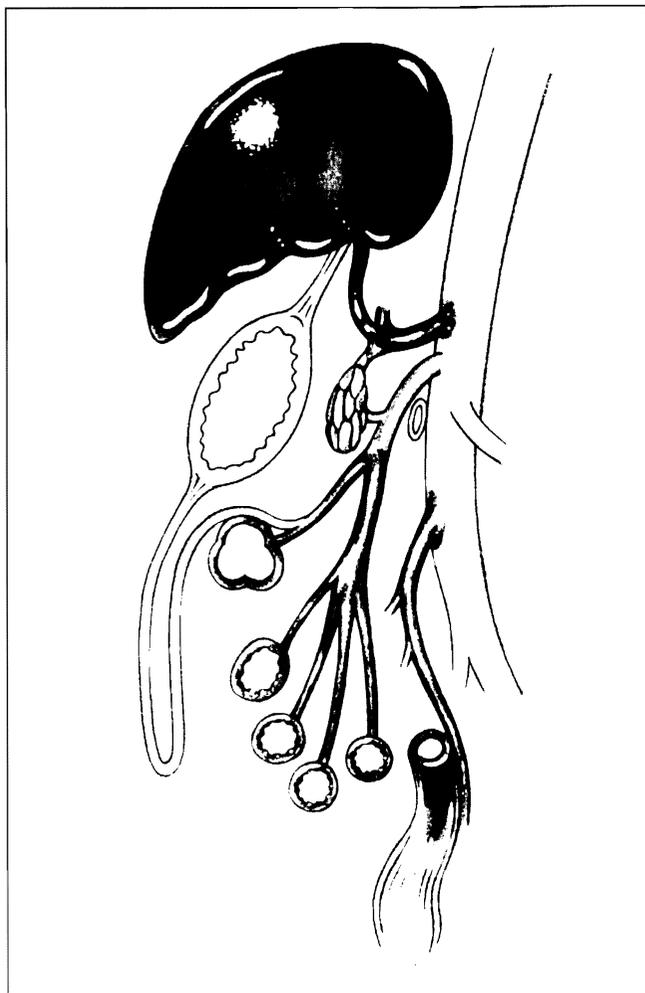


Figure 1. The segmental blood supply of the different parts of the gastrointestinal tract is shown. (From Fung JJ, Abu-Elmagd K, Todo S. Intestinal and multivisceral transplantation. Digestive tract surgery a text and atlas 1996, 1229-1261 Lippincott-Raven, used with permission).

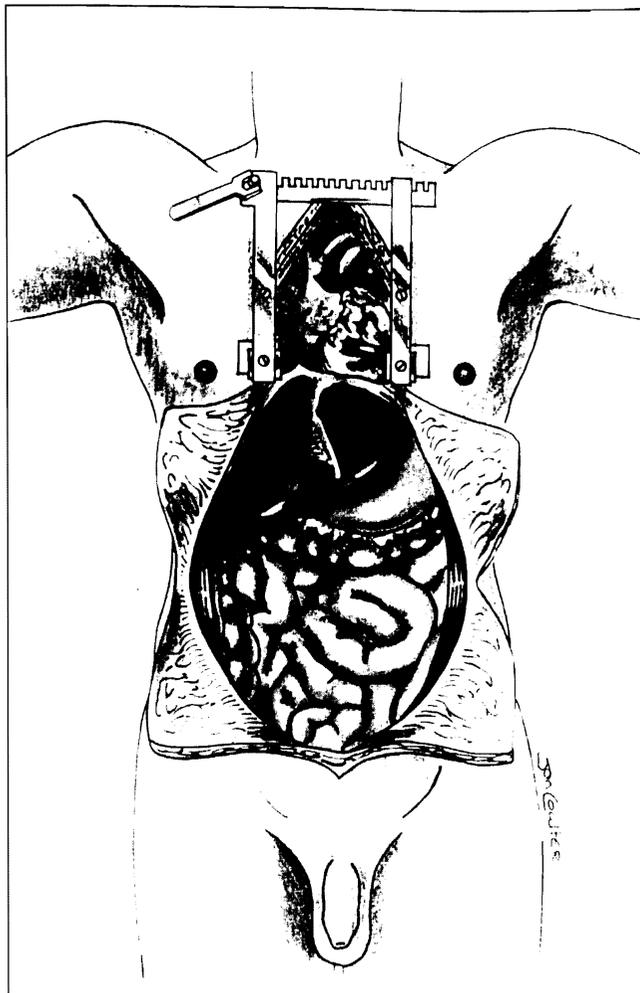


Figure 2. Donor operation with an abdominal transverse cruciate incision. (From Fung JJ, Abu-Elmagd K, Todo S. Intestinal and multivisceral transplantation. Digestive tract surgery a text and atlas 1996, 1229-1261 Lippincott-Raven, used with permission).

