Progress report

Current status of intestinal transplantation

The successful development of clinical intestinal transplantation remains an exciting challenge for the transplant surgeon, immunologist, and gastroenterologist. Bowel transplantation was first attempted in 1901 by Carrel who transplanted portions of small intestine into the neck of dogs.\(^1\) Interest was rekindled in 1959 when Lillehei showed that autotransplantation of the small intestine into the dog was feasible.\(^2\) Despite recent major improvements in techniques, however, and the introduction of new immunosuppressive regimens which have seen the flourishing of liver, heart, heart/lung and pancreatic transplant programmes, the clinical results of small intestinal transplantation remain dismal.

Two major problems confront us: first, the complex immunological phenomena occurring after small bowel transplantation, which include both classical graft rejection and graft versus host disease, do not appear to be easily controlled by current immunosuppressive protocols, and require elaborate treatment of both graft and host.\(^1\)\(^2\) Second, the physiological functions of the graft are severely deranged by the process of transplantation and further immunological damage will not only hamper recovery but destroy the barrier functions so vital to recipient survival.

A series of clinical intestinal transplants were performed in the early 1970s by several institutions, with only one survivor beyond two weeks. More recently small intestinal transplants have been carried out in several major transplant centres in Europe and North America and two European recipients have survived beyond six months (personal communication). While small intestinal transplantation remains hazardous, however, it can not be considered a true therapeutic option for patients who are satisfactorily maintained on total parenteral nutrition. The purpose of this review is to summarise the progress made so far and to highlight the areas in which further research is required before small bowel transplantation becomes a practical therapeutic option.

The immunological problem

Small bowel transplantation between two unrelated individuals within a given species causes two distinct but coexistent immunological reactions. First, cell mediated graft rejection by the recipient and second, graft versus host disease, in which lymphocytes (within Peyers patches and mesenteric lymph nodes) transplanted along with the graft attack the recipient. These responses were first recognised in the rat by Monchick and Russell and later confirmed by Kirkman et al.\(^5\)\(^6\) They transplanted fully vascularised loops of small intestine bringing out the ends of the graft as cutaneous endenterostomies. Transplantation without immunosuppression using Lewis (Lew) donors and Brown Norway (BN) recipients resulted in primarily graft
destruction eight to 11 days after surgery. They were able to dissect their studies immunologically by using inbred parental Lewis or Brown Norway rats and (Lewis x Brown Norway) F1 hybrids. These hybrids rats possessed major histocompatibility antigens of both parents and therefore could not recognise Lewis or Brown Norway parental tissue as foreign. Thus when F1 were used as donors for either Lewis or Brown Norway recipients, graft rejection occurred without graft versus host disease. Similarly when Lewis or Brown Norway intestine is placed in (Lewis x Brown Norway) F1 recipients graft versus host disease developed but rejection did not occur. This model has now become a standard tool for the investigation of small bowel transplantation immunology.

In the rejection model ((Lewis x Brown Norway) F1 → Lewis) graft rejection occurs six to nine days after surgery. At necropsy there is a dense infiltration of the graft with mononuclear cells, gross mucosal oedema and sloughing. The native gut appears essentially normal. More detailed studies of the evolution of rejection have shown that three days after transplantation there is only slight mucosal damage, restricted to the crypts. There is also a vascular lesion evident affecting the arterioles and venules at the junction of the mucosa and submucosa. Endothelial cells are enlarged and are associated with intravascular lymphoid cells. By day 6 there is villus shortening but the villous epithelial cells are morphologically normal with prominent brush borders; the crypts are prolonged with extensive cell damage. The lamina propria becomes distended with a mononuclear lymphoid cell infiltrate. By the time of complete rejection (day 9) there is gross villous shortening and the epithelial cells have lost these brush borders. There is no increase in intraepithelial lymphocytes. The crypts are now also shortened and the vascular lumen is completely occluded. These observations suggest that the vascular endothelium and crypt epithelium are the initial sites of injury. As villous cells originate from the crypts the villous damage could be secondary to crypt damage. In addition ischaemia secondary to vascular occlusion could play a role.

