Archives of Disease in Childhood 1992; 67: 976–979

REGULAR REVIEW

Recent progress in intestinal transplantation

Celia Ingham Clark

Transplantation of the kidney, liver, or heart is now a well established and successful treatment for irreversible organ failure. It has been much more difficult to achieve success in intestinal transplantation, although experimental and clinical work has been carried out in this field since the late 1950s. However, in the last three years there have been several successful human small bowel transplants in both adults and children. The problems associated with intestinal transplantation include difficulties with preservation and operative technique, as well as a high incidence of rejection, graft-versus-host disease (GVHD), and postoperative infection. These problem areas are discussed and the history of human small bowel transplantation is reviewed.

Indications for transplantation

Intestinal failure can be defined as an inability to maintain nutrition and/or positive intestinal fluid and electrolyte balance without special measures.[1] This may follow massive resection or may be caused by motility disorders or extensive disease inhibiting absorption. The commoner causes of irreversible intestinal failure include congenital atresias, gastroschisis, volvulus, and necrotising enterocolitis in neonates,[2] volvulus, visceral myopathy, and mucosal abnormalities such as congenital enteropathies in older children, and Crohn's disease, resection for volvulus or desmoid tumours, and mesenteric infarction in adults.[3]

In most cases of intestinal failure, especially those in infants, the residual intestine adapts, although it may take over two years to achieve resumption of a full enteral diet.[3] Factors that mitigate against reversibility of intestinal failure are excessive loss of healthy bowel in relation to total length for age,[2] absence of the ileocaecal valve and right colon,[4] and poor function of the residual intestine.[5] In some patients adaptation is insufficient to permit cessation of parenteral nutrition and intestinal failure is therefore permanent. At present, individuals in this group who survive are committed to permanent parenteral nutrition. Even if this can be delivered at home, it is associated with a very abnormal lifestyle and with complications which include sepsis, central venous thrombosis, and metabolic disorders.[6] For patients with irreversible intestinal failure, transplantation should be the treatment of choice. However, the results of transplantation to date have been so poor that parenteral nutrition has been the safer option. This situation may be changing.

Professorial Surgical Unit, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE

Correspondence to: Mrs Ingham Clark.

Problems are associated with small bowel transplantation because the intestine is one of the largest lymphoid organs in the body. In addition there are normally bacteria within the gut lumen, and the mucosa is extremely sensitive to ischaemia. The large lymphoid content of the small bowel renders it highly immunogenic. It is also much more liable to initiate GVHD than other solid organ grafts. The bacterial content has the potential to cause systemic sepsis if the mucosal barrier is damaged. The sensitivity to ischaemia makes it difficult to successfully preserve the small bowel in vitro.

Donors

Although there are theoretical immunological advantages in using live related donors, it may be difficult to harvest a long enough segment of intestine to permit adequate graft function in the recipient without compromising the nutritional status of the donor. Transplantation from mother to baby may avoid this problem as a relatively short graft would be required. Most human transplants have been performed using cadaveric donors. This is associated with a greater discrepancy between histocompatibility antigens in graft and host and therefore a greater risk of graft rejection. In addition, most donors have been critically ill in intensive care units. During this time the intestine is often subjected to periods of hypoperfusion, and it may also contain abnormal bacteria such as *Staphylococcus epidermidis*, which can translocate from the bowel and cause systemic infection.[7]

Preservation

The ideal method of intestinal graft preservation has not yet been determined. Experimental evidence suggests that vascular perfusion with Collins' solution allows reasonable preservation for up to six hours.[8] The gut lumen also requires perfusion and cleansing, perhaps with an antibacterial agent. The mucosal sensitivity to ischaemia is important. Mucosal sloughing commences after only 30 minutes of warm ischaemia.[9] Experimental data suggest that the addition of mucosal nutrients such as glutamine may improve small bowel preservation.[10]

Technique

Standard microsurgical techniques, based on the original work of Carrell in the 1900s have been used to construct successful vascular anastomoses in small bowel transplantation.[11]

In most instances the superior mesenteric vein draining the graft has been anastomosed to the iliac vein or inferior vena cava of the recipient. However, this effectively creates a portocaval shunt which may lead to long term complications. Graft venous drainage into the recipient portal vein, although technically difficult, is more physiological and may be associated with fewer metabolic complications.[12] Portal drainage may also convey an immunological advantage.

