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Small bowel transplantation: an overview

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Abstract Small bowel transplantation (SBT) would, in theory, be the treatment of choice for patients suffering from the short bowel syndrome. Although SBT has been done with a considerable degree of success in some centers [36, 145], it is by no means an established or widely applicable therapy for those with short bowel syndrome. The small bowel is unique among vascularized organ grafts because it not only elicits a vigorous rejection reaction but is also capable of inducing graft-versus-host disease (GVHD). Rejection of the graft does not only lead to loss of function but also to bacterial translocation. The risk of fatal sepsis is aggravated by the immunosuppression given to prevent rejection. Here, the history of SBT is described, and recent developments in experimental and clinical SBT, as well as future prospects for this theoretically optimal treatment modality for patients dependent on total parenteral nutrition (TPN) for life, are outlined.

Key words Small bowel transplantation

History

In 1959, Lillehei et al. [73] described, for the first time, a technique for orthotopic small bowel transplantation (SBT) in the dog. Many experimental studies followed and several patients received a small bowel transplant. However, the initial enthusiasm for SBT waned when it became evident that rejection and sepsis were recurrent problems that could not easily be solved and when total parenteral nutrition (TPN) was introduced as satisfactory therapy for otherwise untreatable patients. With the introduction of the potent immunosuppressive agent cyclosporin A (CyA) came a renewed interest in SBT, which is presently on the verge of becoming an established procedure in transplant medicine.

Experimental models of small bowel transplantation

A number of models are used to study SBT, each having its own advantages and disadvantages. Monchik and Russell [90] first used parent and F1 hybrid rats in SBT. By using rats from two inbred parent (P) strains and their offspring (F1), they were able to distinguish graft-versus-host disease (GVHD) from rejection. Transplantation from P to F1 produces only GVHD, whereas in the reverse siutation only rejection occurs. The relevance of these one-way semiallogeneic models to the clinical situation, in which both GVHD and rejection may occur, is uncertain [114] and, hence, fully allogeneic combinations, in which the graft is transplanted from P1 to P2, are used to study the possible interaction between GVHD and rejection. Syngeneic transplantation from P1 to P1 can be used to study the effects of ischemia and lymphatic and neural disruption while the immunologically induced traumas are circumvented (Table 1). In large animals, syngeneic transplantation finds its equal in autotransplantation, in which the arterial and venous blood supply are divided and reanastomosed, the lymphatics and nerves are disrupted, and the bowel is cut and reanastomosed [73, 84, 107].

With respect to the position of the bowel, two models are used. In one, the bowel is placed heterotopically; the recipient small bowel remains in situ, and the graft is placed as a Thiry-Vella fistula with both ends of the graft anasto-

Table 1 Immunological reactions after small bowel transplantation

Model	GVHD	Rejection
P1 → P1	–	–
F1 → P	–	+
P → F1	+	–
P1 → P2	+	+

mosed as stomas in the abdominal wall of the recipient. The oral end of the graft may also be ligated or placed as a duodenostoma, whereas the distal end is anastomosed end-to-side to the terminal ileum of the recipient bowel.

In the orthotopic model, the recipient small bowel is resected and the graft is placed in continuity with the remaining duodenum and terminal ileum of the recipient. In this model, recipient survival is dependent upon the functioning of the graft. Although orthotopic SBT (OSBT) may be the preferred model [38, 68], the reported longer operative time and higher incidence of complications [62, 63] have resulted in a number of studies in which heterotopic SBT (HSBT) has been used [150]. In skilled hands, however, the operative time and technical success rate for both techniques are not significantly different [159]. Results obtained after HSBT and OSBT are not comparable [38, 68]. After HSBT, rejection of the graft is defined as the development of a palpable abdominal mass and necrosis of stomas [38, 68]. However, the graft may become encapsulated and fibrotic rather than necrotic and perforated, and the recipient may survive despite the graft loss, which makes the end point of rejection more difficult to define [38, 123]. Moreover, probably due to a lack of intraluminal nutrients, atrophy of the mucosa occurs [151], and the permeability of these grafts 7 days postoperatively is significantly higher than after OSBT. Graft survival after HSBT can be prolonged more easily than after OSBT [38]. In conclusion, OSBT may be the preferred model for both immunological and functional studies.

Venous drainage of the graft may be in the portal or in the systemic circulation. Although technically more demanding [131], portoportal drainage is the more physiological route. Beneficial effects of this route on graft survival have been reported [63, 123], although they may be of minor importance [69]. Portocaval shunting may cause metabolic complications, such as a rise in blood ammonia levels, and liver atrophy. The effects of portocaval shunting after SBT appear to be minor, and either type of venous drainage may be used safely [53, 63, 123, 131].

