Proceedings of the Nutrition Society (2003), **62**, 727–737 DOI:10.1079/PNS2003288

Gut failure and abdominal visceral transplantation

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Despite the reported high survival with total parenteral nutrition (TPN) therapy for patients with intestinal failure, a considerable number of patients do not escape the potential risks of TPN-associated complications, including hepatic failure, vanishing of central venous access and line sepsis. Thus, intestinal, liver–intestinal and multivisceral transplantation have recently emerged to rescue those who can no longer be maintained on TPN. Before this development, and for nearly three decades, small-bowel transplantation was plagued with uncontrolled rejection, graft *v*. host disease and fatal infection. These barriers stemmed from the large gut lymphoid mass and heavy microbial load contained in the intestinal lumen. The recent improvement in survival after the clinical introduction of tacrolimus with achievement of full enteric nutritional autonomy qualified the procedure by the US Health Care Financing Administration as the standard of care for patients with intestinal and TPN failure. The decision was supported by a decade of clinical experience with cumulative improvement in patient and graft survival. In addition, the introduction of new effective immunoprophylactic agents and novel therapeutic approaches has contributed to a further increase in the therapeutic advantages of the procedure. The present review article outlines the current clinical practice of intestinal transplantation and defines new management strategies with the aim of raising the level of the procedure to be a better alternative therapy for TPN-dependent patients.

Intestinal failure: Total parenteral nutrition: Abdominal visceral transplantation: Intestinal transplantation and gut failure

Indications

The US Health Care Financing Administration has recently considered, in response to the author's formal request, intestinal, liver–intestinal and multivisceral transplantation as the standard of care for patients with irreversible intestinal and total parenteral nutrition (TPN) failure (Abu-Elmagd *et al*. 2002*a*). The therapeutic efficacy of each of the three types of intestinal transplantation was clearly demonstrated with long-term rehabilitation and cost-effectiveness that compared favourably with the government expectations for other abdominal and thoracic organ transplantation. In the decision memorandum it was concluded that small bowel and related transplantation appear to be potentially life-saving options for patients who failed TPN and would therefore otherwise face certain death. However, the report was not able to determine whether the risks and benefits of isolated small-bowel transplant might yield a net benefit to patients who can continue on TPN. Accordingly, a well-designed prospective study that compares isolated intestinal transplant with TPN therapy among patients who meet an agreed-upon definition of low and high risk for TPN failure is required. The indications for transplantation, with special references to the causes of intestinal failure and definition of TPN failure, are now described.

Intestinal failure

Irreversibility of intestinal failure is an essential prerequisite for transplantation at the present time. The diagnosis should be declared only after the optimal utilization of the currently-available medical and surgical therapeutic modalities to enhance gut adaptation. Short gut syndrome, whether surgical or congenital, is the most common indication for intestinal transplantation. Other common indications include

Abbreviations: GVHD, graft *v*. host disease; TPN, total parenteral nutrition.

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dysmotility, neoplastic and malabsorption syndromes. The different causes of intestinal failure and indications for the three different types of intestinal transplantation are: (1) short gut syndrome: intestinal atresia, midgut volvulus, gastroschisis, abdominal trauma, necrotizing enterocolitis, Crohn's disease, mesenteric vascular thrombosis, surgical adhesions; (2) motility disorders: hollow visceral myopathy and/or neuropathy, total intestinal aganglionosis, other dysmotility syndromes; (3) gut malabsorption: microvillus inclusion disease, selective autoimmune enteropathy, radiation enteritis, inflammatory bowel disease; (4) gastrointestinal neoplasm: mesenteric desmoid tumour, diffused intestinal polyposis, Gardener's syndrome, other large benign unresectable mesenteric masses.

Total parenteral nutrition failure

Based on compiled data in the literature, Abu-Elmagd *et al*. (2002*a*) were the first to establish the clinical criteria of TPN failure as stated in the Medicare document. The four defined criteria are: (1) impending liver failure; (2) limited central venous access; (3) multiple line infections; (4) frequent episodes of severe dehydration despite intravenous fluid replacement. The manifestations of impending hepatic failure include high serum bilirubin, elevated liver injury tests, enlarged spleen, low platelet count, gastro-oesophageal or stomal varices, coagulopathy and cirrhosis. Vanishing of the central venous access and repeated episodes of line infections or dehydration are considered life-threatening complications because of the potential risk of lacking venous access, systemic sepsis, pulmonary embolism, acute respiratory distress syndrome and renal failure. A serious but commonly unrecognized complication of TPN, that has been recently documented, is the failure of full development of the central nervous system among the paediatric patients and development of brain atrophy among the adult population (Idoate *et al*. 1999). Other unacknowledged complications are the development of major bone disease, metabolic disorders, uncorrectable trace element toxicity or deficiency and, above all, limitations on social and personal activities of both patients and their caregivers (Howard & Hassan, 1998; Messing *et al*. 1999).

Isolated intestine

The operation is indicated for patients with irreversible gut failure that is limited to the small intestine. The coexistence of portal hypertension should be considered in patients with long-term TPN therapy and/or hypercoagulable syndromes. The type and extent of portal hypertension, as well as the extent of liver damage, determine simultaneous hepatic replacement (Abu-Elmagd *et al*. 2001). Gastro-oesophageal varices and ascites are uncommon features with short gut syndrome, resulting from reduced or absent mesenteric circulation. Patients with isolated splenic vein thrombosis should undergo splenectomy or, preferably, shunt surgery along with isolated intestinal transplantation. In contrast, those patients with extensive porto-mesenteric thrombosis should be considered for either combined liver–intestinal or multivisceral transplantation, particularly when the splenic vein is involved in the thrombotic process. Patients with modest portal hypertension presented with mild splenic enlargement, platelet count > 50 000, no gastro-oesophageal varices and minimal to moderate portal fibrosis without marked intrahepatic cholestasis should be cautiously considered for isolated intestinal transplantation. In such patients the venous drainage of the intestinal graft should be directed into the recipient systemic circulation.

Combined liver–intestine

En bloc hepato–intestinal transplantation is indicated for patients with irreversible failure of both organs. In most of these cases liver failure is commonly the result of TPN therapy. Another common indication is liver failure combined with porto-mesenteric thrombosis. In those patients who are not TPN dependent intestinal replacement is surgically indicated to reconstitute adequate portal flow to the hepatic allograft and effectively eradicate the mesenteric varices. The hypercoagulable state, in the absence of liver failure, is not an indication for simultaneous liver replacement, but with lifelong commitment for anticoagulation therapy (Giraldo *et al*. 2000).

Multivisceral

The operation is indicated for patients with irreversible failure or neoplastic disorder of the abdominal visceral organs, including the small bowel. The common causes of failure or need for replacement include hollow visceral myopathy and/or neuropathy, extensive gastrointestinal polyposis, mesenteric desmoid or gastrointestinal stromal tumours and symptomatic total splanchnic vascular thrombosis.