Motility studies of the upper and lower gastrointestinal tract are also mandatory for patients with pseudo-obstruction syndromes. Furthermore, cases of thrombotic disorders require abdominal visceral angiography and special hematologic studies including measurement of protein C, proteins S, and antithrombin III in the serum, and detection of factor II and V mutations.

In patients with desmoid tumors, new imaging techniques such as MRI should also be used to delineate the extent of the tumor, including its relation to the adjacent vital structures. Finally, particular attention should be paid to assess the extent of liver damage and status of hepatic reserve. If the liver injury tests are elevated, a liver biopsy should be performed to assess the need for liver replacement.

#### DONOR SELECTION

The criteria used to select potential small bowel donors are the same as those used for the isolated liver allografts. Hemodynamically stable and young age donors are usually preferred. All donors should be ABO identical to the recipient, and of smaller size and weight.

The histocompatibility locus antigens (HLA) match of the donor and recipient is not required with no attempts to deplete the donor lymphoid mass. Transplanting the intestine across a strong positive lymphocytotoxic cross-match should be avoided when possible, particularly with isolated intestinal grafts.

Cytomegalovirus (CMV) positive grafts are currently not used for CMV seronegative isolated intestinal recipi-

ents.<sup>10</sup> Selective gut decontamination should be attempted in all donors.

Amphotericin-B, tobramycin/gentamicin, and polymyxin-E are given through a nasogastric tube once the donor has been accepted and then every 6 hours until the time of procurement. University of Wisconsin (UW) solution is used for the *in situ* flush and for the preservation of the graft. The abdominal visceral organs are usually harvested *en bloc* and fashioned on the back table based on the intraoperative findings and recipient needs.

#### TECHNICAL ASPECTS OF THE DONOR OPERATION

A key factor in the success of intestinal transplantation is the procurement of good quality graft. In order to perform the proper donor operation for

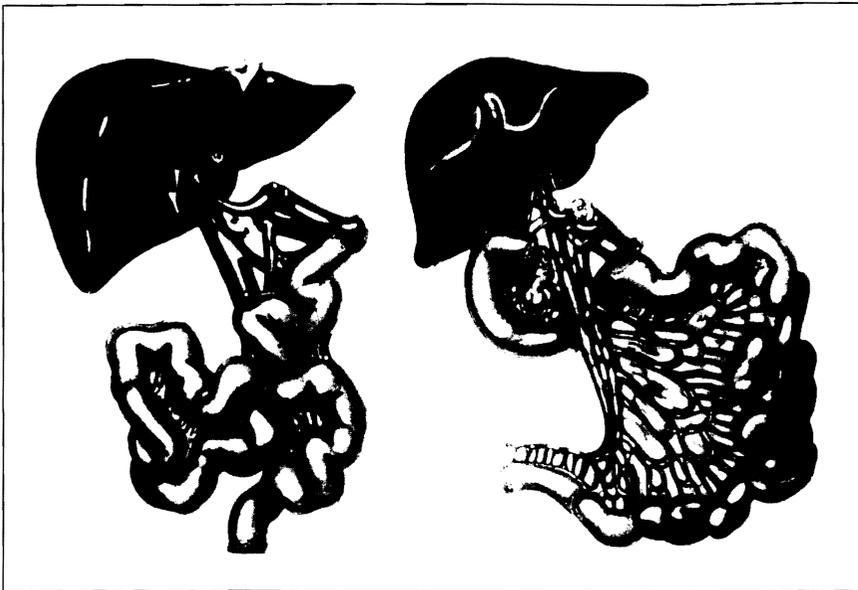


Figure 3. Composite liver and intestinal graft with preservation of the duodenum in continuity with the graft jejunum and hepatic biliary system. Note transection of the pancreas to the right of the portal vein with preservation of the pancreaticoduodenal arterial and venous arcade. The technique reduces the time of the recipient operations and avoids the potential risk of biliary reconstruction.



Figure 4. The split graft prepared for implantation. Vascular homografts have been attached with an aortic conduit to the left side, and separate arterial and venous grafts to the right side. IVC, inferior vena cava; RPV, right portal vein; RHA, right hepatic artery; RDH, right hepatic duct; CBD, common bile duct; PV, portal vein; HA, hepatic artery; CA, celiac artery; SMA, superior mesenteric artery; SMV, superior mesenteric vein. [From Reyes J, Fishbein T, Bueno J, et al. Reduced-size orthotopic composite liver-intestinal allograft. *Transplantation* 1998, 66: 489-492, used with permission].

the three different grafts, it is important to know the embryonic origin of the blood supply of the different parts of the alimentary tract as shown in Figure 1.