Lillehei et al. [73] were the first to describe a technique for functional bowel transplantation in the dog. After the bowel had been removed, it was autotransplanted and subsequently had good function. Different models of heterotopic and orthotopic placement of the bowel, with either systemic or portal venous drainage, are used as preclinical models for the immunological and functional studies. Since pigs are inexpensive, easily cared for, and gain weight rapidly, they are also used in SBT [35, 54, 106].

Histology

The sequence of histological changes after SBT is well defined, although there may be slight differences, depending on the model studied [46, 76, 90, 120].

In our BN-to-WAG fully allogeneic, orthotopic total SBT model, early intestinal lesions on days 4–6 post-transplantation were characterized by mild infiltration of the lamina propria and submucosa by mononuclear cells and neutrophils and by mild multifocal death of crypt epithelial cells. The number of mononuclear cells increased to moderate over a period of a few days, while only a few neutrophils were seen after 6 days. Crypt cell death was also observed on days 7–12 post-transplantation, but it never became a prominent feature. Fibrin thrombi in mucosal capillaries were observed with increasing frequency during the course of graft rejection. This was associated with extensive necrosis of the mucosa at 11 and 12 days after grafting. Widespread thrombosis, resulting in ischemia, is probably the principal cause of graft necrosis. Mononuclear cells accumulated around blood vessels in the mesentery. At 11–12 days post-transplantation, early changes in the arteries included endothelial hypertrophy, and this was followed by mild intimal proliferation and thrombosis.

The mesenteric lymph node became rapidly depleted of lymphocytes, which were replaced by large mononuclear cells, presumably macrophages, and increasing numbers of fibroblasts.

Immunohistochemical changes generally predate histological ones. In rats, a huge number of macrophages are seen infiltrating the submucosa, peaking on day 7. Increasing numbers of T cells are seen starting on day 3 in the submucosa, whereas their numbers are increased in the crypts on days 5 and 7 [44]. In humans, increased number of macrophages and CD 4^+ cells are found in the lamina propria, and crypts express HLA-DR antigens [49]. Others have found pericryptic infiltrates of CD 3^+ cells and HLA-DR expression on crypt enterocytes 3–5 days before histological changes became apparent [6]

Immunosuppression with cyclosporin

Before CyA became available, other immunosuppressive agents were used in attempts to prolong small bowel allograft survival. Taylor et al. [141] used high doses of azathioprine in the artificial model of transplantation of a small segment of small bowel as a Thiry-Vella fistula in the neck of dogs. Only marginal prolongation of graft survival was found. Preston et al. [104], using the same model, added prednisone to azathioprine and found prolongation of graft survival from 9 to 27.5 days. Addition of antilymphocyte serum (ALS) to this regimen prolonged graft survival to a mean of 38 days [41].

Interest in SBT has been rekindled since the introduction of the potent immunosuppressant CyA [57]. Reznick

Table 2 Use of FK 506 in rat small bowel transplantation. OSBT, Orthotopic small bowel transplantation; HSBT, heterotopic small bowel transplantation; pc, portocaval venous drainage; pp, portoportal venous drainage; nr, not reported