In most experimental and clinical cases of small bowel transplantation the graft has initially been placed out of continuity with the native intestine. This is to avoid anastomotic breakdown which would be a risk in the presence of ischaemia associated with early rejection. Therefore the ends of the graft are either both exteriorised as stomas,[13 14] or the proximal end is anastomosed to the native jejunum and the distal end brought out as a stoma.[15 16] This latter technique allows normal upper gastrointestinal secretions and enteral nutrition to flow through the graft, which should improve mucosal nutrition.[17] In either case, the graft is put into continuity with the native intestine at a second operation at a later date.

Rejection

Small bowel allografts are highly immunogenic because they contain large amounts of lymphoid material in the mesenteric lymph nodes, Peyer's patches, and lamina propria of the intestinal wall. In experimental studies in rodents, rejection has been consistently prevented with cyclosporin monotherapy.[18 19] However, results have been less consistent in large animal models.[20 21] In human transplantation rejection episodes have occurred in almost every case despite treatment with multiple immunosuppressive drugs.[13–16] The most successful small bowel transplants have been carried out using a combination of cyclosporin, azathioprine, and prednisolone with a short course of the anti-T cell monoclonal antibody OKT3,[22] or the new immunosuppressive drug FK506 with prednisolone.[23]

The diagnosis of rejection has usually been made using histological and immunohistochemical evaluation of multiple mucosal biopsy specimens.[24] However, histological signs of rejection may be patchy and multiple biopsies are necessary.[15] Because the small bowel normally contains many lymphocytes a cellular infiltrate *per se* is not indicative of rejection. Morphological evidence of rejection includes villous shortening, crypt lengthening, and epithelial sloughing, although these are late signs.[25] Early signs of rejection include loss of intracytoplasmic brush border enzymes, identified by immunohistochemical analysis[26] and a submucosal mononuclear cell infiltrate.[27] Functional tests for rejection are largely based on assessment of mucosal permeability. Absorption of ^{51}Cr-EDTA is increased in rejection, and this test has been used successfully in human transplantation.[28]

Acute rejection can be reversed in rodent models, and this has also been achieved after human transplantation. Conventional treatment such as antilymphocyte globulin or steroid boluses have achieved reversal of acute rejection.[14 16] If rejection cannot be reversed the graft must be removed promptly because in the absence of an effective mucosal barrier, bacteria can readily enter the host circulation and cause septicaemia. Once a rejecting small bowel graft has been removed the patient may revert to total parenteral nutrition, and in at least two instances a second transplant has been undertaken at a later date.

Small bowel allografts have been shown to be infiltrated by host cells in the absence of rejection[23 29] therefore immunohistochemical staining for host cells is not an indicator of rejection. Graft cells normally migrate to host lymphoid tissues after small bowel transplantation and the disappearance of graft cells from peripheral lymph nodes and spleen of the recipient is associated with graft rejection, preceding histological changes in the graft (P Lear, C Ingham Clark, *et al*, unpublished observation). Fine needle aspiration cytology of lymph nodes and staining for graft derived cells might be used as a test for rejection.

Liver/small bowel transplantation

It has been known for many years that combining liver transplantation with grafting of another organ reduces the risk of rejection of the second organ.[30] This protective effect appears to be considerable in small bowel transplantation. Combined liver/small bowel transplantation was initially performed in patients with liver failure resulting from long term parenteral nutrition,[28] but after several successful cases this technique has now been used in some patients with normal liver function.[22] This latter treatment is controversial on ethical grounds, and efforts are continuing to find better immunosuppressive treatment regimens to achieve improved results for pure small bowel transplantation.

GVHD

GVHD is a common problem in bone marrow transplantation, but rare in most solid organ grafts because they contain relatively little lymphoid tissue. It is a potential problem in small bowel transplantation because the large amount of lymphoid tissue in the graft can mount an immunological reaction against foreign major histocompatibility complex antigens of the host. GVHD will only occur if there are immunocompetent T lymphocytes within the graft.[18] Therefore treatment strategies to prevent GVHD must be directed towards these cells. In experimental models GVHD has not been completely prevented by cyclosporin treatment.[31] Pretreatment of the donor with irradiation,[32 33] antilymphocyte serum,[34] or anti-T cell monoclonal antibodies[35] can prevent GVHD. Such measures are generally inappropriate in live-related transplants. Donor irradiation may not be practicable in clinical transplantation, and the window of opportunity to treat cadaveric donors with drugs is very short.