Contraindication

The cumulative experience with solid organ transplantation was the basis of establishing the exclusion criteria for each of the three intestinal transplant operations. Marked cardiopulmonary insufficiency, aggressive malignancy, advanced autoimmune diseases, AIDS and existence of life-threatening intra-abdominal or systemic sepsis are the currently adopted contraindications for intestinal and multivisceral transplantation. With age not being a decisive factor, the survival outcome measures that have been established by the US government (US Health Care Financing Administration) serve as quality control, with exclusion of facilities that fail to achieve these expectations.

Patient evaluation

The candidacy for intestinal and composite visceral transplantation is determined after full assessment of the recipient organ systems. The nutritional status and functions of the residual gut are the first to be evaluated. The continuous need for TPN despite proper dietetic and optimal pharmacological therapy is a surrogate marker of irreversibility of gastrointestinal failure.

The cause of intestinal failure and extent of the primary disease determine the algorithm of the evaluation process. Patients with enterocyte and mural diseases should undergo thorough radiological, endoscopic and histological

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examination of the remaining gastrointestinal tract. Cases with pseudo-obstruction undergo gut-motility studies to define the type and extent of the disease. Patients with thrombotic disorders need specific haematological tests to define the etiology of the hypercoagulable syndrome. Full abdominal visceral angiographic studies are indicated in patients with vascular and thrombotic disorders to assess the status of the splanchnic circulation. In these and other high-risk patients imaging of the upper- and lower-extremities central venous system is mandatory to guide safe establishment of adequate venous accesses at the time of surgery.

The functional status of the native liver is crucial for determination of the type of intestinal graft needed. This status can be assessed from the results of the liver injury tests, abdominal imaging studies and liver biopsy. In addition, status of the hepatic vessels, presence of portal hypertension and coexistence of any other abdominal organ diseases can be identified.

The extent of the work-up needed to carefully assess the cardio-pulmonary and other body organ systems is commonly guided by patient age, complexity of the medical and surgical history, and nature of the primary disease.

Surgery

Donor

A good quality and suitable size graft is the key for successful intestinal transplantation. Stable and ABO-identical young donors are preferred. Smaller size donors are preferred to compensate for the contracted abdominal cavity. The current shortage in cadaveric donors for combined liver–intestinal and multivisceral grafts stimulated the utilization of newborn, reduced-sized and ABO-compatible composite visceral grafts for a few paediatric recipients at our and other transplant centres. Selective decontamination of the gut should be attempted in all donors, and the University of Wisconsin solution is currently used by all US transplant centres for both *in situ* flushing and cold storage. However, Custidiol® (Dr Franz Köhler Chemie GmbH, Alsback-Hähnlein, Germany) has been used recently at the Pittsburgh centre instead of the University of Wisconsin solution, with excellent results.

No attempts have been made by most centres to deplete the donor lymphoid tissue by anti-lymphocyte antibodies or to match donor and recipient human leucocyte antigen. However, allograft cytoreduction with low-dose *ex vivo* irradiation and simultaneous donor bone-marrow-cell infusion has been recently introduced (Abu-Elmagd *et al*. 2001) after successful pre-clinical trials (Murase *et al*. 1995, 2000). If possible, the isolated intestinal grafts should not be transplanted across a positive T-cell lymphocytotoxic cross-match (Bond *et al*. 2000) and cytomegalovirus-negative patients should receive cytomegalovirus-negative grafts (Todo *et al*. 1995*a*).

Procurement

The embryonic origin and segmental vascular supply of the different abdominal viscera is the Achilles heel for successful retrieval of these organs separately or en bloc (Fig. 1). The full multivisceral specimen is envisioned as a grape cluster with a double central stem consisting of the celiac and superior mesenteric trunks. The grapes or individual organs can be divided or retained according to the surgical objectives (Fig. 2). The liver and small bowel are retrieved in continuity with their central vascular structure and the C loop duodenum is preserved in continuity with the jejunum and biliary system (Fig. 3). The multivisceral graft that usually includes stomach, duodenum, pancreas, intestine and liver can be tailored according to patient needs by excluding the liver (Fig. 4(A)) or including the kidney (Fig. 4(B)). This graft is quite different from the previously-termed ‘cluster’, since the latter includes only the duodenum and pancreas en bloc with the liver.

Recipient operation

The surgical implantation of the different types of the intestinal allograft is often complicated as a result of previous

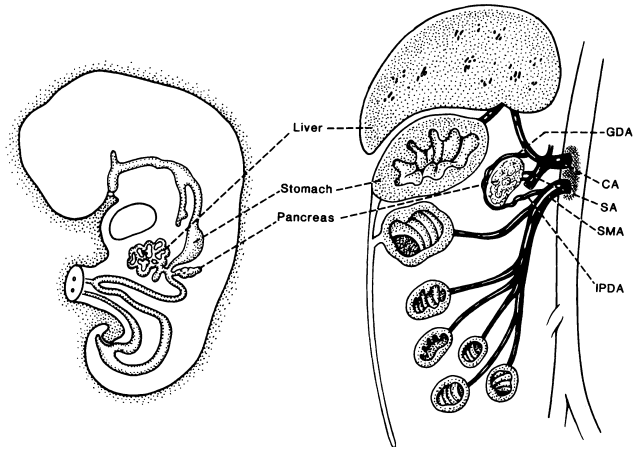

Fig. 1. Embryonic origin of liver, pancreas and alimentary canal. Note the shared axial blood supply and its segmental distribution. GDA, gastroduodenal artery; CA, celiac axis; SA, splenic artery; SMA, superior mesenteric artery; IPDA, inferior pancreatico-duodenal artery. (From Abu-Elmagd *et al*. 2000; reproduced with permission.)

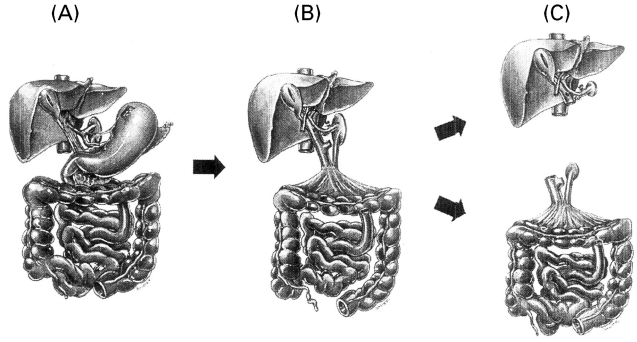

Fig. 2. Tailoring of the intestinal allograft, according to the patient’s need, either *in situ* or during the back table procedure. Note that the colon is no longer used as part of the intestinal allograft. (A), A full multivisceral graft; (B), liver plus intestine graft; (C), intestine graft alone. The liver allograft is used for another recipient.