Author	Model[a]	FK 506 dose (mg/kg)	Additonal treatment/ remarks	Survival[b] (days)	GVHD
Hoffmann et al. [45]	HSBT-pc	2 mg/kg, days 3–6		34.9 ± 30.8	None
		2 mg/kg, days 3–6 + 1 mg/kg, days 8–30, qod		50.6 ± 46.5	None
		1 mg/kg, days 8–30, qod	One-way rejection	83.0 ± 82.6	None
		1 mg/kg, days 8–30, qod	One-way GVHD	188.0 ± 72.1	12.5 %
Lee et al. [70]	OSBT	2 mg/kg, days 0–4		> 180	None
de Bruin et al. [10]	OSBT-pc	2 mg/kg, days 0, 1, 2, 4, 6		28.5 ± 6.8 SE	Severe
		2 mg/kg, days 0, 1, 2, 4, 6	5 Gy donorirr	31.1 ± 5.7 SE	None
Fukuzawa et al. [32]	HSBT-pc	0.3 mg/kg, days 0–14	1.0 mg/kg, days −8– −4	9.8 ± 2.8	nr
		0.3 mg/kg, days 0–14	1.0 mg/kg, days −8– −4 + DST, day −8[c]	62.2 ± 33.6	nr
Murase et al. [94]	OSBT-pp	0.15 mg/kg, days 0–13		44.5 median	Mild, self-limiting[d]
		0.15 mg/kg, days 0–13		"20–30 days"	Severe
Murase et al. [93]	OSBT-pc	0.64 mg/kg, days 0–13		121, median	None
Santiago et al. [116]	HSBT-pc	0.3 mg/kg, days 0–13		6.8 ± 0.8	nr
		1.0 mg/kg, days 0–13		12.4 ± 8.4	nr
		2.0 mg/kg, days 0–13		17.4 ± 4.7	nr
		0.3 mg/kg, days 0–13	donor 2 mg/kg FK, days −3, −2, −1	41.2 ± 3.8	nr
		None	donor 2 mg/kg FK, days −3, −2, −1	12.2 ± 1.9	
Tadeka et al. [140]	HSBT	0.32 mg/kg, days 0–13	minor HC incompatible	80 % > 175	nr
		0.32 mg/kg, days 0–13	major HC incompatible	38.0 ± 6.3	nr
Hatazawa et al. [42]	OSBT	1.0 mg/kg per day, 8 weeks, s.c.		"> 8 weeks"	None
Stangl et al. [136]	nr	10 mg/kg CyA, days 0–5		27.3 ± 4.8	
		10 mg/kg CyA, days 0–5	FK 506, 2 mg/kg, days 13–15	> 270	None
Utsunomiya et al. [147]	OSBT-pc	0.1 mg/kg, days 0–29		13.4 ± 3.07	nr
		0.3 mg/kg, days 0–29		34.6 ± 12.79	nr
		0.5 mg/kg, days 0–29		32.6 ± 26.16	nr
Yamataka et al. [158]	nr	1.0 mg/kg, days 3–5, i.p.		"> 20"	nr
		1.0 mg/kg, days 3–5, i.p., + α-ICAM-1, 1 mg/kg, days 1–3		"> 20"	nr

[a] Fully allogeneic model, unless otherwise stated. FK was administered intramuscularly, unless otherwise stated
[b] Mean survival in days, unless otherwise indicated
[c] DST + donor-specific blood transfusion
[d] Murase et al. 1991: mild, self-limiting GVHD in BN-to-Lew combination, severe GVHD in Lew-to-BN combination

et al. [108] first reported prolongation of graft survival to a mean of 90.6 days after intramuscular (i.m.) administration of 25 mg/kg per day. Many dogs died of pneumonia, perhaps due to the malnutrition caused by chronic rejection of the grafts or due to the high dose of CyA. Discouraging results in both dogs and pigs have also been reported by others [105].

In both unidirectional and fully allogeneic rat models, CyA is able to significantly prolong small bowel allograft survival [122]. This is highly dependent upon the rat strain combination used. We have shown that in the BN-to-WAG rat donor-host combination, long-term allograft survival is easy to achieve using short courses of CyA, whereas in the reverse WAG-to-BN model, CyA has only a limited efficacy in prolonging graft survival [9]. In unidirectional P-to-F1 hybrid models, CyA appears to be less effective in preventing GVHD [58].

In large animal models, prolongation of graft survival is hard to achieve, but continuous intravenous (i.v.) infusion of CyA has been shown to result in long-term allo-

graft survival (122 ± 33 days) in pigs, without any animals dying from rejection [34]. These results were achieved with 15 mg/kg CyA given i.v. for 7–10 days, followed by 30 mg/kg per day orally, tapered to 15 mg/kg over 3–4 months. However, high CyA blood levels of approximately 600–700 ng/ml were measured that could lead to toxicity in the kidney [28] and bowel [19] and to an unacceptably high risk of developing malignancies [100]. Recently, it was reported that MHC matching prolonged survival of segmental ileal grafts in nonimmunosuppressed beagle dogs [43] and that graft rejection can be prevented with CyA when donor and recipient are fully MHC-matched: CyA dosages in this group were 15 mg/kg i.m. from 1 day before surgery until the end of the 1st postoperative week and 30 mg/kg per day orally until day 200 post-transplantation. Recipients of an MHC-matched graft survived for a mean of 211 days without signs of rejection during CyA therapy. MHC-mismatched dogs survived for a mean of 113 days with four of six animals showing rejection that occurred during CyA treatment [88].