In the graft versus host disease model (Lewis → (Lewis x Brown Norway) F1) death occurs approximately 13–16 days after transplantation. Clinically the rats develop a classic hunched posture, pink paws, ruffled fur, and diarrhoea (from the native gut). Splenic and lymphoid enlargement occurs in the early stages of the disease followed by atrophy. At histology the intestinal graft is normal. By day 5 the lymphatic tissue of the graft (Peyers patches and mesenteric lymph nodes) and host lymphatic tissue (lymph nodes and spleen) undergo progressive lymphoid depletion. This is initially accompanied by proliferation of histiocytoid cells and immunoblasts. These immunoblasts disappear over the following days, giving way to lymphopenia until normal lymph node and splenic architecture is lost. An enteritis develops in the host bowel between the ninth and 12th day with a generalised mononuclear cell infiltrate in the lamina propria. This is followed by patchy crypt necrosis and villus shortening. By day 14 the mucosa is beginning to slough. The epidermis becomes thickened and infiltrated with mononuclear and polymorphonuclear cells. Organs such as the kidney and pancreas remain normal.

Graft versus host disease is caused by donor lymphocytes migrating into the host. This can be reduced, even abolished, if the mass of lymphoid tissue in the graft is reduced by either irradiation before transplantation.
Graft versus host disease does not occur after transplantation of intestine from T-cell depleted parental donors into F1 hybrid recipients. The graft versus host disease response can be restored by reconstitution of the donor with syngeneic T-cells prior to graft donation. This confirms that donor T lymphocytes mediate graft versus host disease. Furthermore a local graft versus host response can be produced by inoculating spleen cells from (Lewis×Brown Norway) F1 rats with clinical graft versus host disease (after small intestinal transplantation) into the footpad of syngeneic recipients. This results in ipsilateral inguinal lymph node enlargement. Similar lymph node enlargement in (Lewis×Brown Norway) F1 recipient rats which cause graft versus host disease. This has been confirmed by studies after small intestinal transplantation between DA and PVG parental rat strains using monoclonal antibodies raised against donor strain specific major histocompatibility complex antigens. Graft derived cells accumulate in large numbers in all host lymphoid tissue in untreated animals. This phenomenon is transient and occurs simultaneously with the development of spontaneously resolving clinical graft versus host disease. The same features are identified in immunosuppressed animals although the cellular infiltrate into the host is far greater. This infiltrate spontaneously regresses two to three weeks after transplantation and the animal and graft survive indefinitely.

Rejection and graft versus host disease reactions are less clearly defined in the dog. Dogs survive six to 12 days after transplantation without immunosuppression. The spectrum of graft rejection is not a uniform at necropsy, indeed mucosal changes may be slight and indistinguishable from autotransplanted controls. In rejection there is an infiltrate of lymphocytes and plasma cells into the lamina propria on the fourth day. As in the rat, epithelial damage begins in the crypts and the villi become progressively shorter before sloughing. These features of rejection are inconsistent and it has often been difficult to give a cause of death. It is worth emphasising that the histological appearance of rejection may be subtle and villous shortening with an increase in mitotic figures in the crypts being the only features. Such architectural features are not specific for rejection and can be seen after ischaemia. Indeed the cardinal histological signs of rejection; fibrinoid necrosis, mononuclear cell infiltration and luminal obliteration of blood vessels are infrequently found in the canine model and the diagnosis of rejection must be circumspect.

The disparity in the results of these studies may be due to the patchy nature of the rejection reaction. Overall the immunological response of the dog to small bowel transplantation is variable with some dogs displaying classical rejection, some graft versus host disease and others in whom there is a mixed picture.

There is a suggestion that an immunological balance exists between rejection and graft versus host disease. In one study, untreated dogs died nine days after transplantation with features of graft versus host disease. Graft irradiation with 150 rads before transplantation resulted in rejection without graft versus host disease. After an intermediate dose of 50 rad, longer host survival was noted, with less aggressive rejection than in the heavily irradiated graft. The question arises as to whether immuno-
competent cells within the graft protect against rejection. Further study is required to substantiate this hypothesis.