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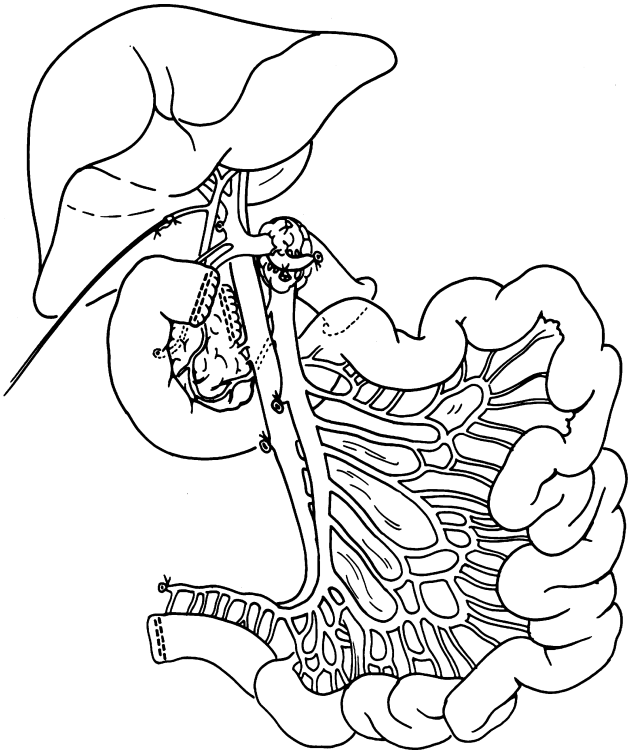

Fig. 3. Composite liver and intestinal graft with preservation of the duodenum in continuity with the graft jejunum and hepatic biliary system. (From Abu-Elmagd *et al*. 1998; reproduced with permission.)

multiple abdominal surgeries with the presence of extensive abdominal adhesions, contracted abdominal cavity and considerable portal hypertension, particularly in patients who require composite visceral graft. With intestine-only transplantation, portal venous drainage (Fig. 5) should always be attempted, particularly in patients with inadequate hepatopetal portal flow, splenectomy, de-arterialized native liver and caval filters. The systemic caval drainage should be limited to patients with frozen hepatic hilus, portal vein thrombosis, marked hepatic fibrosis and previous intestinal transplant. With combined hepatic–intestinal transplantation (a) a porto–caval shunt is created during the early phase of the operation, with the aim of compressing and permanently draining the residual recipient splanchnic venous bed (Fig. 6) and (b) the piggyback technique has been our common practice to avoid the veno–venous bypass because of the common occlusion of the upper-extremities central venous system in most patients. With full multivisceral transplantation, removal of the left upper abdominal organs eliminates the need for porto–caval shunt (Fig. 7). The new technique of reconstructing the venous outflow of the modified multivisceral allograft (Fig. 8(A)) maintains the porto-splenic circulation intact during graft placement and preserves the spleen that may protect the patient from the risk of post-transplant B-cell lymphoma (Abu-Elmagd *et al*. 2001). In recipients with pancreato-duodenectomy the biliary system is reconstructed by preserving a segment of the donor distal bile duct and performing a choledocho-choledochostomy (Fig. 8(B)).

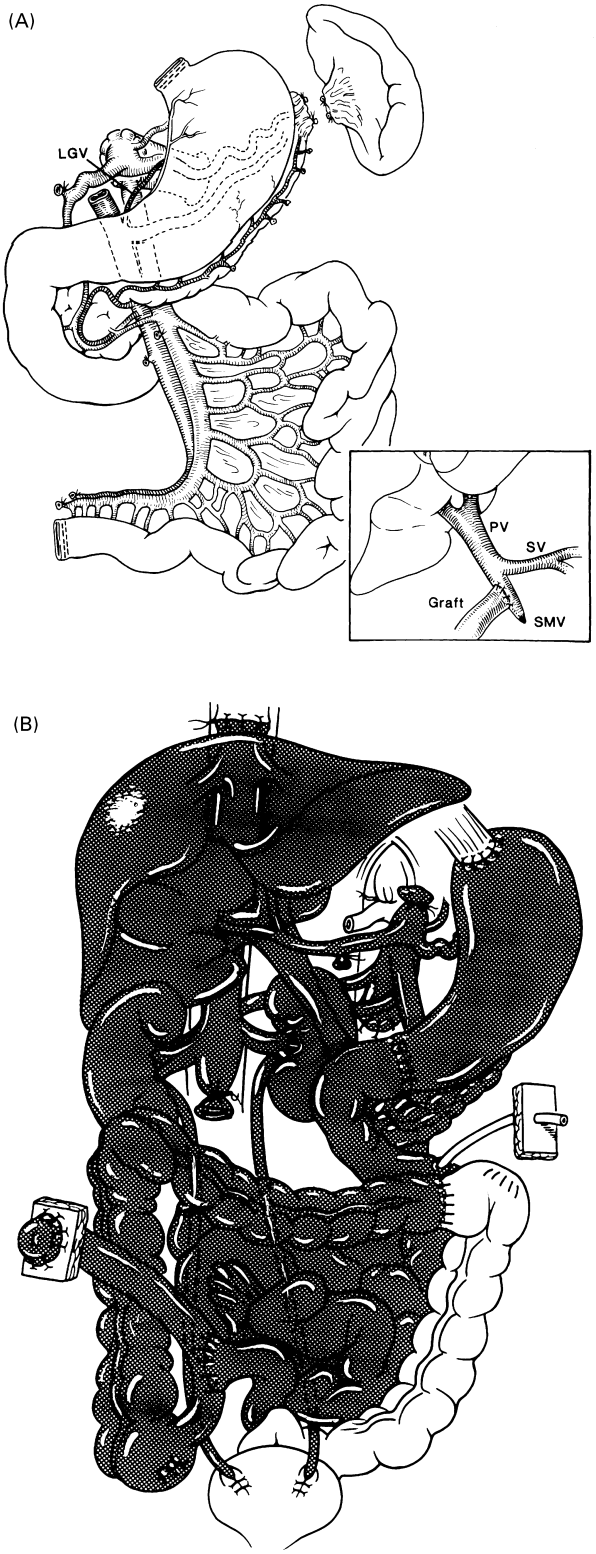

Fig. 4. (A) Modified multivisceral graft that contains stomach, duodenum, pancreas and small intestine. Note preservation of the gastroepiploic arcade and left gastric pedicle with venous drainage to the side of the recipient superior mesenteric vein (SMV) stump (inset). LGV, left gastric vein; PV, portal vein; SV, splenic vein. (From Abu-Elmagd *et al*. 2000*a*, reproduced with permission.) (B) Full multivisceral graft with inclusion of the kidney. (From Todo *et al*. 1995*b*; reproduced with permission.)

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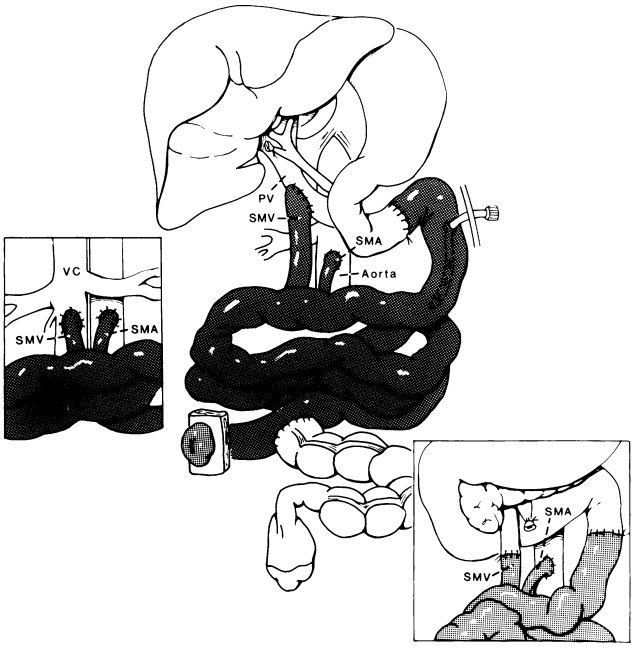

Fig. 5. Isolated intestinal transplantation. Note the different techniques of draining the allograft superior mesenteric venous (SMV) drainage to the recipient portal system or inferior vena cava (VC; insert). PV, portal vein; SMA, superior mesenteric artery. (From Todo *et al.* 1992; reproduced with permission.)