Pretransplant CyA treatment (pretreatment) of the recipient is associated with a reduced incidence of acute rejection in kidney transplantation [47]. Moreover, Kahan et al. [51] and Rogerson et al. [110] found that low plasma CyA levels in the early postoperative period are associated with a higher incidence of rejection following human renal transplantation. However, in an experimental rat study we were unable to significantly prolong small bowel allograft survival after preloading the recipient with high-dose CyA, as compared to postoperative immunosuppression only, although no acute rejection occurred (unpublished data). It is generally thought that oral administration of CyA should be avoided [57] since the disrupted lymphatics of the graft are unable to transport this lipophilic drug to the blood. Although we have shown that absorption of orally administered CyA after total small bowel resection is severely impaired [11], we found no lowered plasma trough levels in the 1st week post-transplantation. This finding is consistent with observations by Aeder et al. [1] and LaRosa et al. [64], who found that oral and intraluminal CyA absorption within 1 week after transplantation did not differ significantly from preoperative or control values. This indicates that there must be an alternative mechanism by which CyA is delivered to the blood. By administering CyA intraperitoneally to normal dogs, Cohen et al. [17] have shown that some absorption may take place via the peritoneum. It is possible that after transplantation CyA in the lymph leaks into the peritoneal cavity through the disrupted lymphatics and is subsequently reabsorbed. Thus, even before lymph vessel continuity is re-established 4–10 weeks post-transplantation, as is shown to happen in different models [61, 113, 121], orally administered CyA is absorbed. It has, however, been shown that CyA absorption is highly variable and unpredictable during the early postoperative period and, moreover, that rejection can impair the ability of the graft to absorb CyA [17]. Therefore, it seems justified to advocate parenteral administration as the main route, especially in the first months after transplantation. Whether concomitant oral treatment can be of benefit due to local immunosuppressive effects needs to be investigated.

Other forms of immunosuppression

FK 506 and rapamycin (RAPA) are both macrolides produced by *Streptomyces* species with potent immunosuppressive activity [14]. FK 506, like CyA, counteracts mitogenic or antigenic stimulation at an early stage of T-cell activation, whereas RAPA intervenes in events more closely related to DNA synthesis. All three drugs exert their action via a class of binding proteins known as immunophilins, which possess cis-trans peptidyl prolyl isomerase activity. There is evidence that FK 506 and RAPA bind to the same binding site, whereas CyA binds to the similar, but nonidentical, cyclophilin. Probably as a result of this, RAPA has been shown to antagonize the FK 506-induced inhibition of T-cell proliferation, and FK 506 has been shown to antagonize the action of RAPA, although potentiation of either drug may be achieved using equimolar concentrations of the two agents. Combinations of CyA and FK 506 or RAPA invariably result in a greater inhibition of mitogen and alloantigen-induced T-cell responses.

RAPA suppresses a wider spectrum of T- and B-cell activation pathways than FK 506 or CyA. Interest in these two agents for use in SBT is a direct result of the potency of RAPA and FK 506 in prolonging graft survival [144].

FK 506

Hoffman et al. [45] performed an extensive study on the use of FK 506 for SBT in rats (Table 2). They showed that long courses of FK 506 are more effective than CyA in the prevention of acute rejection and lethal GVHD in semiallogeneic models. Short courses of 2 mg/kg on days 0–6 post-transplantation prevented rejection in the fully allogeneic ACI-to-Lew model. In the model used, a 20 times higher dose of CyA was needed to obtain comparable survival times. No clinical GVHD was observed. Using the BN-to-Lew rat model, Lee et al. [70] found similar results, while Stangl et al. [136] showed in the same model that FK 506 is able to reverse an ongoing chronic rejection process. We were unable to find superior immunosuppressive effects of short-course FK 506 over CyA using the fully allogeneic WAG-to-BN rat strain combination [10]. Moreover, after FK 506 treatment, severe GVHD was seen. This was also observed by Murase et al. [94] in the BN-to-Lew combination giving 0.15 mg/kg for 14 days. Hatazawa et al. [42], on the other hand, observed

prolonged survival after administration of 1 mg/kg per day for 8 weeks in the same model.

Masutani et al. [82] found in a P-to-F1 hybrid model that 14 days after HSBT using 0.32 mg/kg per day, FK 506 animals showed no histological signs of GVHD, and Markus et al. [79] showed that FK 506 is able to reverse ongoing GVHD after bone marrow transplantation better than CyA and RAPA.

Rapamycin

Continuous i.v. administration of 0.80 mg/kg of RAPA for 14 days was shown to significantly prolong allograft survival [138]. Using Lew and (LBN) F1 hybrid one-way models, it was shown that RAPA is able to suppress both isolated rejection and GVHD, although its effect on GVHD is less potent than on rejection [52]. Chen et al. [15], however, found RAPA to be equipotent in suppressing isolated rejection and GVHD in the same model. They also showed that RAPA is synergistically effective with CyA. Similar immunosuppressive efficacy as with CyA was achieved with a five times lower dose of RAPA after fully allogeneic rat SBT [138]. No toxicity was reported in these studies.