Graft irradiation effectively prevents GVHD

but carries the risk of radiation damage to the bowel itself.[36] Ex vivo graft treatment with monoclonal antibodies or anti-T cell immunotoxins has been attempted but uniform success has not been achieved.[37 38] In clinical transplantation, GVHD has developed in several patients; in some cases it has been fatal and in others it has regressed in association with changes in the immunosuppressive treatment.[14 21] Further work is required to determine how to prevent GVHD consistently.

Infection

The small bowel is the only solid organ transplant which normally contains bacteria. Flushing the lumen of the intestinal graft before transplantation will not remove bacteria that inhabit the mucous layer adherent to the mucosa, and attempts to maintain gut sterility with enteral or parenteral antibiotics and sterile food are not consistently successful. It is therefore inevitable that most small bowel grafts will be colonised by bacteria.

An important function of the small bowel is to act as a barrier against microbial entry to the body. The ischaemia associated with transplantation leads to a temporary loss of this barrier, therefore antibiotic prophylaxis must be given to cover the peritransplantation and early post-transplantation period. In rejection mucosal barrier function is impaired; bacteria enter the circulation and can be found in many organs.[39] GVHD is also associated with damage to the mucosal barrier of the native bowel and systemic sepsis.[40] Recent work has shown that the range of bacteria within the intestine changes in both rejection and GVHD. The organisms that translocate from the bowel lumen to infect the host are not all normal enteric commensals. *S epidermidis*, a common cause of multisystem sepsis in sick patients in intensive care, is also commonly found in many organs during small bowel allograft rejection.[40] Therefore, in any rejection or GVHD episode, evidence of systemic infection should be sought and appropriate antibiotic treatment given immediately. Confirmation of the source of the infection can be achieved by culturing the same organisms from the stomal output or faeces of the patient.

Human small bowel transplantation

The first human small bowel transplant was undertaken in 1964. By 1971 seven cases of human small bowel transplantation had been reported in the literature.[41] All failed, most due to technical deficiencies or acute rejection. One patient lived for 76 days, taking nutrition through the transplanted intestine for part of this time, before dying of systemic infection associated with rejection.[41]

These poor results, and the introduction of total parenteral nutrition in the early 1970s, meant that few further attempts at small bowel transplantation were made until after the introduction of cyclosporin with its potent selective immunosuppressive action on T lymphocytes. With this new agent available, further attempts at small bowel transplantation were undertaken in patients who had sustained severe complications on total parenteral nutrition, particularly hepatic failure.[15] Most patients still suffered irreversible acute rejection, but one child transplanted in Paris and an adult transplanted in Kiel, are still living and receiving all fluid and nutrition by the enteral route, now two and a half and three years after transplantation respectively.[14 16]

Three years ago the first successful liver/small bowel transplant was carried out by Grant *et al* in London, Ontario.[28] The patient only experienced one early rejection episode and is fit and well at present, taking a normal diet. Four further transplants have been performed in this series and three of the five patients are well with functioning grafts.[22] In May, 1990, Starzl carried out the first of a series of small bowel and small bowel/liver transplants using the new immunosuppressant FK506 which had previously been shown to be effective in liver transplantation. The early results of the series have been reported by Iwaki *et al*,[23] and all of these patients have achieved full enteral nutrition and still have functioning grafts. Since then, at least six more patients have received small bowel transplants in Starzl's series, and apart from one who died from GVHD all have achieved full enteral nutrition via the grafted small bowel and the grafts continue to function.[42] However, all of these patients underwent serious postoperative complications necessitating continued hospital stay for between four and eight months after transplantation.