**Immunosuppression with Cyclosporin A**

The efficacy of cyclosporin A has been investigated intensively in various models of small bowel transplantation (Table 1). In the unidirectional rat rejection model ((Lewis×Brown Norway) F1→Lewis) a number of groups have been able to achieve prolonged recipient survival with parenteral cyclosporin A without histological features of graft rejection.\(^6\)\(^8\)\(^22\)\(^23\) Indeed some studies have shown that cyclosporin A is only required for seven days.\(^6\)\(^22\)\(^23\) It should be noted that graft survival is difficult to assess in some rat studies as the graft is not in continuity with the native gut; defunctioned loops tend to atrophy because of the lack of luminal contents.\(^6\)\(^22\)\(^23\)

Cyclosporin A is less successful in preventing graft *versus* host disease in the unidirectional graft *versus* host disease model (Lewis→(Lewis×Brown Norway) F1) (Table 1). Some groups have reported no difference in recipient survival or histological findings from untreated controls\(^1\)\(^5\)\(^25\) though others have achieved good results.\(^1\) Failure of cyclosporin A to prevent graft *versus* host disease has also been reported in bone marrow transplantation which requires either higher doses, or alternative additional immunosuppression.\(^26\) In the fully allogeneic rat model (Lewis→Brown Norway) results with cyclosporin A have in general been encouraging, but low dose cyclosporin A (<15 mg/kg/day) results in reduced survival.\(^22\)\(^27\)\(^29\)

Consistent longterm host survival has not been achieved in dogs treated with cyclosporin A (Table 1); a few dogs have survived for longer than six

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Nutrition</th>
<th>Immunosuppression</th>
<th>Recipient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Rat</td>
<td>Native gut</td>
<td>CsA 15 mg/kg/d ip for 7 days</td>
<td>100 d (n=5)*</td>
</tr>
<tr>
<td>22</td>
<td>Rat</td>
<td>Native gut</td>
<td>CsA 15 mg/kg/d po</td>
<td>3/11 rats &gt;56 d</td>
</tr>
<tr>
<td>24</td>
<td>Rat</td>
<td>Native gut</td>
<td>CsA 15 mg/kg/d ip for 7 days</td>
<td>100% &gt;150 d*</td>
</tr>
</tbody>
</table>

**Graft versus host disease alone**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Nutrition</th>
<th>Immunosuppression</th>
<th>Recipient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Rat</td>
<td>Native gut</td>
<td>CsA 15 mg/kg/d for 44 days</td>
<td>44-54 d (n=4)</td>
</tr>
<tr>
<td>14</td>
<td>Rat</td>
<td>Native gut</td>
<td>CsA 15 mg/kg/d for 14 days</td>
<td>71% at 150 d (n=28)</td>
</tr>
<tr>
<td>25</td>
<td>Rat</td>
<td>Native gut</td>
<td>CsA 15 mg/kg/d sc for 5 days</td>
<td>20-4 (5-4) d (n=7)</td>
</tr>
</tbody>
</table>