Both FK 506 and RAPA may prove to be the more potent, less toxic immunosuppressants needed for successful clinical SBT, but this has yet to be evaluated clinically.

Immunomodulation

It has been widely recognized that preconditioning of the recipient with donor-specific blood transfusions (DST) may lead to prolongation of allograft survival in both experimental [80] and clinical [97] transplantation. In the BN-to-WAG rat donor-host combination, DST are very effective in prolonging heart and kidney graft survival [80]. However, three pretransplant DST had no effect on total or segmental SBT in this model. When DST was combined with low-dose CyA administration, no additional prolongation of graft survival could be measured [8]. Similar results were reported by Fecteau et al. [30]. In contrast, Martinelli et al. [81] did find a synergistic effect of CyA and DST, and with FK 506, DST acts synergistically as well [32].

These findings indicate that DST may contribute to the prevention of rejection, but more studies are needed to determine whether DST can be a therapeutic option in living related SBT.

Ultraviolet B (UV-B) irradiation of transfused cells intensifies the effects of DST in rat transplantation models. UV-B-irradiated leukocyte transfusions in combination with short-term, low-dose CyA immunosuppression is significantly efficacious in prolonging small bowel allograft survival. The mechanism includes, at least in part, a component of donor-specific unresponsiveness [157].

Graft-versus-host disease after small bowel transplantation

Monchik and Russel [90] first showed that transplantation of the small bowel may produce a lethal GVHD in P-to-F1 hybrid rat models. This GVHD shows histological similarities to that induced by bone marrow transplantation [92] and is caused by T lymphocytes originating from the transplanted gut and its mesenteric lymph nodes [58, 149]. Clinically, it is characterized by dermatitis, alopecia, a hunched posture and, eventually, death of the animal. Observations in unidirectional GVHD or rejection models are of uncertain relevance to the clinical situation, in which a two-way reaction between rejection and GVHD may occur [57]. In fully allogeneic SBT, rejection rather than GVHD seems to predominate [31, 69, 90]. In some fully allogeneic models, 30%–50% of the animals show clinically overt GVHD, distinguished from that in the one-way model by its nonlethal, short-lived nature. Little is known about the interaction between rejection and GVHD in these models. Cohen et al. [16] investigated the effect of graft irradiation with 0.5 and 1.5 Gy prior to transplantation in a canine small bowel allograft model. They found that pretreatment with 1.5 Gy leads to rejection of the small bowel allografts in 9.2 days. Pretreatment with 0.5 Gy, however, prolonged graft survival to a mean of 28 days. Therefore, they hypothesized that there is a balance between rejection and GVHD, and that the development of subclinical GVHD after 0.5 Gy irradiation results in prolonged graft survival.

Since the early 1960s it has been known that GVHD depresses the host's immunological reactivity [48]. This is best shown by clinical results obtained with T-cell-depleted bone marrow transplantation. On the one hand, T-cell depletion significantly reduces acute GVHD; on the other hand, it substantially increases graft rejection [137]. GVHD is also known to be immunosuppressive after experimental spleen, cell, and small bowel transplantation [35].

Histopathologically, GVHD is characterized by a loss of the normal architecture of the spleen, lymph nodes, and thymus [22, 35, 124]. This leads to profound immunosuppression with impaired humoral and cell-mediated immune responses [35]. This immunosuppression probably accounts for the observed in vivo balance between rejection and GVHD.

Diflo et al. [26] observed a short, sublethal GVHD approximately 4–6 weeks after fully allogeneic transplantation in immunosuppressed animals. Donor pretreatment with ALS completely eliminated GVHD but had no effect on graft survival in these immunosuppressed hosts. Gundlach et al. [39] found that mesenteric lymphadenectomy, a method that has been shown to eliminate GVHD [102], does not influence the course of acute graft rejection in nonimmunosuppressed recipients. CyA was not effective in preventing chronic rejection following mesen-

teric lymphadenectomy, whereas the same dosage of CyA fully prevented rejection of normal small bowel grafts. They suggested that the absence of an immunosuppressive effect caused by a GVH reaction had led to chronic rejection in this model.