Thus in the last two years there have been a number of successful small bowel transplants. Most have been associated with postoperative complications, often due to infection. However, the recipients were extremely ill patients, some of whom were in advanced stages of liver failure at the time of surgery. In some American centres transplantation is now being offered to patients before they develop life threatening complications of total parenteral nutrition, and a corresponding reduction in postoperative morbidity is anticipated. In Europe, intestinal transplantation should be considered as a therapeutic option for patients who are failing on total parenteral nutrition. The European Intestinal Transplant Study Group is interested to receive details of any patient who might be an appropriate candidate for transplantation. There are grounds for optimism for many of the people currently committed to permanent parenteral nutrition.

1 Lennard-Jones JE. Indications and need for long-term parenteral nutrition: implications for intestinal transplantation. *Transplant Proc* 1990;**22**:2427–9.
2 Grosfield JL, Rescoria FJ, West KW. Short bowel syndrome in infancy and childhood. *Am J Surg* 1986;**151**:41–6.
3 Mughal M, Irving M. Home parenteral nutrition in the United Kingdom and Ireland. *Lancet* 1986;**ii**:383–6.
4 Wilmore DW. Factors correlating with a successful outome following extensive intestinal resection in newborn infants. *J Pediatr* 1972;**80**:88–95.
5 Rickham PP, Irving I, Shmerling DH. Long-term results following extensive small intestinal resection in the neonatal period. *Prog Pediatr Surg* 1977;**10**:65–75.
6 Cooper A, Floyd TS, Ross AJ, Bishop HC, Templeton JM Jr, Ziegler MM. Morbidity and mortality of short bowel syndrome acquired in infancy: an update. *J Pediatr Surg* 1984;**19**:711–8.
7 Marshall JC, Chritou NV, Horn R, Meakins JL. The microbiology of multiple organ failure: the proximal