Continuity of the gastrointestinal tract is usually restored by conventional surgical procedures. The stapler technique, however, has been recently utilized in Pittsburgh with good results. At the end of the operation a jejunostomy and gastrostomy tube is inserted for immediate post-operative decompression and early enteral feeding. The creation of a temporary vent chimney or simple loop ileostomy is always needed to provide easy access for surveillance endoscopy (Figs. 5–7). The time of stoma closure, that is usually 3–6 months after transplantation, is determined by the post-operative course and functional status of the intestinal graft.

Post-operative management

The standard post-operative care of the intestinal and multivisceral recipient has been fully described elsewhere (Abu-Elmagd *et al*. 1992, 1994; Reyes *et al*. 1993). The primary focus of the present report, however, is the recent advances in the post-operative immunosuppressive therapy, with special emphasis on graft immune-modulation and induction of transplant tolerance.

Immunosuppression

The worldwide primary immunosuppressive regimen has been tacrolimus and steroids. Various induction protocols have been utilized recently by different centres to reduce the observed high risk of rejection. Azathioprine, mycophenolate mofetil, and more recently sirolimus, are used from the outset as a third agent in selected cases (Abu-Elmagd *et al*. 2001). Steroids, anti-CD3 antibodies, thymoglobulin and campath are utilized to treat rejection episodes.

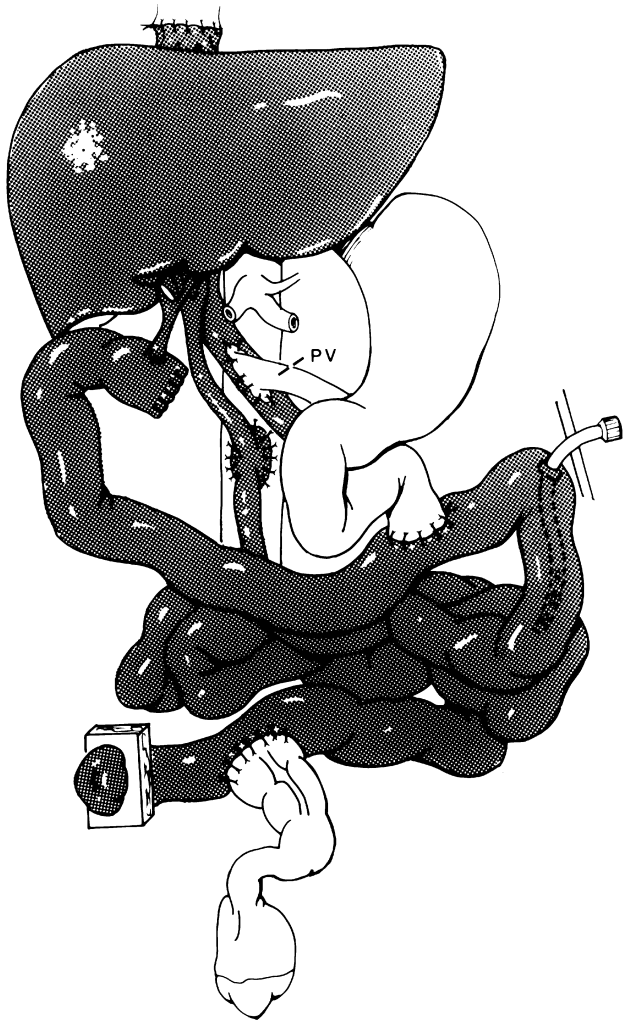

Fig. 6. Combined liver and intestinal transplantation without preserving the donor duodenum and head of pancreas, before the new modification shown in Fig. 3. Note the porto–portal shunt. In recent years a permanent porto–caval shunt is routinely preformed. PV, portal vein. (From Todo *et al.* 1992; reproduced with permission.)

Induction therapy was first used for Pittsburgh intestinal recipients in 1995 (Abu-Elmagd *et al*. 1998). This immunoprophylactic approach was triggered by the proven deleterious effect of rejection on survival outcome (Todo *et al*. 1995*a*). Cyclophosphamide was first used until the clinical introduction of the humanized immunoglobulin G1 monoclonal antibody daclizumab. This antibody is directed at one subunit of the human interleukin 2 receptor. Daclizumab (zenapax) is used in the Pittsburgh centre at an intravenous dose of 1–2 mg/kg body weight for a total of five doses (Abu-Elmagd *et al*. 2000*b*). The first dose is administered within a few hours before surgery and the remaining four doses are given at 2, 4, 6 and 8 weeks after transplantation.

Graft immune-modulation and recipient preconditioning

Despite some improvement in survival with induction therapy, the chronic need for heavy maintenance immuno-

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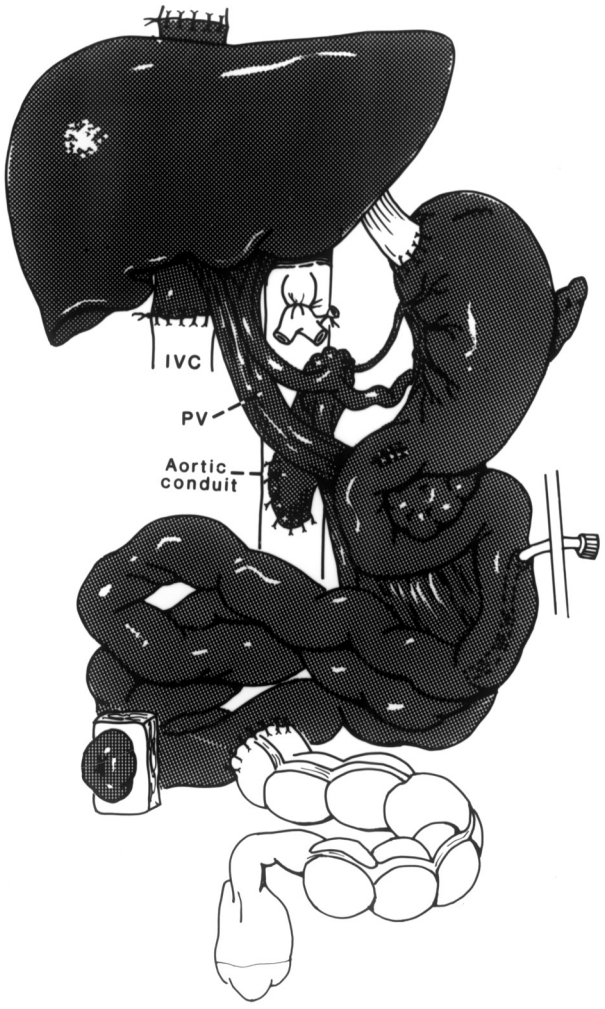

Fig. 7. Full multivisceral transplantation with a common arterial conduit that is anastomosed to the common Carrel aortic patch of both the celiac trunk and superior mesenteric artery. IVC, inferior vena cava; PV portal vein. (From Todo *et al.* 1992; reproduced with permission.)

suppression continues to limit the clinical applicability of the procedure and erodes its long-term survival benefits. To overcome such an impediment, a novel immunomodulatory strategy has been introduced recently to enhance tolerogenicity and acceptance of the human intestinal allograft (Abu-Elmagd *et al*. 2002*b*).

