Functional aspects of small bowel transplantation: past, present, and future

Small bowel transplantation poses two major problems. Firstly, transplanting the small bowel between two unrelated individuals results in two different immunological reactions: host versus graft reaction (graft rejection) and graft versus host reaction. The large amount of transplanted lymphoid tissue is responsible for this highly immunogenic character of an intestinal allograft. Secondly, the surgical procedure of small bowel transplantation inevitably involves transection of the intestinal wall with intrinsic and extrinsic denervation, interruption of lymphatic drainage, and preservation-induced injury. Each component of this procedure may alter the intestinal physiology adversely. Immunological reactions and immunosuppressive agents may further compromise the normal intestinal functions. This review considers the functional aspects of experimental small bowel transplantation, with emphasis on enteric motility; hormonal, immunological, and nutritional aspects; and intestinal barrier function.

Motor function
In autotransplanted dogs, Ballinger showed altered small bowel motility by barium x ray studied. In a syngeneic rat small bowel transplant model, Taguchi evaluated the effect of transplant on intestinal smooth muscle contractility and the associated neural control mechanisms, and found that neither the contractile properties of smooth muscle nor the responses to several neuropeptides, nor the excitatory response to electrical stimulation had changed. Inhibitory innervation did change, however, probably reflecting the degeneration of adrenergic nerve endings as a result of extrinsic denervation. He suggested that loss of one aspect of inhibition does not interfere with motility, because neural control of the small bowel seems to be predominantly intrinsic.

In a dog model, Dennison reported normal intestinal myoelectrical activity by the second day after autografting and allografting, and recovery of intestinal transit by the 10th day after autografting. Others suggest that motor activity is absent for several weeks after autotransplantation in dogs. Subsequently, the autografted small bowel recovers the ability to generate normal migrating motor complexes, but the postprandial myoelectrical activity remains consistently and permanently absent. This suggests that the response to feeding is dependent on the integrity of the extrinsic nerves. However, infusion of the postprandial hormones, cholecystokinin (CCK) and pentagastrin, induced a normal pattern of contractions, suggestive of a modulating effect by hormones without input from the extrinsic nerves.

These changes in fasting or postprandial responses, or both, could result in luminal bacterial overgrowth, which might contribute to the failure of the small bowel graft and infectious complications.

Hormone function
The gastrointestinal tract is innervated by a network of intrinsic and extrinsic neurons containing peptides. Changes in the content and amount of these neuropeptides in response to denervation after small bowel transplantation may have local and distant effects on small bowel functions, particularly since the gut is the largest endocrine organ of the body.

Gebhardt examined the patterns of hormone distribution after heterotopic and orthotopic small bowel transplantation in rats. Heterotopic transplantation resulted in mucosal atrophy and a decrease in vasoactive intestinal peptide (VIP) and CCK concentrations. When the heterotopic graft was brought into the orthotopic position, however, these values returned to normal. LaRosa reported that small bowel transplantation, and thus extrinsic denervation, does not affect baseline intraluminal substance P and serotonin concentrations, or the physiological responses of these neuropeptides to intraluminal stimuli. Similar results were reported by Tietelbaum with somatostatin, VIP, and substance P after syngeneic and allogeneic small bowel transplantation in rats. Progressive reduction in neuropeptides was seen only in cases of small bowel graft rejection. In contrast, Nelson showed that in vivo neural isolation of canine jejun ilealum results in temporal adaptation of enteric neuropeptides. After extrinsic and intrinsic denervation, VIP and substance P concentrations were increased but neuropeptide Y values in both tissue and plasma were reduced. In addition, VIP and substance P concentrations increased progressively over time after surgery (198% and 217% mean maximal increases, respectively). As VIP and substance P induce a proserotonin effect, and neuropeptide Y a preabsorptive effect, these factors may have contributed to the profuse watery diarrhea observed in this model.

Nelson ascribed the discrepancy between his findings and other reports to the relatively short follow up in earlier studies. The altered neuropeptide concentrations after denervation may also modulate smooth muscle contractility and cause altered motility, as reported by Sarr.

The exact role of denervation on gastrointestinal hormone concentrations has not yet been elucidated, but adaptive changes in the neuropeptides of the gut may alter the enteric physiology after transplantation. The influence of neuropeptides in modulating the gastrointestinal neuroimmune axis would be of interest since it has been shown that VIP exerts potent immunosuppressive actions via T cell-specific mechanisms, which may play a role after transplantation.