**Rejection with graft versus host disease**

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Nutrition</th>
<th>Immunosuppression</th>
<th>Recipient survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Man</td>
<td>Tx gut</td>
<td>CsA 6-9 mg/kg/d for 4 then 4 mg/kg/d</td>
<td>10 d (n=1)</td>
</tr>
<tr>
<td>17</td>
<td>Dog</td>
<td>Tx gut</td>
<td>As above + methylprednisolone</td>
<td>52-2 (4-15) d (n=12)</td>
</tr>
<tr>
<td>19</td>
<td>Dog</td>
<td>Tx gut</td>
<td>CsA 17 mg/kg/d + prednisolone</td>
<td>125-7 (58-6) d (n=12)</td>
</tr>
<tr>
<td>20</td>
<td>Dog</td>
<td>Tx gut</td>
<td>CsA 25 mg/kg/d</td>
<td>103-3 (39-4) d (n=11)</td>
</tr>
<tr>
<td>23</td>
<td>Rat</td>
<td>Tx gut</td>
<td>CsA 15 mg/kg/d im</td>
<td>100% &gt;8 mo*</td>
</tr>
<tr>
<td>27</td>
<td>Rat</td>
<td>Native gut</td>
<td>CsA 10 mg/kg/d for 4 days then 2.5 mg/kg for 30 days</td>
<td>18-5 (5-7) d (n=8)</td>
</tr>
<tr>
<td>28</td>
<td>Rat</td>
<td>Native gut</td>
<td>CsA 25 mg/kg/d for 14 days</td>
<td>&gt;21 d*</td>
</tr>
<tr>
<td>29</td>
<td>Rat</td>
<td>Native/Tx gut</td>
<td>CsA 20 mg/kg/d sc</td>
<td>112 (92-122) d (n=10)</td>
</tr>
<tr>
<td>30</td>
<td>Dog</td>
<td>Tx gut</td>
<td>CsA 16 mg/kg/d iv tapering to 8 mg/kg/d at day 8</td>
<td>45 (38) d (n=9)</td>
</tr>
<tr>
<td>31</td>
<td>Dog</td>
<td>Native gut</td>
<td>CsA 20 mg/kg/d po</td>
<td>63-3 (15-5) d (n=6)</td>
</tr>
<tr>
<td>32</td>
<td>Dog</td>
<td>Tx gut</td>
<td>CsA 16 mg/kg/d iv tapering to 8 mg/kg/d</td>
<td>27-7 (13-8) d (n=6)</td>
</tr>
<tr>
<td>33</td>
<td>Pig</td>
<td>Tx gut</td>
<td>CsA 15 mg/kg/d iv for 10 days then 30 mg/kg/d po for 4 mo</td>
<td>121 (33) d (n=6)</td>
</tr>
<tr>
<td>34</td>
<td>Pig</td>
<td>Native gut</td>
<td>CsA 25 mg/kg/d po</td>
<td>34 (13) d (n=11)</td>
</tr>
</tbody>
</table>

Nutrition indicates whether nutrients were absorbed by the native gut or by transplanted (tx) gut. Recipient survival indicated the maximum recipient survival when a number of immunosuppression regimes were used.

*The survival time was either not stated or the animals were killed for experimental purposes.

CsA = cyclosporin A.
months. In some studies death within the first eight postoperative weeks was entirely due to graft rejection. In others, however, only some of the deaths could be ascribed to rejection. Death through malnutrition, secondary to graft versus host disease has been reported as a cause of death though no diagnostic features could be found. This highlights the difficulty of diagnosis of graft rejection and graft versus host disease as the histological features can be non-specific or slight.

In the pig long term host survival is possible but high blood concentrations of cyclosporin A appear to be essential. Best survival rates have been achieved when cyclosporin A (15 mg/kg/day) is given intravenously for seven to 10 days after surgery and then orally at 30 mg/kg/day. Oral administration alone, even at high dosage, does not appear to achieve adequate blood levels.

A different approach to small bowel transplantation is to use grafts from immunologically naive foetal donors rather than adults. Work in the 1970’s on transplantation of mouse foetal small intestine implanted under the renal capsule showed that survival and growth of transplanted foetal intestinal isografts was possible. The mucosa of allografts without immunosuppression were destroyed in six to seven days. This has been performed in rats where the intestine has been placed in the paravertebral gutter; the graft develops its own blood supply from the surrounding tissues. Although cyclosporin A has been shown to prevent rejection it is not yet clear whether such grafts can support host nutrition.