### Isolated Intestine

The retrieval procedure starts with a cruciate abdominal incision (Figure 2). The greater omentum is carefully dissected and separated from the transverse mesocolon. After an extensive Kocher maneuver is completed, the cecum, ascending colon, and mesenterium are mobilized from the retroperitoneum. The right and middle colic vessels are divided and the ileum is transected at the ileocecal valve. The proximal jejunum is divided close to the ligament of Trietz. The third and fourth portion of the duodenum are further mobilized and dissected from the root of the mesentery by dividing several numerous branches from the superior mesenteric vessels. By transecting the pylorus and neck of the pancreas, the portal and the superior mesenteric vessels are exposed, dissected from the pancreas and duodenum by interrupting small pancreatic and duodenal archades. Isolated harvesting of both the intestine and pancreas are technically feasible and were successfully performed in more than 8 donors in our series. The abdominal aorta is cannulated after systemic heparinization of the donor and perfused with UW solution. To separate the liver from the intestine, the portal vein is transected above the confluence of the superior mesenteric and splenic vein. A Carrel patch is fashioned at the origin of the celiac trunk and the superior mesenteric artery. The intestine is then removed and immersed in the UW solution. A vascular conduit is then usually anastomosed, when indicated, to the superior mesenteric vessels during the back table procedure.

### Liver/intestine

The liver is initially mobilized from its suspensory ligaments and the entire colon is mobilized from its retroperitoneal attachment with division of the gastrocolic omentum. The vessels within the mesentery of the terminal ileum, right, transverse and left colon are divided and the entire colon is rotated to the left and removed out of the field after dividing the distal ileum, as previously described with the standard multiple organ harvest.<sup>11</sup> After completing



Figure 5. Different type of intestine and composite intestinal grafts. (From Furukawa H, Abu-Elmagd K, Reyes J, et al. Technical aspect of intestinal transplantation Surgical Technology International II, Universal Medical Press, Inc. pp. 165-170, 1994 used by permission).

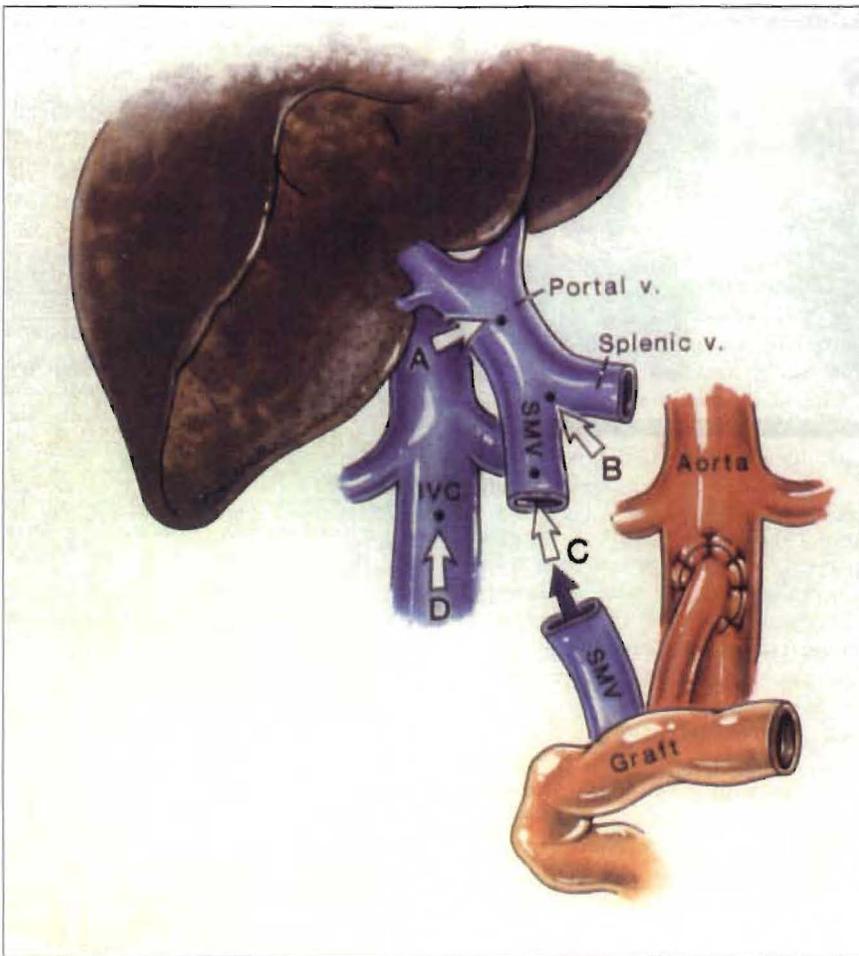


Figure 6. Vascular anastomosis of the isolated intestinal transplantation. Four type of venous anastomosis of the donor superior mesenteric vein (SMV) to (A) the main trunk of the portal vein, (B) the confluence of the superior mesenteric vein and the splenic vein, (C) the distal end of the superior mesenteric vein, (D) the inferior vena cava of the recipient. (From Furukawa H, Abu-Elmagd K, Reyes J, et al. Technical aspect of intestinal transplantation Surgical Technology International II, 1994, p. 165-170).