Immune function
The small bowel contains a large accumulation of lymphoid tissue in mesenteric lymph nodes, Peyer's patches, lamina propria, and epithelium. Little is known

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of the immune function of the transplanted small bowel, although it is obvious that long term survival with a graft necessitates a well functioning local immune system.15

In an effort to understand the immune function of transplanted small bowel, Xia and Kirkman reported a consecutive series of studies about specific secretary immunoglobulin A (sIgA) production against cholera toxin in a rat small bowel transplantation model.16-20 They found no difference in total sIgA production after syngeneic or allogeneic small bowel transplantation, but noted that allografts are less effective in producing a primary sIgA response against cholera toxin than isografts.16 After priming the donor, however, small bowel allografts are capable of producing a secondary sIgA response to a booster of cholera toxin seven days after transplantation.17 Cyclosporin A treatment has no effect on total sIgA production, but it suppresses the sIgA response to cholera toxin in both allografts and isografts.18 This inhibitory effect of cyclosporin A lasts as long as the recipients are receiving it. In another experiment the authors showed that cyclosporin A only inhibits sIgA production against a T cell dependent antigen such as cholera toxin, but not against a T cell independent antigen (tinitrophenyl-lipopoly saccharide).19 Xia suggested that this unresponsiveness against T cell dependent antigen cyclosporin A treated recipients explains the high incidence of septic complications after small bowel transplantation. Recently, he showed that priming of the recipient with cholera toxin before transplantation abrogates the inhibitory effect of cyclosporin A on specific sIgA production against cholera toxin.20 This finding may be relevant to clinical transplantation, since immunity against an infectious agent may be useful in controlling the transplant. This could mean that functional recipient lymphocytes repopulate the graft and produce the secondary immune response after boosting with cholera toxin.

**Nutritional function**

Small bowel transplantation is only worthwhile if the graft is capable of maintaining adequate nutrition in adult recipients, and normal growth and development in children without parenteral nutrition support. After an initial postoperative weight loss, rats regain normal weight after total isografting and allografting.21-23 Some investigators found normal weight gain even after a segmental small bowel graft consisting of either jejunum, ileum, or only part of the jejunum.21 24 25 This suggests that transplanted small bowel has the ability to adapt, which had been confirmed by Kirsch, who found an increased diameter of the graft with hypertrophied villi.25 Kimura, De Bruin, and Oki designed fatal models of short bowel syndrome, in which transplantation of 40 cm of jejunum resulted in normal growth, whereas rats with a 20 cm jejunal graft showed suboptimal weight gain.22 26 27

Small bowel transplantation in large animals has yielded more controversial data, probably because only occasional long term survivors have been reported. Dogs with a total autotransplant regained their pretransplant weight either soon or after several management changes.33 Some authors reported a 10 to 15% weight loss after total small bowel or 100 cm ileal autografting.3 Long term surviving dogs with a total small bowel allograft maintained their body weight, but after one year the weights of the two long term survivors reported by Diliz-Perez fell to a lower but eventually stable level.31 32 Transplantation of 100 cm ileal allografts in dogs by Collin resulted in 88% of pretransplant weights.33 In contrast, pigs with a total small bowel allograft experienced a weight gain comparable with that of control pigs.34 35 Kimura showed that pigs transplanted with a segmental jejunal allograft (25% of total small bowel length) increased their body weight by almost 40% after six months, whereas all enterectomised control pigs suffered from malnutrition with progressive weight loss.36 Kimura concluded that porcine segmental small bowel allografts maintain their compensatory capacity and hypertrophy after massive small bowel reduction. Recently, we showed that dogs with a major histocompatibility complex (MHC) matched, orthotopic segmental graft, consisting 25 to 30% of total small bowel length, regained their preoperative body weight after 20 weeks.37 We are now performing orthotopic segmental small bowel transplants in immature dogs, which show a near normal weight gain (unpublished data).

**NUTRIENT ABSORPTION**

With regard to clinical small bowel transplantation, absorptive function of the transplanted bowel is the most important physiological determinant of graft function. It is likely that absorptive function after transplantation will be altered – at least temporarily – because of harvest injury, extrinsic denervation, transection of intrinsic neural continuity, and disruption of lymphatics. At present, however, intestinal absorptive function after transplantation is not fully understood and inconsistent studies have been reported. The different results may be explained by the varied experimental protocols. In addition, differences may be related to either the transplantation procedure itself or the immunological phenomena that follow. Nutrient absorption studies after transplantation in rats showed prolonged malabsorption of fat and fat soluble vitamins (A and D) as well as carbohydrates, glycine, and reduced glucose stimulated electrophysiological parameters.21 23 38 Other rat studies showed normal faecal fat excretion, normal glucose and vitamin B-12 uptake, and relatively normal electrophysiological characteristics in non-rejecting small bowel grafts.21 22 39 40