We showed that irradiation of the donor with 10 Gy 1 day before fully allogeneic SBT in the WAG-to-BN rat model completely eliminated GVHD and significantly shortened survival times [114]. Moreover, CyA treatment of the recipient was unable to completely override this effect [115]. Pretreatment of the donor with ALS also eliminated clinical GVHD and led to significantly accelerated rejection [12]. When our recipients of a graft pretreated with ALS received immunosuppressive treatment with CyA, no adverse effect on graft survival was seen any more, whereas clinical GVHD remained suppressed. This important finding is in accordance with earlier findings from our laboratory [115]. The usefulness of manipulating this balance for future clinical SBT remains to be established since it is as yet unclear whether this balance theory is a rat strain-dependent phenomenon and whether GVHD will even be a clinical problem.

Prevention of GVHD in SBT often implies reducing the immunogenicity of the graft also. In attempts to control both rejection and GVHD, reducing the immunocenicity and, consequently, diminishing the number of leukocytes in the graft, has been carried out. Moreover, in the recipient, the immunosuppression used to prevent rejection also suppresses GVHD, although in semiallogeneic rat models CyA appears to be less effective in preventing GVHD than in preventing rejection. FK 506 may even enhance GVHD [10, 94].

Several donor pretreatment modalities have been shown to abrogate or diminish clinical GVHD following experimental SBT. Total body irradiation of the donor prior to transplantation completely eliminates GVHD [23, 67, 90], as does pretreatment of the donor with ALS [130], mesenteric lymphadenectomy [23], and reducing the length of the graft [55].

High levels of the cytokine tumor necrosis factor alpha (TNFα) are measured in rats with lethal GVHD after SBT in a P-to-F1 GVHD model [103]. Blocking of TNFα activity reduces the mortality of GVHD after experimental bone marrow transplantation and prevents skin and gut lesions of GVHD [101]. This suggests that anti-TNFα antibody therapy could be helpful in reducing the severity or lethality of GVHD. Other cytokines may also be involved in the pathogenesis of GVHD [91] and are important in graft rejection as well. Anticytokine therapy might, therefore, prove to be valuable in concert with other immunosuppressive modalities.

Graft physiology

The small bowel exhibits nutritional, motor, hormonal, and immunological functions. After transplantation, changes in these functions may be expected for several reasons including the ischemia, lymphatic disruption, and denervation caused by the transplant procedure, the immunological processes arising after allogeneic transplantation, and the immunosuppressive drugs given. The small bowel transplant must be able to overcome the symptoms of short bowel syndrome. In the adult recipient, long-term prevention of malnutrition, and in children, normal growth and development followed by long-term prevention of malnutrition, are prerequisites for successful clinical SBT.

Nutritional function

A sensitive functional test is whether a small bowel transplant recipient is able to grow and develop normally. Several studies have shown that rats are able to gain weight normally after allogeneic total SBT [11, 125]. However, rats grafted with a segmental small bowel transplant may develop impaired nutritional parameters [125] or grow suboptimally [11, 96], although Kirsch et al. [59] have shown that there were no significant differences in growth between sham-operated rats, animals with 50% of their bowel (jejunum) intact, and animals transplanted orthotopically with 50% of their total bowel length of jejunum 150 days post-transplantation. Moreover, just like the native gut after bowel resection, the transplanted intestine is capable of adaptation (i.e., increased bowel diameter and increased villus height) [59]. In dogs, conflicting data have been reported. Long-term surviving, allografted dogs maintain their preoperative body weight but have only slightly better nutritional parameters than dogs with short gut syndrome [27]. Weight after transplantation of a 100-cm-long segmental ileal allograft was maintained at 88% of its preoperative weight [18]. Autotransplanted dogs did not attain their preoperative weight until 1 year after transplantation [107]. Moreover, it has been reported that substantial nutritional disturbances can be expected from lymphatic and neural division alone [3]. Recently, it was shown that autotransplanted adult dogs regain their preoperative weight within 1 year after transplantation. One year post-transplantation, these animals still had elevated stool moisture content and developed steatorrhea and impaired D-xylose absorption [143]. However, MHC-matched, CyA-treated recipients of a 45- to 65-cm-long allograft of terminal ileum did not differ in growth or fecal fat content from sham-operated controls, indicating adequate nutritional function (Meijssen et al., submitted). In young pigs, total small bowel allografts are able to adequately sustain the recipients' growth at a rate comparable to that of normal controls [34]. Porcine segmental jejunal allografts comprising approximately 25% of the

small bowel length are incapable of doing the same; by 180 days after transplantation animals had increased their weight by only 40 % [56], as compared to more than 100 % in 4 weeks in Grants' animals. From these studies it seems that, from a nutritional point of view, allotransplantation will be possible. Taking into account its limitations (living related donation, abdominal size), as much bowel length as possible should be transplanted. More studies are needed to determine whether long-term functioning of SBT is feasible in both juvenile and adult recipients as opposed to long-term total parenteral nutrition, and how compromised functions may be restored.