an extensive Kocher maneuver the right gastric and gastroepiploic vessels are divided and the pylorus is transected, which allows the stomach to be reflected cephalad. The distal pancreas and the spleen are then mobilized and reflected medially. The dissection of the tail and body of the pancreas is then continued until the confluence of the splenic and superior mesenteric vein is identified. The pancreas is then transected at the level of the neck leaving the head and uncinate process in continuity with the duodenum and carefully preserving the superior and inferior pancreaticoduodenal arcades (Figure 3). This step could be done *in situ* or on the back table. This technique significantly decreased the rate of biliary complications and shortened the operative time.

In a pediatric case, the left lateral hepatic segment and small bowel were successfully transplanted after an *in situ* split was performed at our institution to overcome a donor/recipient size mismatch in a 3-year-old child who was dying because of combined liver-small bowel failure (Figure 4).

#### Multivisceral Graft

The harvest of a multivisceral graft, which includes the stomach, duodenum, pancreas, intestine, and liver is similar to the technique used for the liver/intestine retrieval.<sup>11-14</sup> The key portion of the operation is the proper orientation of the organs and their vascular pedicles. The gastrohepatic ligaments and its contents are left intact, but the gallbladder is opened and flushed. The gastroesophageal junction is transected using the gastrointestinal stapler. Splenectomy is carried out either during the harvesting procedure or on the back table by ligating the splenic vessels close to the splenic hilus in order to avoid injury of the tail of the pancreas. After completion of the UW aortic flush, the multivisceral graft is removed *en bloc*. Placement of the arterial conduit and performance of the pyloroplasty are done on the back table.

#### RECIPIENT OPERATION

The technique used for removing the remaining native organs and implanting the intestinal graft either alone or in combination with other abdominal organs varies according to the nature of the primary disease and extent of previous abdominal surgery. Figure 5 shows

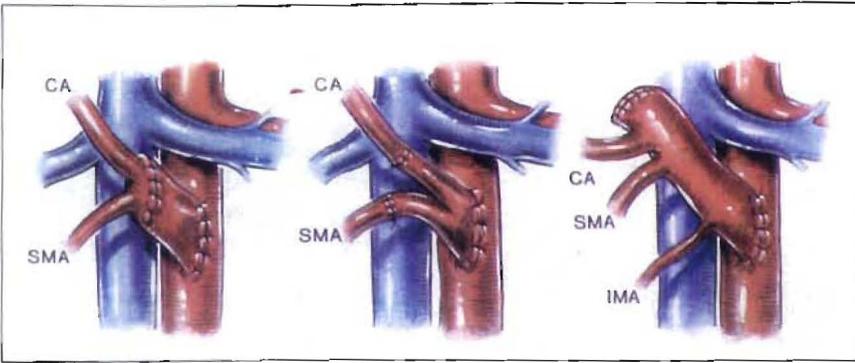


Figure 7. Types of arterial grafts used as vascular conduits for combined hepatic - intestinal and multivisceral grafts. The first arterial anastomosis shown is the one most often used. CA celiac artery; IMA inferior mesenteric artery; SMA superior mesenteric artery. (From Furukawa H, Abu-Elmagd K, Reyes J, et al. Technical aspect of intestinal transplantation Surgical Technology International II, Universal Medical Press, Inc., 1994, p. 165-170).

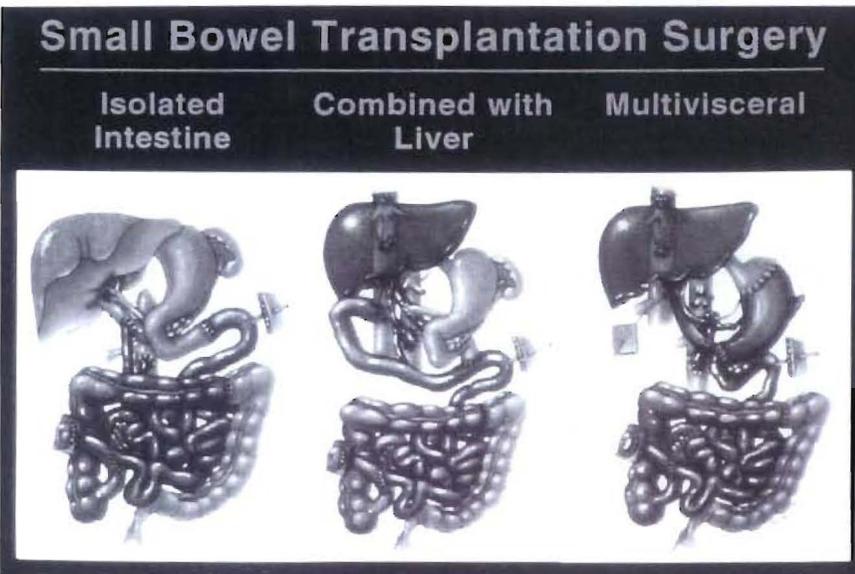


Figure 8. Isolated and composite intestinal transplantation.