In dogs and pigs, absorptive functions of jejunum (D-xylene, folate), ileum (vitamin B-12), and jejunouileum (fat, fat soluble vitamins, cyclosporin A) have been studied in autotransplants and allotransplants. In a modified autotransplantation model without peritransplant ischaemia, Sarr showed normal D-xylene and folate absorption.30 Normal D-xylene absorption has also been reported in allotransplant experiments.41 42 43 This may suggest that absorption of D-xylene and folate does not require neural or lymphatic continuity. Several others reported reduced D-xylene absorption by small bowel allografts, but this could be related to rejection of the graft.31 32 The reduced D-xylene absorption found by Raju in autotransplants may be ascribed to bacterial overgrowth, because a similar phenomenon was found by other investigators in autotransplanted dogs that survived more than one year after transplant.44 45 46 This late malabsorption correlated with significant bacterial overgrowth, probably as a result of permanently impaired small bowel motility.39

Vitamin B-12 absorption and faecal fat excretion are normal in autografts and allografts in both dogs and pigs.30 34 35 43 This suggests that vitamin B-12 absorption occurs without extrinsic and intrinsic neural and lymphatic continuity. Normal fat absorption in the presence of disrupted lymphatic drainage is of interest even in the early period after transplant.30 We also found near normal faecal fat excretion in segmental orthotopic small bowel allografts in dogs.37 Re-establishment of lymphatic drainage occurs two weeks after small bowel transplantation, and is fully achieved by four to six weeks.44 47 An explanation for this
early fat absorption may be the opening of lymphovenous communications in the mesentry if the lymphatic drainage is obstructed as a pathway for absorption of fat until the regenerated lymphatics take over. Impaired intestinal absorption of fat has been reported by Thompson in canine small bowel autotransplants more than 12 months after transplantation, probably because of bacterial overgrowth in the transplanted jejunum and ileum.

Adequate cyclosporin A absorption in the small bowel is vital for a recipient with an allograft. Cyclosporin A is a lipophilic agent and is absorbed through the lymphatic drainage. Schraut suggested that cyclosporin A absorption in the early period after transplant may be compromised because of disrupted lymphatics. This has been underlined by investigators who found a low incidence of small bowel graft rejection if cyclosporin A was administered parenterally in the peritransplant period. Other investigators found normal cyclosporin A absorption after oral or intraluminal treatment, even in the first week after transplant.51 52 Cohen explained this by cyclosporin A absorption via the peritoneal membrane.53 According to Cohen, cyclosporin A leaks into the peritoneal cavity through the disrupted lymphatics, after which it is absorbed. It may be that cyclosporin A is absorbed via lymphovenous anastomoses in the mesentry. However, during the early period after transplant it seems justified to treat the recipient with parenteral cyclosporin A, because plasma concentrations may be unpredictable during this time and rejection episodes will impair the absorptive capacity for cyclosporin A. Complicating factors may be that cyclosporin A itself reduces nutrient absorption and adversely affects the microvasculature of the small bowel.55

WATER AND ELECTROLYTE ABSORPTION
Several studies in rats have shown that net absorption of electrolyte solutions is decreased early after small bowel transplantation.57 58 Extrinsic denervation may be the underlying cause, since denervated small bowel secretes water and chloride from the crypts as a consequence of loss of sympathetic input.58 59 Using electrophysiological measurements we found indirect evidence that extrinsic denervation leads to increased secretory activity of the crypts in a heterotopic autotransplant model in dogs.60 It has been suggested that extrinsic denervation after small bowel transplantation plays a much more important part in the fluid and electrolyte balance than in the absorption of nutrients. Watson found that glucose can reverse the secretory state found with isotonic saline, which implies that glucose electrolyte solutions may be clinically useful in promoting electrolyte absorption after transplantation. Sigalet observed an increase in sodium/glucose cotransporter activity after small bowel transplantation, which may be compensatory and restore the electrolyte balance. However, a recent canine study found no significant effect on jejunal absorption using a balanced physiological saline solution before or after transplantation.61 At present, it is uncertain whether regeneration of extrinsic neural continuity or adaptation to chronic denervation takes place.