A series of controlled rat studies have shown that the quantity and lineage profiles of the passenger leucocytes contained in different organ grafts strongly affect the quantity and lineage of microchimerism, graft survival and function (Murase *et al*. 1995). In these experiments the intestinal passenger leucocytes have been shown to be less tolerogenic, with a higher risk of graft *v*. host disease (GVHD) than the passenger leucocytes of the liver and bone marrow cells, both of which include large numbers of immature leucocytes and cells of myeloid origin. Accordingly, depletion of the mature T-cells in the intestinal allograft with low-dose *ex vivo* irradiation combined with donor bone-marrow-cell replacement should improve the clinical outlook of intestinal transplantation by reducing the risk of rejection without increasing the risk of GVHD (Murase *et al*. 2000). The unmodified bone marrow cells are recovered from the donor thoraco-lumbar vertebrae and infused intravenously as a single dose ($3–5 \times 10^8$ cells/kg) into the intestinal recipient within 12 h after revascularization. The intestinal component of the allograft is irradiated on the back table with a single dose of 7·50 Gy.

The encouraging preliminary results of combined graft irradiation and leucocyte infusion (Abu-Elmagd *et al*. 2001), together with the recent revelation of the mechanism of graft acceptance (Starzl *et al*. 1992; Starzl & Zinkernagel, 1998, 2001), stimulated the recent initiation of a clinical trial of thymoglobulin pretreatment and post-transplant tacrolimus monotherapy (Abu-Elmagd *et al*. 2002*b*). With host preconditioning and limited use of post-transplant immunosuppression, the seminal mechanism of clonal exhaustion–deletion may be protected with the achievement of donor-specific non-reactivity and organ engraftment that may not require maintenance therapy for stability. The intravenous thymoglobulin pretreatment dose is 5–10 mg/kg, which is covered with 2 g methylprednisolone intravenously. The total dose is completed before graft revascularization and the bone marrow cells are infused 10–12 h after completion of the thymoglobulin dose. Post-transplant treatment is with tacrolimus only, with a target 12 h trough level of 15–20 ng/ml. Rejection episodes are treated with the conventional therapy.

Immunological monitoring

Intestinal allograft rejection is diagnosed from clinical observations, endoscopic findings and histopathological examination of mucosal biopsies (Abu-Elmagd *et al*. 1992). Surveillance endoscopy with random mucosal biopsies, particularly of the allograft ileum, is performed at least once weekly for the first 3 months, and every 3–6 months thereafter and whenever it is clinically indicated. The clinical, endoscopic and histological criteria adopted for the diagnosis of intestinal rejection are described elsewhere (Abu-Elmagd *et al*. 1992, 1994; Todo *et al*. 1992; Lee *et al*. 1996). Zoom video endoscopy (Kato *et al*. 2000) and serum citrulline levels (Pappas *et al*. 2001) have been utilized recently for the diagnosis of acute rejection. The future availability of non-invasive, more sensitive and highly-specific tools to detect early rejection will undoubtedly ease the post-operative management and improve the therapeutic benefits of the procedure.

The early diagnosis of GVHD requires a high index of clinical suspicion and availability of a highly-advanced immunohistochemical technology. The examination of suspicious skin and gastrointestinal tract lesions allow the identification of donor leucocytes with the *in situ* hybridization technique using the Y-chromosome-specific probe or the immunohistological staining of donor-specific human leucocyte antigen. Other GVHD target organs should also be closely observed and biopsy samples taken when indicated. Prompt augmentation of immunosuppressive therapy including steroids is usually effective with the early diagnosis of GVHD.