gastrointestinal tract as an occult reservoir of pathogens. *Arch Surg* 1988;**123**:309–15.
8 Schraut WH, Lee KKW, Tsujinaka Y. Intestinal preservation of small bowel grafts by vascular washout and cold storage. In: Deltz E, Thiede A, Hamelmann H, eds. *Small bowel transplantation*. Berlin: Springer-Verlag, 1986:65–73.
9 Robinson JWL, Mirkovitch V. The recovery of function and microcirculation in small intestinal loops following ischaemia. *Gut* 1972;**13**:784–9.
10 Stangl MJ, Lee KKW, Banner B, Schraut WH. Ex vivo normothermic perfusion of small bowel grafts prior to transplantation. *Transplant Proc* 1990;**22**:2436–8.
11 Lillehei RC, Goott B, Miller FA. The physiological response of the small bowel of the dog to ischaemia including prolonged in vitro preservation of the bowel with successful replacement and survival. *Ann Surg* 1959;**150**:543–60.
12 Schraut WH, Abraham VS, Lee KKW. Portal versus caval venous drainage of small bowel allografts: technical and metabolic consequences. *Surgery* 1986;**99**:193–8.
13 Cohen Z, Silverman RE, Wassef R, *et al*. Small intestinal transplantation using cyclosporine. *Transplantation* 1986; **42**:613–21.
14 Deltz E, Schroeder P, Gundlach M, Hansmann ML, Leimenstoll G. Successful clinical small bowel transplantation. *Transplant Proc* 1990;**22**:2501.
15 Grant D, Sommerauer J, Mimeault R, *et al*. Treatment with continuous high dose intravenous cyclosporine A following intestinal transplantation. *Transplantation* 1989;**48**:151–2.
16 Goulet O, Revillon Y, Jan D, *et al*. Small bowel transplantation in children. *Transplant Proc* 1990;**22**:2499–500.
17 Feldman EJ, Dowling RH, McNaughton J, Peters TJ. Effects of oral versus intravenous nutrition on intestinal adaptation after small bowel resection in the dog. *Gastroenterology* 1976;**70**:712–9.
18 Kirkham RL, Lear PA, Madara JL, Tilney NL. Small intestinal transplantation in the rat—immunology and function. *Surgery* 1984;**96**:280–6.
19 Lee KKW, Schraut WH. Structure and function of orthotopic small bowel allografts in rats treated with cyclosporine. *Am J Surg* 1986;**151**:55–60.
20 Diliz-Perez HS, McClure J, Bedetti C, *et al*. Successful small bowel allotransplantation in dogs with cyclosporine and prednisone. *Transplantation* 1984;**37**:126–9.
21 Grant D, Duff J, Zhong R, *et al*. Successful intestinal transplantation in pigs treated with cyclosporine. *Transplantation* 1988;**45**:279–84.
22 McAlister V, Grant D, Wall W, Ghent C, Zhong R, Duff J. Clinical experience with small intestine transplantation. *Transplant Proc* 1992 (in press).
23 Iwaki Y, Starzl TE, Yagihashi A, *et al*. Replacement of donor lymphoid tissue in small bowel transplants. *Lancet* 1991; **337**:818–9.
24 Brousse N, Canioni D, Rambaud C, *et al*. Intestinal transplantation in children: contribution of immunohistochemistry. *Transplant Proc* 1990;**22**:2495–6.
25 Rosemurgy AS, Schraut WH. Small bowel allografts: sequence of histologic changes in acute and chronic rejection. *Am J Surg* 1986;**151**:470–5.
26 Schroeder P, Schweizer E, Hansmann ML, *et al*. Monitoring in small bowel transplantation using cytochemistry and immunohistochemistry: a comparison of different techniques. *Transplant Proc* 1991;**23**:675–6.
27 Hannsmann ML, Deltz E, Gundlach M, Schroeder P, Radzun H-J. Small bowel transplantation in a child. Morphological, immunohistochemical and clinical results. *Am J Clin Pathol* 1989;**92**:686–92.
28 Grant D, Wall W, Mimeault R, *et al*. Successful small bowel/liver transplantation. *Lancet* 1990;**335**:181–4.
29 Ingham Clark CL, Cunningham AJ, Crane PW, Wood RFM, Lear PA. Lymphocyte infiltration patterns in rat small bowel transplants. *Transplant Proc* 1990;**22**:2460.
30 Calne RY, Sells RA, Pena JR, *et al*. Induction of immunological tolerance by porcine liver allografts. *Nature* 1969; **223**:472–6.
31 Diflo T, Maki T, Balogh K, Monaco AP. Graft-versus-host disease in fully allogeneic small bowel transplantation in the rat. *Transplantation* 1989;**47**:7–11.
32 Monchik GJ, Russell PS. Transplantation of small bowel in the rat: technical and immunological considerations. *Surgery* 1971;**70**:693–702.
33 Deltz E, Ulrichs K, Schack T, *et al*. Graft-versus-host reaction in small bowel transplantation and possibilities for its circumvention. *Am J Surg* 1986;**151**:379–86.
34 Shaffer D, Maki T, Demichele SJ, *et al*. Prevention of graft-versus-host disease with preservation of allograft function by donor pretreatment with anti-lymphocyte serum. *Transplantation* 1988;**45**:262–9.
35 Shaffer D, Simpson MA, Milford EL, *et al*. Donor pretreatment with monoclonal antibody for prevention of graft-versus-host disease following small bowel transplantation: effect of depletion of T-cell subsets. *Transplant Proc* 1991;**23**:679–81.
36 Lee KKW, Schraut WH. In vitro allograft irradiation prevents graft-versus-host disease in small bowel transplantation. *J Surg Res* 1985;**38**:364–72.
37 Stangl MJ, Lee KKW, Lee TK, Moynihan HL, Schraut WH. Graft pre-treatment with monoclonal antibodies prior to small bowel transplantation. *Transplant Proc* 1990;**22**: 2483–4.
38 Smith GJ, Ingham Clark CL, Crane PW, Lear PA, Wood RFM, Fabre JW. Ex vivo perfusion of intestinal allografts with anti-T-cell monoclonal antibody/ricin A-chain conjugates for the suppression of graft-versus-host disease. *Transplantation* 1992 (in press).
39 Grant D, Hurlbut D, Zhong R, *et al*. Intestinal permeability and bacterial translocation following small bowel transplantation in the rat. *Transplantation* 1991;**52**:221–4.
40 Price BA, Cumberland NS, Ingham Clark CL, Wood RFM, Lear PA. Bacterial supercolonisation and the potential for translocation following small bowel transplantation. *Br J Surg* 1991 (in press).
41 Kirkham RL. Small bowel transplantation. *Transplantation* 1984;**37**:429–33.
42 Tzakis A, Todo S, Abu-Elmagd K, *et al*. Small bowel transplantation in humans. *Transplant Proc* 1992 (in press).