Barrier function
Impaired gut barrier function is a possible aetiological factor in the development of multiorgan failure.52 The high incidence of infectious complications and sepsis after small bowel transplantation may be a result of excessive immunosuppression, but a compromised barrier function of native or grafted small bowel may also be important. We evaluated the mucosal integrity of acute rejecting intestinal grafts by analysing albumin contents in the graft effluent and found a protein losing enteropathy corresponding with rejection, which suggests that the mucosal barrier is highly permeable during a rejection episode.53

In a study in rats Grant showed that rejection of orthotopic small bowel grafts leads to increased intestinal permeability to Cr-EDTA and increased bacterial translocation from the lumen of the graft to the host's mesenteric lymph nodes, liver, and spleen. He proposed that bacterial translocation may stimulate immune responses, which contributes to the intensity and rapidity of small bowel graft rejection. In a heterotopic rat model, Fabian reported increased bacterial translocation not only in small bowel allografts, but also in isografts, suggesting that the transplantation procedure itself affects the intestinal permeability independently of rejection. Browne showed that the transplantation procedure itself leads to Gram negative aerobic overgrowth within the transplanted small bowel segment and ascending colon. Significant translocation of bacteria to the mesenteric lymph nodes occurred only when cyclosporin A was added. Remarkably, Gram negative organisms were more commonly isolated from the native mesenteric lymph nodes that from the graft, which suggests translocation through both native and transplanted small bowel. Cyclosporin A facilitates distant dissemination to liver, spleen, and lung once translocation has occurred. Therefore, both bacterial overgrowth and immunosuppression are associated with transplantion and sepsis after small bowel transplantation.

Future directions
Future research should be directed to a better understanding and prevention of acute and chronic rejection. The induction of specific tolerance or improved immunosuppressive agents may be a prerequisite for the success of clinical transplantation. MHC matching may be valuable in reducing the vigorous immunosuppressive regimen. In addition, MHC matching may pave the way for living-related intestinal transplantation.

New approaches to prevent infectious complications are an important science and the gut mucosal barrier should be considered. In this context selective gut decontamination, early enteral feeding, and modified total parenteral nutrition may be important tools. Potential beneficial effects of glutamine, short chain fatty acids, and polyamines added to enteral or parenteral nutrition should be investigated.

The possible protecting effect of a liver graft in conjunction with a small bowel graft is an important issue. Although experimental studies and one clinical case showed the superiority of combined small bowel liver transplantation, this benefit could not be confirmed in the first reported series of intestinal transplantation either in composite visceral grafts or alone. The convalescence of the eight patients who received an intestinal graft alone was more trouble free than after small bowel liver or multivisceral transplantation, with no greater difficulty in control of rejection. This suggests that small bowel liver transplantation should be reserved for specific indications, such as coexisting liver failure from total parenteral nutrition or a hepatic inborn error of metabolism. It is too early, however, to predict the function of the chronically tolerated intestinal graft, whether transplanted alone or as part of an organ complex.

Recent clinical small bowel transplantations should be critically evaluated. The combination of extending our experimental knowledge and clinical experience should...
result eventually lead to safe clinically effective transplantation from both immunological and functional points of view.

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Special report

Gastrointestinal endoscopy in general practice

The summary of the report of a working party of the endoscopy section of the British Society of Gastroenterology is printed here.

Increasing emphasis on primary care in the NHS has prompted suggestions that a number of services should be provided in general practice. The report considers the possibility of providing gastrointestinal endoscopy in general practice.

Commissioners of health care are responsible for ensuring access to high quality, safe, endoscopic services. Careful consideration of the safety of potential providers, as well as the capital and revenue costs is essential: duplication of services must be avoided.

For the safety of both patients and staff, the following standards must be met wherever endoscopy is performed:
1. Endoscopists must be adequately trained. Endoscopic and interpretive skills must be maintained by a sufficient workload and continuing interaction with other endoscopists and specialists.
2. Adequate equipment must be available, together with safe facilities for its cleaning and maintenance.
3. Providers must adhere to professional guidelines for sedation, monitoring, and recovery.
4. There must be sufficient numbers of trained and experienced support staff.
5. A safe environment must be provided, to comply with Health and Safety Executive and Control of Substances Hazardous to Health regulations.

6. Anaesthetic and resuscitation facilities must be provided on site for the management of complications of sedation and procedures, particularly for patients at risk because of age or medical condition.

Because of the risks, therapeutic gastroscopy, colonoscopy, endoscopic retrograde cholangiopancreato-graphy, and endoscopy in children should be confined to hospitals, where support for the management of complications is present.

The working group concluded that providers of endoscopy must conform to standards both of safety for staff and patients and of the quality of the services. Some endoscopic procedures could be provided in general practice if these standards are met. It seems likely, however, that it would not be possible or cost effective to provide the level of support required for anything other than routine diagnostic gastroscopy and flexible sigmoidoscopy in fit adults and even there, the case is in doubt.

Copies of the full report may be obtained from the Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB.

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