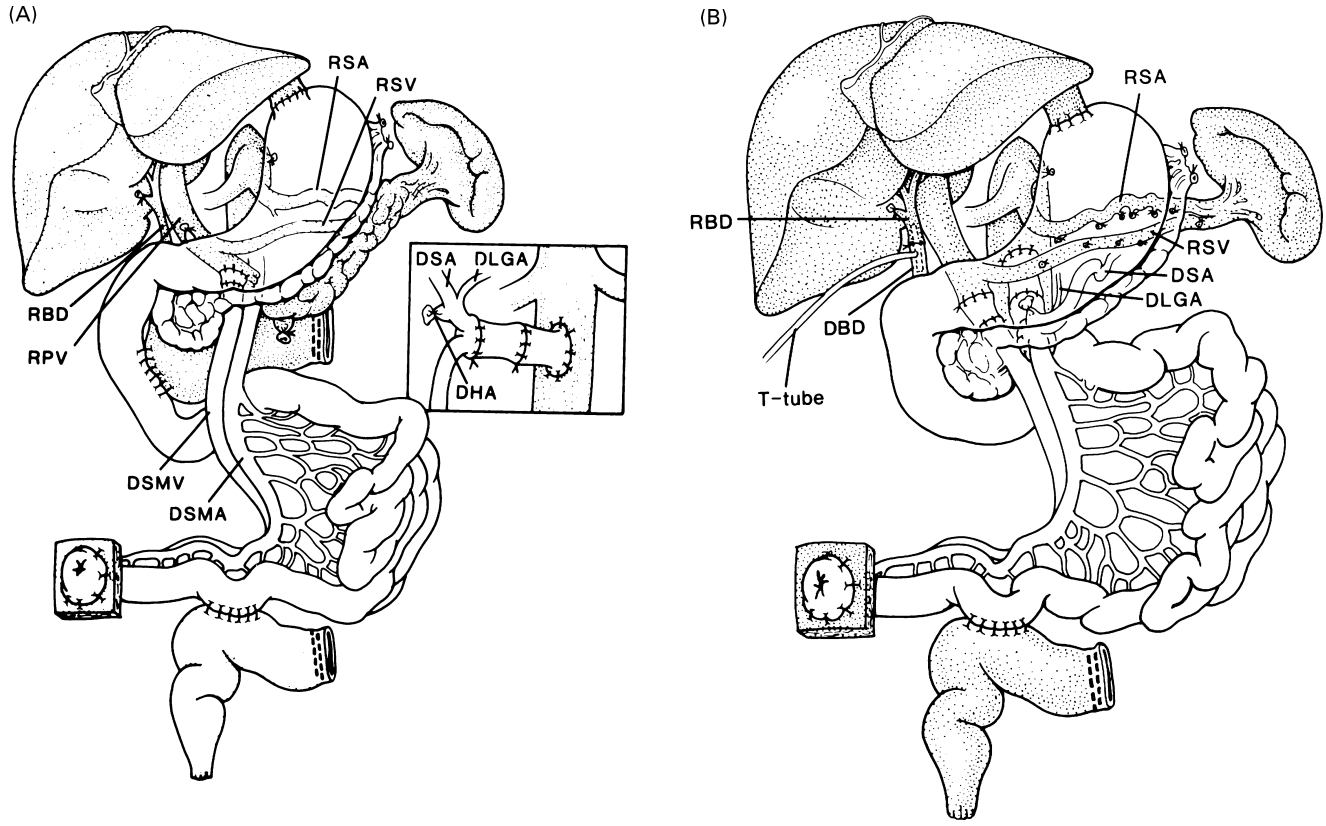

Fig. 8. Transplantation of a modified multivisceral graft (unshaded organs) containing the pancreas and all the hollow intra-abdominal viscera. (A) Native liver, spleen, pancreas and a C-loop of duodenum have been retained and drained through a side-to-side host-to-graft duodenal anastomosis. RBD, recipient bile duct; RPV, recipient portal vein; RSA, recipient splenic artery; RSV, recipient splenic vein; DSMV, donor superior mesenteric vein; DSMA, donor superior mesenteric artery; DSA, donor splenic artery; DLGA, donor left gastric artery; DHA, donor hepatic artery. (From Abu-Elmagd *et al.* 2001; reproduced with permission.) (B) Native spleen is preserved with maintenance of the recipient porto–splenic circulation during graft insertion. Note the duct-to-duct biliary reconstruction. DBD, donor bile duct. (From Abu-Elmagd *et al.* 2001; reproduced with permission.)

Nutrition and graft function

The achievement of full nutritional autonomy requires flexible and complex management strategies, particularly for recipients of composite visceral grafts. The conversion from parenteral to enteral alimentation is gradual and usually commences within the first two post-operative weeks. Opiates, loperamide and kaolin–pectin mixture are used for high stomal output or diarrhoea and prokinetic agents are used to treat gastrointestinal dysmotility.

Standard hepatic and pancreatic function tests are used to track the organ functional status. Successful complete withdrawal of TPN with establishment of full gastrointestinal nutritional autonomy has been the most valuable tool in judging intestinal graft function. Anthropometric measures, including weight, height (children) and upper arm measurement of fat and muscle, as well as serum albumin levels, are helpful in evaluating any clinically-observed changes in the patient nutritional status.

Infection prophylaxis

Protocols for antimicrobial prophylaxis and active treatment are similar to those used for solid organ recipients. In addition, selective gut decontamination is used for 1–2 weeks post-operatively and during moderate to severe rejection episodes. Chronic viral and protozoal prophylaxis is with gancyclovir for cytomegalovirus and Epstein-Barr virus and bactrim for *Pneumocystis carinii*. The newly-developed techniques of PP65 anti-genmia test and semi-quantitative polymerase chain reaction assay of Epstein-Barr virus in the peripheral blood has allowed early detection, preemptive treatment and monitoring of the virus-associated syndromes with better survival outcome (Abu-Elmagd *et al.* 2001).

The concept of infectious implications of rejection that have been previously demonstrated with liver transplantation is even more applicable with the intestine because a disrupted mucosal barrier quickly creates a lethal environment for the total body. The paradoxical therapeutic philosophy of treating infection-relatable rejection with prompt increase in immunosuppression, in addition to systemic and local antibiotic therapy, is of utmost importance in preventing or stopping bacterial translocation among intestinal transplant recipients (Abu-Elmagd *et al.* 1994).

Current clinical status

Worldwide experience

Between April 1985 and May 2001 a total of 651 patients received 696 intestinal transplants at fifty-five centres (Grant, 2001). Of the 696 transplants, 180 (28 %) were performed at

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the University of Pittsburgh. There has been a steady increase in the number of centres and procedures performed per year. Of the 651 recipients, 61 % were children and 56 % were male. Of the transplanted grafts 291 (42 %) were isolated intestine, 310 (44 %) were combined liver–intestine and ninety-five (14 %) were multivisceral. The leading causes of intestinal failure and indications for transplant were gastroschisis (21 %), volvulus (18 %), dysmotility (18 %), necrotizing enterocolitis (12 %), intestinal atresia (7 %) and microvillus inclusion (6 %) in children and mesenteric ischaemia (22 %), Crohn's disease (13 %), gastrointestinal neoplasm (13 %) and trauma (12 %) in adults. Of this total population of recipients, 52 % were hospitalized at the time of transplant and 48 % were at home. The re-transplantation rate was 7 % among children and 5 % for adults.

Survival

As of 31 May 2001 and according to the most recent database of the International Intestinal Transplant Registry that was reported in Stockholm at the VIIth International Small Bowel Transplant Symposium (September 2001; Grant, 2001), a total of 335 intestinal recipients were alive, with an overall survival rate of 51 %. The leading causes of death were sepsis (*n* 166), rejection (*n* 33), technical complications (*n* 31), lymphoma (*n* 26) and respiratory failure (*n* 22). With the cumulative increase in survival over the last 10 years, the 1- and 5-year survival rates for grafts that were transplanted after February 1995 were 61 and 42 % respectively. Interestingly, there was no difference in survival between the three different types of the intestinal allografts, with the leading causes of graft removal being rejection (57 %), technical failure (21 %) and infection (8 %).

The decade of experience of the University of Pittsburgh has been reported recently (Abu-Elmagd *et al.* 2001). Between May 1990 and February 2000 a total of 165 transplants were given to 155 consecutive recipients. The Kaplan-Meier actuarial survival rate for this total population of recipients was 75 % at 1 year, 54 % at 5 years and 42 % at 10 years (Fig. 9), with achievement of full nutritional autonomy in > 90 % of the survivors. Recipients of liver–intestinal grafts had the best prognosis for continued survival beyond 5 years (Fig. 10). Both patient and graft survival have improved since 1994 compared with the premoratorium experience, with 1- and 5-year patient survival rates of 78 and 63 % respectively (Fig. 11). Although the reasons for improvement must be considered indeterminate because of the complexity of the cases and the treatment strategies, induction therapy, bone-

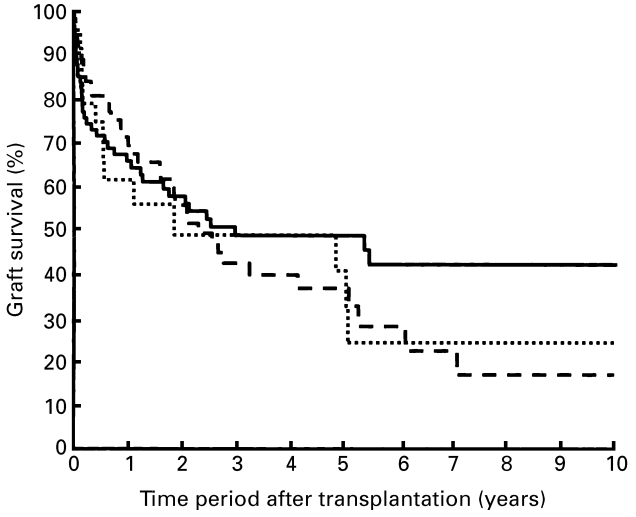

Fig. 10. Kaplan-Meier survival of the three different types of the intestinal allografts. (---), Isolated intestine (*n* 65); (—), liver–intestine (*n* 75); (·····), multivisceral (*n* 25). The liver–intestine transplant patients had a significantly better survival rate than the other two groups of transplant patients after 10 years ($P = 0{\cdot}5$). (From Abu-Elmagd *et al.* 2001; reproduced with permission.)