the three different types of intestinal allografts. The abdominal cavity is usually entered through an extended cruciate incision, especially in cases with multiple previous abdominal surgery and portal hypertension with marked vascular adhesions. In general, the abdominal dissection is easier when the small bowel alone has to be transplanted because of the absence of significant liver disease and portal hypertension. The upper abdomen exenteration performed during multivisceral transplantation is the most difficult part of the three procedures, particularly in the presence of liver failure and extensive vascular thrombosis. Contracture of the abdominal cavity and defective abdominal wall in patients with previous multiple abdominal surgeries combined with

post-reperfusion edema of the transplanted bowel presents another technical challenge at the time of closure of the abdominal wall incision. In the majority of cases, small sized donors and innovative techniques are required to accommodate the allograft and reconstruct the recipient abdominal wall. Temporary use of synthetic materials and utilization of split thickness skin grafts or myocutaneous flaps are usually needed for some recipients.

#### Isolate Intestine

The superior mesenteric artery of the isolated intestinal graft is anastomosed in an end to side fashion to the recipient infrarenal aorta. In difficult cases, an interposition graft is anastomosed first to the recipient aorta. Controversy still exists regarding the venous

drainage of the isolated intestine (Figure 6). Based upon our current results, systemic venous drainage does not significantly affect the risk of rejection graft survival.<sup>15</sup> Therefore, the current recommendation is to utilize the systemic drainage for cases with difficult hilar dissection, previous transplantation, and prolonged cold ischemia time.

The proximal end of the intestinal graft can be anastomosed to the recipient duodenum, or residual native jejunum. A jejunostomy tube is always inserted for early graft decompress and enteral feeding. In patients with previous proctocolectomy, the distal end of the intestinal graft is exteriorized as an end ileostomy. An ileocolic or ileoileal anastomosis is performed in patients with residual native colon or ileum. A temporary vent chimney is always performed for patients in whom continuity of the distal gastrointestinal tract is achieved. The ileostomy allows easy access for endoscopies and constant surveillance of the graft. Surgical closure of the vent ileostomy is recommended 3 to 6 months after transplantation. For grafts that contain part of the donor colon, a Bishop-Coop ileostomy is usually required.

#### Liver/intestine

With combined liver/intestine transplantation, recipients are subjected to the well known hemodynamic and metabolic changes that commonly occur during the anhepatic phase, and after reperfusion. In these patients, the use of the veno-venous bypass is usually compromised by the coexistence of significant stenosis or thrombosis of the superior vena cava due to the long-term use of central venous catheters. Therefore, the procedure of choice for the hepatectomy is the piggy-back technique.<sup>16</sup>

With the combined liver-small bowel transplantation, venous drainage of the native left splanchnic venous system to the recipient cava (portocaval shunt) is required before dissection of the native gut in order to minimize the operative blood loss. The conversion of portocaval shunt to portoportal shunt after reperfusion of the allograft is not recommended in cases with small donor portal vein in order to avoid the potential risk of portal vein thrombosis. The arterial inflow is established by an end-to-side anastomosis between the arterial graft and the recipient infrarenal aorta. The arterial