**Other forms of immunosuppression**

Conventional immunosuppression with prednisolone and azathioprine appears to be ineffective. Transplantation across the major histocompatibility complex reduces graft survival and matching of major histocompatibility complex antigens will be essential in clinical transplantation. Pretransplant blood transfusion with donor specific blood can extend host survival time. The value of this is difficult to assess as suboptimal doses of cyclosporin A were used in this study and survival times were not as good as those achieved with cyclosporin A alone. In most studies of rats venous drainage of the graft is directly into the inferior vena cava. This may have a detrimental effect on graft survival when compared with portal venous drainage as the liver is an immunological filter. Graft rejection in the unidirectional rejection model is less rapid when the graft is drained through the portal vein in preference to the inferior vena cava (11-8 versus 22-8 days). Such a finding may be immaterial, because in clinical transplantation the recipient portal vein is likely to be thrombosed from primary disease. Graft irradiation or lymph node resection to reduce the quantity of lymphoid tissue transplanted can prevent graft versus host disease. In vivo irradiation may not be practical as it may in the long term cause radiation enteritis, but in vitro irradiation with intestinal shielding is a real possibility. Donor pretreatment with polyclonal antilymphocyte serum has been shown to prevent graft versus host disease in the unidirectional rat graft versus host disease model. In fully allogeneic models such treatment may lead to increased graft rejection by the recipient. The practical constraints of clinical transplantation may make transfusion of the donor prior to organ harvesting impractical.
Graft Function

The critical functional test of transplanted small bowel is whether it can prevent malnutrition in the absence of nutrient absorption from native gut. A number of investigations have shown that rats with fully allogeneic grafts replacing the native intestine are able to gain weight at a comparable rate to isograft or unoperated controls. Blood glucose concentrations in transplant recipients after the instillation of maltose into the intestinal lumen are similar to controls. This is not only a test of absorptive function but also of mucosal integrity as maltose is hydrolysed by the brush border enzyme maltase to glucose before its absorption. Serum triglyceride and cholesterol concentrations are also normal indicating lipid absorption and metabolism to be preserved. Thus rat small bowel grafts appear to be able to absorb nutrients adequately. As longterm survival of dogs with small bowel transplantation has not been reliably achieved there are less functional data than with the rat. Dogs living for more than six months after transplantation are well but no details about weight and functional parameters have been reported. Many allografted dogs lose weight after surgery, however, and have diarrhoea.

In most animal models venous drainage is into the inferior vena cava which creates a subtotal portosystemic shunt. This leads to a rise in serum ammonia and amino acids similar to those found in models of hepatic encephalopathy. These changes can be minimised by feeding a low protein diet.

An inevitable consequence of small bowel transplantation is graft denervation. This is of importance because salt and water absorption is under tight neurological control by the autonomic nervous system. Water, electrolyte, glucose and glycine absorption has been studied in the rat unidirectional rejection model ((Lewis$\times$Brown Norway) F1→Lewis) treated with cyclosporin A. In allografts there is a reduction of water and sodium absorption rates from a glycine-saline infusate, a reduction of sodium absorption rate from a glucose-saline infusate and net chloride secretion when mannitol-saline is perfused. These transport defects can not be accounted for by immunological factors: there are similar defects in isografts (which by definition can not undergo rejection). Surgical partial denervation of the native intestine reproduces the transport defects. This study does not address the nature of the defect causing the increase in net chloride secretion from mannitol-saline, but it suggests that the reduction in net absorption rates could be because of enhanced secretion. Although the entire neural supply is severed in transplantation this defect is most consistent with a loss of sympathetic innervation which is thought to act as a ‘brake’ inhibiting secretion. As the loss of sympathetic innervation appears to be important $\alpha_2$-adrenergic drugs may be of benefit. This study suggests that diarrhoea may result from transplantation even if immunologically successful. Diarrhoea, however, has not been observed in rats surviving long term. This may be because sufficient length of bowel is transplanted so there is complete absorption of the luminal contents despite a reduction in net absorption rates. Another unexplored possibility is that innervation is reestablished. There does appear to be a degree of mucosal adaptation in longterm surviving rat models (Deltz E, personal communication). Nevertheless, regardless of the explanation, if absorption is compro-
mised because of rejection as well as denervation severe diarrhoea will result.

Motor function is also disturbed by denervation. In denervated canine jejunoileum migrating motor complexes are present but are uncoordinated and are not interrupted by feeding as they are normally. In allografts myoelectric activity is present and intestinal transit is three times more rapid than autograft controls causing diarrhoea. There are little data, however, on the periodicity and coordination of migrating motor complexes. More studies are needed to establish the effects of transplantation and denervation on motor function.