Immune function

The gut mocosa has an important barrier function with regard to luminal food antigens and pathogens [5]. It is constantly challenged by microbial and food antigens, and its responses to these stimuli must be appropriate; infections must be limited but, at the same time, the integrity of the vulnerable mucosa must not be compromised. Intestinal immunity was first observed when protective "coproantibodies" were found in stools of orally immunized rabbits. However, the vulnerable gut mucosa should also be protected against potentially harmful reactions to harmless antigens. Indeed, suppressive mechanisms after immunization with harmless antigens have been observed and are called "oral tolerance" [146]. How the suppressive and inductive immunoregulatory mechanisms are established in the intestine is still not clear. The secretory immunoglobulin (Ig) system is the major effector mechanism of mucosal immunity. Approximately 70 %–80 % of all Ig is produced by B lymphocytes in the mucosa of the small and large bowel. This secretory Ig, which is mainly IgA, is transported to the gut lumen through the epithelial cells of Lieberkühn's crypts.

Numerous T lymphocytes are localized in the gut epithelium. In contrast to the lamina propria T lymphocytes, these intraepithelial lymphocytes (IEL) are in direct line with macromolecules in transit across the epithelium [29]. Their function is still obscure, but they are thought to play a role in cytotoxic as well as suppressive immune reactions. Apart from these solitary cells, the gut also contains organized solitary lymph nodes and lymph node aggregates: Peyer's patches. These are probably the major site of antigen presentation and commitment to sIgA synthesis in the mucosal-associated lymphoid tissue. Sensitized and committed cells migrate via the mesenteric lymph node and the bloodstream to distant gut. IgA-producing cells may also migrate to other mucosal surfaces that are part of the mucosal-associated lymphoid tissue, such as the lung, mammary glands, salivary glands, and lacrimal glands [146].

The immune function of bowel transplants is largely unknown. Both in humans [50] and in experimental animals [66] it was found that graft lymphocytes are replaced by cells of recipient origin without the occurrence of rejection. Xia and Kirkman [154] found no differences in graft total sIgA production after syngeneic and semiallogeneic SBT in rats. Immunosuppression with CyA had no effect on the total sIgA production. However, allografted animals treated with CyA failed to produce significant amounts of specific anticholera toxin sIgA when challenged with choleratoxin at the time of transplantation. The specific immune response to cholera toxin remained completely suppressed as long as the animals received CyA [156]. When allografted animals were boosted with choleratoxin 7 days post-transplantation, after having been primed 1 week before transplantation, normal sIgA levels were measured [155]. The presence of (part of) the recipient's colon could be important since it also contributes to gut mucosal immunology. The effect of different immunosuppressive agents on graft immune function needs to be investigated.

Motor function

The motility of the normal, intact upper gut has been well characterized. The stomach and small intestine display distinct patterns of motility during fasting and feeding. During the fasting or interdigestive period, the upper gut shows a spontaneous and recurrent cyclic pattern of motility, called the migrating motor complex (MMC) or interdigestive myoelectric complex. Feeding interrupts this MMC and induces a less well-defined, noncyclic pattern of intermittent, low-amplitude contractions that persist for a variable period of time, depending on the type and amount of nutrient. These motor patterns are physiologically important. During fasting, the MMC sweeps nondigestable intraluminal debris from the stomach and small intestine ("intestinal housekeeping"). The change in motor pattern caused by feeding is believed to maximize the mixing of food and to facilitate its absorption.

Schiller et al. [119] noted alterations in the motility of jejunal segments transplanted in the neck of recipient dogs. In Lew rats that had received a segmental syngeneic SBT, basal electrical rhythm of the graft was not observed for approximately 2 days after transplantation and did not attain the level of normal rats for at least 3 weeks. MMC was not observed in the transplanted segment until postoperative day 11 and became constant starting on postoperative day 16 [148]. In a dog model of small bowel autotransplantation, in which all extrinsic neural and lymphatic connections to the jejunoileum were transected, the MMC was present, although the coordination between the innervated duodenum and the denervated jejunoileum, present in the normal gut, was lacking [118]. The presence of MMC is of importance since its intestinal housekeeping function is thought to be essential in preventing bacterial overgrowth, a situation also encoun-

tered after SBT (see below). Feeding or infusing the putative postprandial peptide hormones cholecystokinin or pentagastrin induced a normal "fed" pattern of contractions [118]. This implies that the intrinsic nerves of gut are capable of generating these motor patterns without input from the central nervous system.