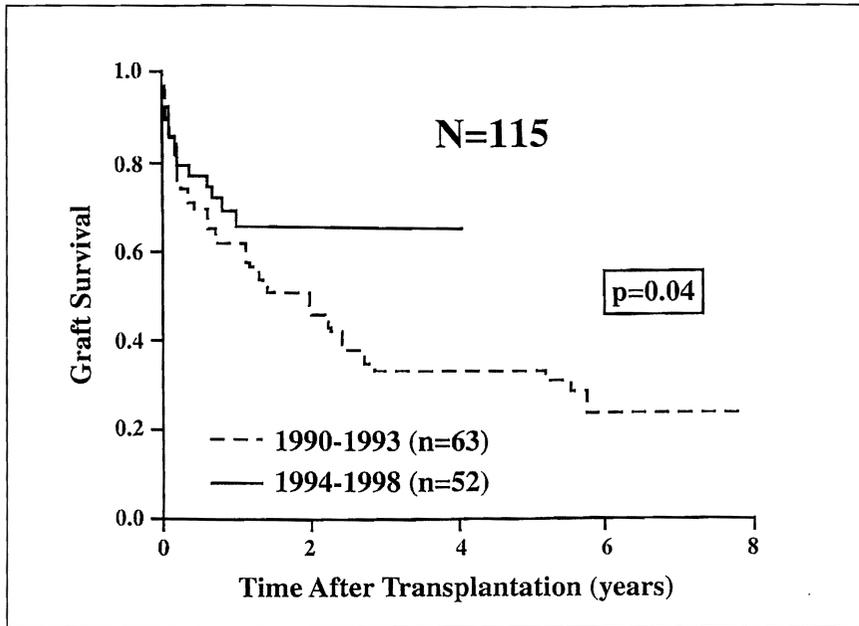


Figure 9. Graft survival according to the time of transplantation at the University of Pittsburgh Medical Center. (From Abu-Elmagd K, Reyes J, Fung JJ, et al. Evolution of clinical intestinal transplantation: Improved outcome and cost effectiveness. *Transplant Proc* (in press) used with permission).

graft (Figure 7) is mounted during the back table procedure and is anastomosed to the Carrel patch, which includes the origin of both the donor celiac trunk and superior mesenteric artery. The graft is flushed with blood and the intestinal continuity is later established as described with the isolated intestinal transplantation.

#### Multivisceral

The multivisceral transplantation is an *en bloc* procedure as shown in Figure 8 (right insert). In this procedure, the proximal alimentary tract anastomosis is established between the recipient esophagus and the donor stomach. Also, the biliary system is temporarily decompressed and the bile flow is externally diverted through a cystic duct catheter to prevent postoperative pancreatitis and to facilitate early diagnosis of ampullary dysfunction (Figure 8).

#### Post-Operative Management

The difficulties in the postoperative management of small bowel transplant recipients are primarily due to multiple immunologic and biologic barriers; the massive lymphoid content of the gut, the heavy bacterial load of the intestinal lumen and the complexity of the graft absorptive and neuroenteric functions. Full details of the postoperative management of the intestinal allograft recipients are described elsewhere.<sup>15</sup>

#### Immunosuppression

The immunosuppressive therapy utilized at our center is based primarily on tacrolimus and prednisone; cyclophosphamide is added as an induction therapy for some patients at a dose of 2 to 3 mg/kg/day for 4 weeks, and then switched to mycophenolate mofetil (15 to 30 mg/kg/day) or azathioprine. In a few cases, azathioprine was given as a third drug from the outset. In the most recent cases, the new humanized IL-2R-specific monoclonal antibody (daclizumab; Zenapax) is added as an induction therapy.

The level of maintenance immunosuppression is individualized and adjusted based upon the clinical course of each patient with the intention to reduce the drug dosage and levels whenever possible. Rejection episodes are treated with steroid bolus/taper and optimization of tacrolimus therapy. OKT3 is used only as a rescue therapy. Upward dose adjustment of mycophenolate, mofetil, azathioprine, or steroids, are frequently needed to compensate for tacrolimus dose reductions mandated by tacrolimus-related adverse effects.

#### PATIENT SURVIVAL

##### Our Experience

In our institution in Pittsburgh, PA, for the period between May 2 1990 and

July 17 1998, a total of 115 intestinal transplant were performed in 109 consecutive patients. The overall patient survival is 72% at 1 year and 48% at 5 years with a graft survival rate of 64 and 40% respectively. With a mean follow-up of  $40 \pm 29$  months (range of 1 to 94), 31 patients are alive with good nutrition beyond the third postoperative year, and 18 are well beyond the 5 year milestone. The survival benefits of intestinal transplantation has been better ( $p = 0.57$ ) achieved among children compared to adults with best outcome among patients between 2 and 17 years of age with a 5 year cumulative survival rate of 68%. Although the survival rate of the isolated intestine and the composite grafts was similar ( $p = 0.72$ ), the cumulative risk of graft loss due to rejection was significantly higher ( $p = 0.045$ ) among the isolated small bowel. Figure 9 depicts the significant improvement ( $p = 0.04$ ) in intestinal allograft survival at our center during the last 4 years with a cumulative rate of 65% at 4 years. These results are due to improvement in surgical techniques and postoperative management of this unique population.