An unique aspect of intestinal transplantation is that rejection reduces cyclosporin A absorption. In small bowel resected dogs, cyclosporin A blood concentrations after oral administration are 45-fold less than in normal dogs indicating the importance of the small intestine as a site of absorption. Lymphatic uptake accounts for most of the absorption from the gut as cyclosporin A concentrations are 12-fold higher in the thoracic duct than blood. It is likely that lymphatic connections are reestablished four to six weeks after transplantation as methylene blue injected into mesenteric lymph nodes can be observed to pass into mesenteric lymph and host at this time. However, cyclosporin A malabsorption continues up to 10 weeks after transplantation. The explanation is not clear but could be due to diarrhoea induced by the olive oil vehicle. (Cyclosporin A is only barely soluble in water and so is dissolved in olive oil when administered orally.) Pretreatment with olive oil ameliorates the cyclosporin A malabsorption, presumably by adaptation to the fat enriched diet. In the clinical context cyclosporin A will have to be administered parenterally for an extended period after transplantation to ensure adequate blood concentrations.

Graft harvesting and storage

Small intestinal grafts for human transplantation will be harvested mainly from cadaveric donors and a new method will be required for storage. Lillehei was unable to extend graft preservation beyond five hours by cooling to 5°C. With graft perfusion, the administration of chlorpromazine and hyperbaric oxygen and cooling preservation could be extended up to 48 hours. Preservation for 24 hours has been achieved with hypothermic perfusion of human plasmanate. Other methods have, at best, provided bowel survival of only 50%. Simple hypothermic storage of canine intestine can be done by perfusing with ice cold Ringers-lactate. All dogs receiving allografts stored in this way for 12 hours survived beyond five days (mean 45-4 days) and 67% of dogs receiving allografts stored for 24 hours survived for five days (mean 22-5 days). The authors attribute the graft survival without the use of metabolic inhibitors to in situ flushing and intraluminal irrigation before cooling which reduces endotoxaemia and damage from pancreatic enzymes.

Monitoring and diagnosis of rejection

Histology remains the gold standard for the diagnosis of rejection. With human small bowel transplants it is possible to obtain daily biopsies if one end of the graft is brought up to the skin as a cutaneous stoma. The histological features of rejection (particularly in the early stages) may be
Functional absorption tests have been suggested for monitoring rejection but these seem too elaborate for routine use. At present there is no accepted blood test for rejection as there is with the kidney (creatinine), liver (LFTS) or heart (CPK). Serum N-acetyl hexosaminidase is a lysosomal acid hydrolase which is raised in association with intestinal ischaemia. The assay is simple and can be completed in less than three hours. In a preliminary study N-acetyl hexosaminidase has been shown to rise before graft rejection though further validation is required. N-acetyl hexosaminidase has the disadvantage that it is not a specific measure of immune activity but more of intestinal damage. This disadvantage may be overcome by assaying procoagulant activity which is a measure of effector function of immunologically activated cells of the monocyte-macrophage lineage. Procoagulant activity has also been used to monitor a case of human small bowel transplantation. Procoagulant activity was low when there was no evidence of rejection and rose as lymphocyte infiltration became apparent in mucosal biopsies.

Small bowel transplantation in man

As many patients with the short bowel syndrome or small intestinal failure can be successfully treated with home parenteral nutrition the indications for small bowel transplantation will be limited unless its mortality and morbidity is low. Nevertheless, home parenteral nutrition is not without problems and is associated with significant morbidity, particularly in children. Therefore the indications for small bowel transplantation would include failure of home parenteral nutrition and congenital causes of small bowel failure such as microvillus atrophy.