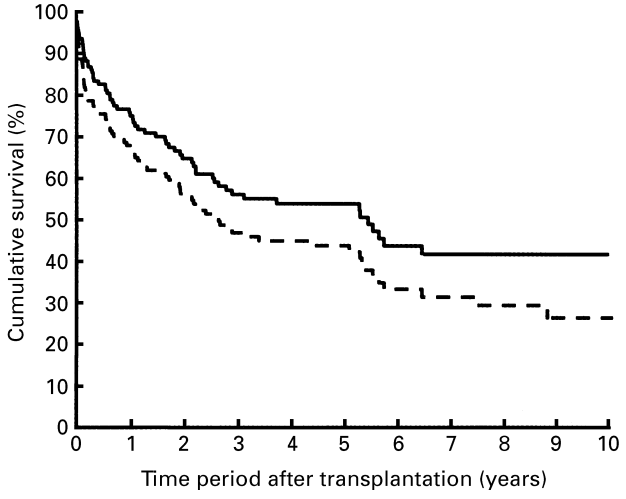

Fig. 9. Kaplan-Meier patient (*n* 155; —) and graft survival (*n* 165; ---) curves for the Pittsburgh intestinal transplant patient population. (From Abu-Elmagd *et al.* 2001; reproduced with permission.)

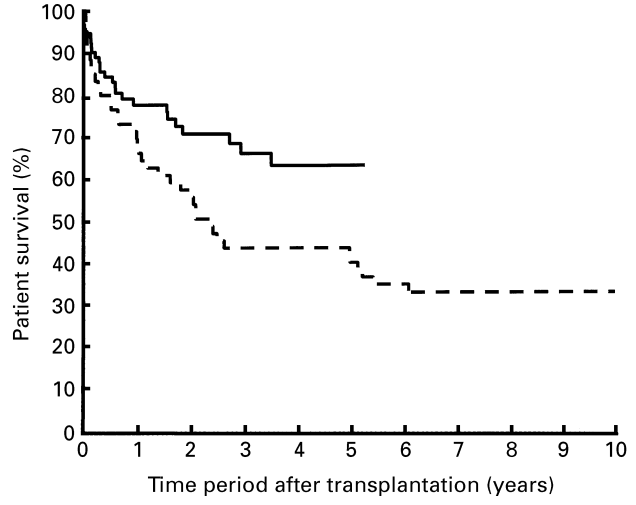

Fig. 11. Patient survival before (1990–4, *n* 62; ····) and after (1995–2001, *n* 93; —) the 1994 moratorium at the University of Pittsburgh. The patient survival was significantly improved after 1994 ($P = 0{\cdot}03$). (From Abu-Elmagd *et al.* 2001; reproduced with permission.)

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marrow augmentation and low-dose *ex vivo* allograft irradiation have contributed markedly to the survival increment.

Risk factors

Multivariate analysis of the Pittsburgh experience identified multiple risk factors that markedly affect patient and graft survival (Todo *et al*. 1995*a*; Abu-Elmagd *et al*. 2001). With rejection and need for heavy immunosuppression being the most detrimental variable, cold ischaemia time, number of previous abdominal operations, operative time, development of post-transplant lymphoproliferative disease, cytomegalovirus disease and inclusion of a large segment of colon with the graft were major risk factors that influenced the survival outcome.

Based on the 1999 and 2001 International Intestinal Transplant Registry data reported by David Grant (1999, 2001), the worldwide survival outcome with intestinal transplantation has been influenced by two important factors, era of transplantation and size of the transplant centre. Graft survival has significantly improved over time ($P = 0{\cdot}0068$; Fig. 12) and both patient and graft survival outcomes are significantly better at centres that have performed more than a total of ten transplants ($P = 0{\cdot}006$; Fig. 13). These two variables are surrogate markers for the cumulative refinement in surgical techniques and post-operative management.

Rejection

Despite the use of new adjunct immunosuppressive agents with different cellular and molecular targets, including cyclophosphamide, mycophenolate mofetil, daclizumab and most recently sirolimus, the overall incidence of intestinal rejection or the ease of management was not dramatically improved (Abu-Elmagd *et al*. 2001). Although it is too early to make definitive assessments of the recent management strategy used in Pittsburgh, it is noteworthy that the risk of rejection, late graft loss and delayed death were reduced with bone-marrow augmentation and low-dose *ex vivo* irradiation (Abu-Elmagd *et al*. 2001).

Early acute rejection has been documented at a markedly higher rate among the isolated intestinal grafts compared with intestine contained in a composite graft (Abu-Elmagd *et al*. 1998, 2001). Although the cumulative risk by the end of the first post-operative year was similar for both types of the intestinal graft, the cumulative risk of graft loss due to acute or chronic rejection was significantly greater among the isolated grafts compared with the composite grafts that contained liver ($P = 0{\cdot}00001$; Fig. 14). It remains to be seen whether the extent of long-term destructive immunity among the intestinal

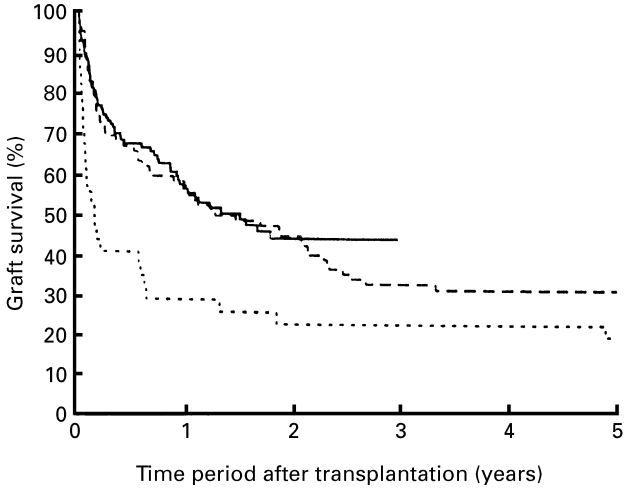

Fig. 12. Graft survival *v.* time of transplant. (—), 1994–February 1997; (---), 1991–3; (·····), pre-1991. Graft survival has significantly improved over time ($P = 0{\cdot}0068$). (From Grant, 1999; reproduced with permission.)