#### Worldwide Experience

A total of 273 intestinal transplant were performed in 260 consecutive patients in 33 centers worldwide. Of these transplants, 41% were isolated intestine, 48% were combined intestine/liver, and 11% were multivisceral. The patient survival at 1 and 5 years was 80% and 55% for the isolated intestine, 65% and 40% for the combined liver/intestine, and 45% and 35% for the multivisceral transplants, respectively. The graft survival rate at 1 and 5 years was 50 and 30% (isolated intestine), 60 and 32% (combined liver/intestine) and 40 and 35% (multivisceral) respectively.<sup>5</sup>

#### COMPLICATIONS

##### Transplant Rejection

The diagnosis of intestinal rejection is currently achievable utilizing a high index of clinical suspicion, frequent surveillance endoscopic biopsies, and well established histopathologic criteria.<sup>17</sup> The current incidence of rejection ranges from 73 to 93% and most of the episodes are mild to moderate. About 50% of the episodes occur within the first 3 months after transplantation with

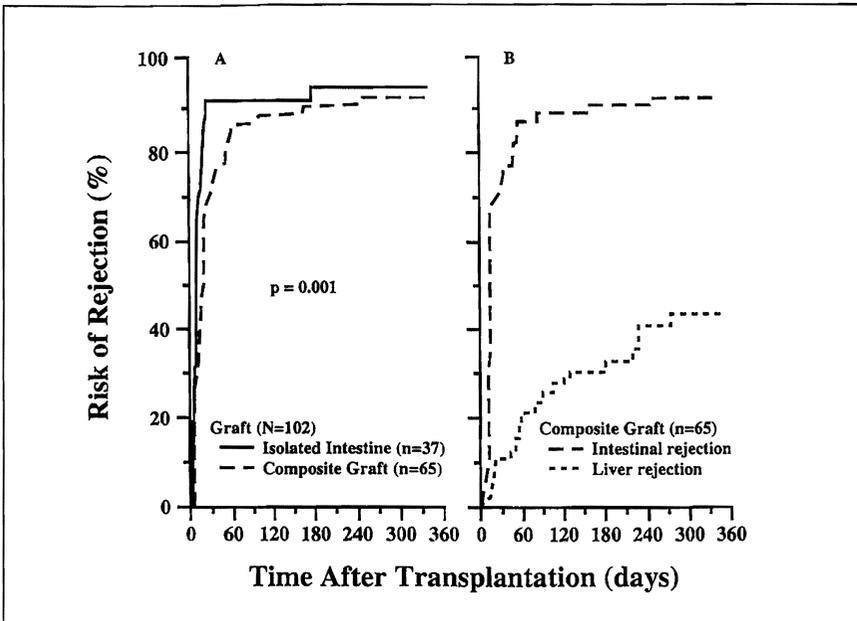


Figure 10. Cumulative risk of intestinal rejection for the isolated intestine and composite grafts that contained liver. (From Abu-Elmagd K, Reyes J, Todo S, et al. Clinical intestinal transplantation: new perspectives and immunologic considerations. *J Am Coll Surg* 1998; 186: 512-527, used with permission).

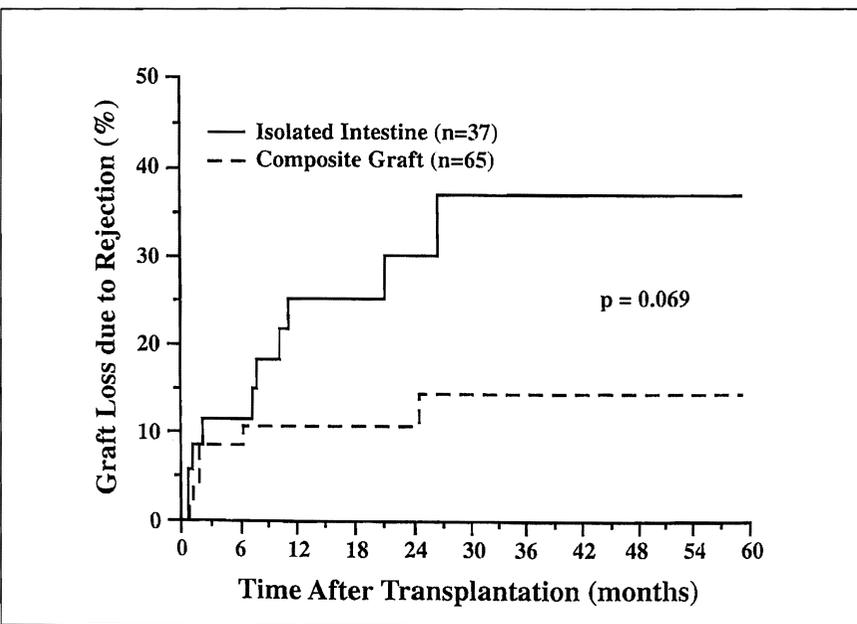


Figure 11. Cumulative risk of graft loss from rejection in the intestine-only and composite visceral grafts that contained liver. (From Abu-Elmagd K, Reyes J, Todo S, et al. Clinical intestinal transplantation: New perspectives and immunologic considerations. *J Am Coll Surg* 1998, 186:512-527, used with permission).

a higher incidence among the isolated intestine compared to the intestine contained in a composite graft and a similar cumulative rejection rate within the first year after transplantation (Figure 10A). However, the rate of intestinal graft loss from rejection is significantly lower among the composite grafts (Figure 11).<sup>18</sup> In the recipients of composite grafts, the incidence of liver rejection is less than half

of that in the intestine (Figure 10B).<sup>18</sup>

### Infections

Bacterial, fungal and viral infections pose a very high risk of mortality in the transplant recipients because of the use of immunosuppressants. With intestinal transplantation, such a risk is significantly increased because of the possible disruption of the mucosal barrier with a

subsequent increase in bacterial translocation. With intestinal rejection, the treatment of the above-described clinical picture paradoxically consists of a rational increase in the dosage of the immunosuppressive drugs.