If successful, small bowel transplantation offers the advantage of patient independence. Home total parenteral nutrition is expensive, costing £35,000 per patient year. It is likely that small bowel transplantation would be cheaper (the annual cost of cyclosporin A treatment for a kidney transplant is approximately £2000). In the precyclosporin era a number of transplants were performed all of which were unsuccessful (Table 2). The first two cases were performed by Detterling in Boston in 1964, neither of which were fully reported. Both were in children; the first died 12 hours after transplantation, the second lived for several weeks, after removal of the graft for necrosis on day 2 post transplantation. The longest surviving transplant patient was a 37 year old woman who had undergone a massive small bowel resection for Gardners syndrome. A 1.7 m length of small intestine was harvested from her HLA-identical sister. After two weeks an episode of rejection was successfully reversed with steroids. She was able to eat for two months and died 76 days after transplantation with E coli septicaemia. Graft versus host disease was suspected before the patients death but could not be proved.

To date five cases of small bowel transplantation using cyclosporin A has been reported. The first patient was a 26 year old woman suffering from Gardners syndrome with an ileostomy who had undergone resection of her entire small bowel because of a large desmoid tumour. One year later small
bowel transplantation was undertaken because of failure of home total parenteral nutrition. She received a graft of proximal jejunum to terminal ileum and was immunosuppressed with intravenous cyclosporin A. The blood groups of the donor and recipient were O and A respectively. On the fourth day she developed a brisk haemolytic anaemia caused by anti-A antibodies derived from donor lymphocytes. On the ninth day graft rejection was suspected by a rising procoagulant activity activity and confirmed by stomal biopsy. She died on day 10. At necropsy the cause of death could not be determined with certainty but cyclosporin A neurotoxicity was suspected; the graft itself was undergoing rejection.

Starzl has reported a technique in which the pancreas is transplanted together with a cuff of duodenum. This method allows the whole pancreas to be transplanted and is technically easier than other methods. Although better results are now being achieved with the pancreas, the duodenum undergoes progressive inflammatory changes and a severe protein losing enteropathy ensues. It is not clear whether this is because of rejection, ischaemia or other factors. This effect can be minimised by using just sufficient duodenum around the ampulla of Vater for anastomosis to the recipient jejunum.

This technique has recently been extended to transplantation of multiple abdominal viscera. Starzl and his colleagues have used this approach to treat two children (aged six and three and a half years) with the short gut syndrome and liver failure secondary to total parenteral nutrition. The procedure involves the transplantation en bloc of stomach, small intestine, colon, pancreas and liver. The monoclonal antibody OKT3 was given perioperatively to suppress graft versus host disease and cyclosporin A postoperatively for rejection. One patient died perioperatively the other patient lived for 193 days before dying from an Epstein-Barr virus-associated lymphoproliferative disorder. At the time of death there was no evidence of rejection or graft versus host disease. Williams and colleagues have performed a similar procedure on two young children (17 and nine months) with short bowel syndrome and liver failure associated with total
parenteral nutrition." The procedure was similar to that of Starzl except that the colon was not transplanted. The donor organs were irradiated with 10 Gy before transplantation. The first child survived only four days however the second child lived for 109 days before dying of a malignant, B-cell lymphoproliferative disorder. At necropsy there was no evidence of rejection of the small intestine or liver. These cases illustrate that it is possible to prevent small intestinal rejection if the patient survives the perioperative period. Effective immunosuppression, however, seems to be at the cost of fatal infection or malignancy.

Conclusions and future prospects

Significant progress has been made since the pioneering experiments of Lillehei. Indefinite graft and host survival has been achieved in rats by many investigators and the grafts appear to provide sufficient nutrition for growth. There has been less success with other species, however, partly because of the difficulty in achieving adequate immunosuppression and important questions remain regarding salt and water absorption and graft motility. The use of selective irradiation of the graft and quadruple therapy (antilymphocyte serum, cyclosporin A, azathioprine and prednisolone) may be the only immunosuppressive regimen which will permit longterm graft survival. Although not yet reported, two transplants have recently been carried out in Europe in which there has been greater than six months graft survival (privileged communication). In addition the European Intestinal Transplantation Study Group has been set up in Kiel to coordinate research into clinical intestinal transplantation. The recent congress of the Transplantation Society confirmed the considerable interest which has now developed in this field and we may be able to look forward to the day when small intestinal transplantation is a realistic prospect.

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