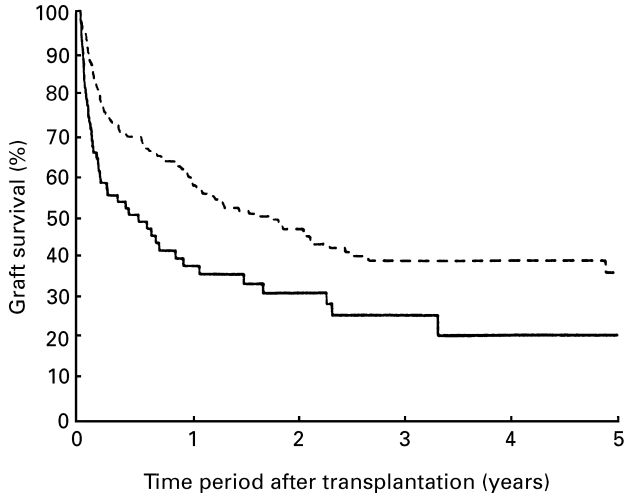

Fig. 13. Graft survival outcomes according to centre size. (—), Less than ten patients; (·····), ten or more patients. Graft survival outcomes were significantly better at centres that had performed more than a total of ten transplants ($P = 0{\cdot}006$). (From Grant, 1999; reproduced with permission.)

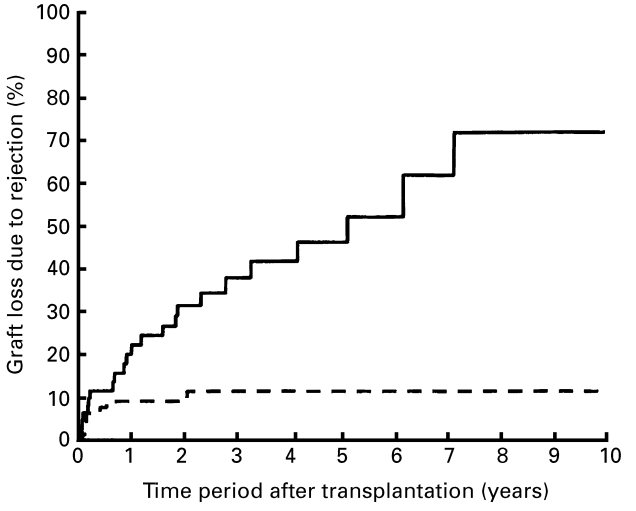

Fig. 14. Cumulative risk of graft loss from rejection in the intestine-only grafts (*n* 65; —) and composite visceral grafts that contained liver (*n* 95; ·····). Cumulative risk of graft loss due to acute or chronic rejection was significantly greater among the isolated intestine grafts compared with the composite visceral grafts that contained liver ($P = 0{\cdot}00001$). (From Abu-Elmagd *et al.* 2001; reproduced with permission.)

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allografts will be greatly affected by the human leucocyte antigen mismatch, systemic venous drainage (isolated intestine) and positive lymphocytotoxic cross-match.

Chronic rejection has been reported at an overall rate of 7–10 % (Abu-Elmagd *et al*. 1998, 2001; Grant, 1999). The cumulative risk is greater among the isolated intestinal grafts compared with the composite grafts that contained liver, with a 5-year rate of 31 % *v*. 7 % (Abu-Elmagd *et al*. 2001). In addition to the type of the allograft, the frequency and severity of acute rejection, recipient age (adults) and race (black) are major risk factors for development of chronic rejection.

Graft v. host disease

Unexpectedly, the incidence of GVHD has been relatively low, despite the large lymphoid mass being contained in the transplanted intestine, with a documented incidence of 5 % (Abu-Elmagd *et al*. 2001). With similar risk among recipients of all three types of intestinal allografts, the disease is self-limited in most cases with augmentation of immunosuppression.

Long-term rehabilitation

The long-term rehabilitation with all three kinds of the intestinal transplant procedure is similar to that achieved with other types of thoraco-abdominal organ transplant. Of a total of 288 worldwide survivors who passed the sixth post-operative month 70 % maintained fully-functioning grafts with complete enteric nutritional autonomy. Interestingly enough, 85 % of these recipients achieved a modified Karnofsky performance score of 90–100 % (Grant, 1999). These therapeutic indices are even higher at centres with vast experience (Abu-Elmagd *et al*. 2001).

Cost-effectiveness

With combined liver–intestinal and full multivisceral transplantation being life-saving operations, the cost-effectiveness of the isolated intestinal and modified (without liver) multivisceral transplants can be examined based on the availability of chronic TPN therapy as an alternative treatment for patients with irreversible gastrointestinal failure and normal liver functions. Based on Medicare data (for USA), the average cost of TPN in 1992 was > US $150 000 per patient per year, not including the cost of frequent hospitalization, medical equipment and nursing care (Howard & Hassan, 1998). With the current average cost of the isolated intestinal transplant, the procedure becomes cost-effective by the second year after surgery (Abu-Elmagd *et al*. 1999).

Current controversies

The recent evolution of combined liver–intestinal and multivisceral transplantation has questioned the therapeutic role of isolated liver replacement in children with TPN-induced liver failure. This controversial issue is fuelled by the previously reported unsatisfactory outcomes with liver-only transplant (Lawrence *et al*. 1994) and the current high mortality among children waiting for composite visceral grafts (Bueno *et al*. 1999). A satisfactory short-term outcome, however, has been achieved recently with isolated liver transplant in a highly-selected group of children who have shown evidence of increasing enteral feeding tolerance and have sufficient length of small bowel for complete enteral adaptation to be reasonably expected (Horslen *et al*. 2000). Even with such a careful selection, some of these isolated liver allografts may not escape the long-term deleterious effects of TPN.

The recently defined syndrome of hollow visceral neuropathy and/or myopathy is not an uncommon indication for intestinal transplant among both the paediatric and adult population. The frequent involvement of the stomach at the time of referral and the well-known progressive nature of the disease dictate, in our opinion, the need for modified (without liver) or full multivisceral replacement. Other groups have advocated a less-extensive operation by limiting the visceral replacement to the small intestine with surgical drainage of the native stomach to the allograft jejunum.

Future considerations

With the recent improvement in patient and graft survival after intestinal transplantation, the procedure should be considered before the development of liver failure. Early referral for isolated intestinal transplant will undoubtedly eliminate the need for combined organ replacement and save a substantial number of cadaveric donor livers that could be used to rescue other patients with isolated liver failure. In addition, further improvement in the survival advantage and cost-effectiveness of the procedure is anticipated.

Awaiting the results of our current preconditioning protocol combined with low-dose *ex vivo* graft irradiation and donor leucocyte replacement, prediction and/or early detection of allograft rejection are required to raise the level of intestinal transplantation to be the standard of care for patients with chronic intestinal failure. The clinical availability of a reliable serum or tissue marker will undoubtedly ease the management of these patients with an increase in most of the therapeutic indices of the operation.

The temporary and permanent effects of enteric ischaemia-reperfusion injury, central gut denervation and lymphatic disruption are important non-immunological factors that may contribute to suboptimal recovery of the complex metabolic and neuroenteric functions of the intestinal allografts. Better understanding of the mechanisms and sequelae of these injuries may increase the practicality of the procedure by opening the way for further refinement in the current methods of organ preservation, graft implantation and recipient management.

Acknowledgements

The authors would like to thank Ms Eileen V. Misencik for preparing the manuscript and each of the staff members at the Intestinal Rehabilitation and Transplant Center for their team efforts. The authors are supported in part by research grants from the Veterans Administration and Project Grant no. DK-29961 and grant no. R01 DK 54232 from the National Institutes of Health, Bethesda, MD, USA.

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https://doi.org/10.1079/PNS2003288 Published online by Cambridge University Press