Intestinal allograft recipients are at high risk of developing systemic and intra-abdominal sepsis. Central line infection and bacterial/fungal translocation, are the two most frequent sources of systemic infections. Patients with incomplete abdominal closure and those who receive a portion of the colon with the intestinal graft are more prone to develop intra-abdominal infections.<sup>10,19,20</sup> Furthermore, surgical manipulation of the transplanted bowel, lymphatic disruption, graft dysmotility, absence of ileocecal valve, suppression of gastric acidity, high steroid dose, postoperative need for temporary intravenous nutrition and enteral-defined formula diet have all been implicated in the development of bacterial overgrowth among the intestinal recipients.<sup>20</sup>

The incidence of cytomegaloviral (CMV) infection, ranges from 23% to 36%.<sup>5,18,21</sup> It has already been reported that the incidence of infection is higher for the CMV positive-to-negative and positive-to-positive donor-recipient combination. The adult population are at a higher risk of developing the CMV disease with a similar rate among the three different types of grafts. The avoidance of using positive-to-negative combination and the development of new strategies to prevent heavy chronic immunosuppression without the penalty of rejection has significantly decreased the incidence of CMV infection.<sup>21</sup>

### POSTTRANSPLANT LYMPHOPROLIFERATIVE DISEASE (PTLD)

The overall incidence of PTLD ranges from 10% to 20% with a higher risk in children of 27%.<sup>5,18</sup> The incidence varies with the three different types of intestinal allograft; 11% for the isolate intestine, 21% for the liver/intestine and 33% for the multi-visceral. The three major risk factors for the development of PTLD are young age, multivisceral transplantation, and recipient splenectomy.

### Lymphatic Leak

A significant problem that may occur

early after intestinal transplantation is the development of a lymphatic leak, which is due to interruption of the lymph vessels at the time of surgery.<sup>22</sup> The initiation of enteral feeding usually produces variable degree of chylous ascites or external leak and determines large amounts of fluid loss. In most patients, the process is usually self-limited and easily controlled with low or fat free diet and use of medium-chain triglyceride enteral formula. In a very few cases, fluid and electrolyte replacement are required for a variable period of time with partial intravenous nutrition.

### Graft-Versus-Host Disease

Despite the large lymphoid mass contained in the intestine, only 11% of the small bowel patients in our series developed graft-versus-host disease (GVHD), which was histologically confirmed in only 5%.<sup>23</sup> The diagnosis is usually based upon the recognition of suspicious skin lesions and development of gastrointestinal symptoms. The skin lesions should be promptly biopsied and studied using conventional histopathologic methods, immunohistopathologic staining for donor-specific HLA antigen, and *in situ* hybridization technique using the Y chromosome-specific probe. This morbidity is usually self-limited and responds to augmentation of immunosuppression.

### COST ANALYSIS

An analysis was performed to compare the cost of an isolated intestinal transplantation to the yearly cost of TPN. With combined liver and intestinal failure the cost analysis is not justified since hepato-intestinal transplantation is the only life-saving treatment for these patients. The cost of the three types of transplants has been significantly reduced at our institution during the last 4 years. The average cost of the operation, between 1990 and 1994, was \$203,111 for the isolated small bowel, \$252,453 for the combined liver-small bowel and \$284,452 for the composite multivisceral graft. Over the last 4 years a significant reduction in the total loading cost have been achieved with an average value of \$132,285, \$214,716 and \$219,098

respectively. Based upon the 1992 Medicare data, the yearly cost of TPN was above \$150,000, not including the cost of frequent hospitalization, medical and nursing care.<sup>24</sup> Therefore, small bowel transplantation becomes cost-effective by the second year after transplantation.

### CONCLUSION

Intestinal transplantation has become a life-saving treatment for patients with irreversible intestinal failure who cannot be maintained on TPN, and a cost-effective therapy for patients who still have the option of TPN.

The long-term rehabilitation following intestinal transplantation alone or in combination with other intra-abdominal organs is similar to that achieved with lung transplantation.<sup>25</sup> It is therefore justifiable to consider intestinal transplantation as a non-experimental procedure. In addition, further immunomodulation of the intestinal allograft by cytoreduction could further improve survival outcome and possibly raise intestinal transplantation to be the standard of care for all patients with chronic intestinal failure. **STI**

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