Hormonal function

A number of hormones are produced by cells scattered diffusely throughout the length of the gut. The physiological role of these peptides is still being evaluated. Intraluminal levels of vasoactive intestinal peptide, somatostatin, and substance P are stable from 4 days after syngeneic SBT to 1 year post-transplantation. During rejection, however, lowered levels of these hormones have been found [142]. LaRosa et al. [65] reported that SBT does not alter the baseline levels of serotonin and substance P or their response to stimuli.

Monitoring of graft rejection

Unlike renal, hepatic, and pancreatic grafts, intestinal grafts have, as yet, no specific, distinguishing serum markers to diagnose rejection. Histology remains the gold standard for the diagnosis of rejection [86], although this method has several short-comings. Full thickness biopsies from the graft have to be taken from cutaneous stomas to reliably recognize rejection [89], which involves the risk of graft perforation. Multiple biopsies are necessary because rejection shows a patchy character and may be easily missed [25, 84, 120]. In view of these limitations, several small bowel function tests have been studied to determine their usefulness as markers for rejection. Function tests of the graft that need biopsy material from the graft, such as the determination of brush border enzyme activity [87, 127], have the same disadvantage of being dependent upon the presence of an enterostoma. Moreover, they do not detect rejection at an earlier stage than does histology. Functional tests, functional absorption tests, and putative serum markers of rejection must be at least as sensitive and as specific as histology in order to be considered an alternative to histology.

In order to be absorbed, the disaccharide maltose must be split into glucose by the brush border enzyme maltase. This glucose is subsequently absorbed and raises the blood glucose level. In this way, the maltose absorption test can be performed as a glucose tolerance test. Billiar et al. [4] studied this test in rats and found that a reduction in maltose absorption preceded histological changes by 1–2 days. They concluded that this test is a reliable, reproducible, and sensitive method for monitoring rejection.

Intestinal absorption of water, sodium, glucose, alanine, and lauric acid have also been proposed as early serum markers. These substances require active transport by the mucosa, and significant decreases in their absorption were found when the first changes in histology were present [25].

Intestinal permeability to ^{51}Cr-EDTA is increased during rejection. In rats, a twofold increase was measured at the time minimal histological signs of rejection were present [37]. Assessment of urinary ^{51}Cr-EDTA as a measure of intestinal permeability has already proved its usefulness, permitting early detection and treatment of an acute rejection episode after clinical small bowel-liver transplantation [36].

Monocyte-macrophage procoagulant activity is a measure of immune activation of mononuclear cells. Measured in peripheral blood mononuclear cells, elevated levels were observed before histological changes of allograft rejection and remained high throughout the course of rejection. This test appears to be an accurate serum marker for the detection of rejection [54, 132].

The lysosomal acid hydrolase N-acetyl hexosaminidase (NAH) is elevated in serum in association with intestinal ischemia. A study performed in rats suggested that determination of serum NAH is a simple and rapid test that can prove useful as a serum marker for small bowel allograft rejection [77]. In contrast to this report, Meijssen et al. [85] found in a dog model that a significant rise in NAH occurred after histological changes related to acute rejection were visible.

Transepithelial potential difference has been studied to determine its value as a diagnostic tool for the early detection of rejection. Madara and Kirkman [76], using an in vitro method, found that a decreased spontaneous transepithelial potential difference, which is an index of baseline active transport resulting from electrogenic sodium absorption and chloride secretion, correlated with histological signs of rejection. Sodium-coupled glucose absorption, which is an index of villus function, and theophylline-stimulated chloride secretion, which mainly measures crypt cell function, decreased when structural changes indicative of rejection became apparent. Lee et al. [71] found that changes in basal transepithelial potential difference parallelled, and often preceded, histological changes of rejection. Because of the invasive nature of their method, they did not consider it a practical clinical tool. In a model of canine small bowel autotransplantation, Meijssen et al. [86] developed a noninvasive method using a double balloon catheter that was inserted in an enterostomy and isolated a loop of bowel in which electrophysiological measurements could be performed. It was shown that in vivo electrophysiological parameters provide a useful tool in the assessment of small bowel autotransplants. A reduction in transepithelial potential difference preceded degenerative mucosal changes in the graft. It was subsequently found that following allotransplantation, electrophysiological parameters correlate with histological alterations of acute rejection, thus dem-

onstrating that serial monitoring of transepithelial potential differences is a noninvasive method for detecting small bowel allograft rejection that circumvents the disadvantages of histological monitoring [84].

Preservation

At present, no consensus exists about the method of choice or preservation solution for a small bowel graft, nor is it known what maximal ischemia time is tolerable. Euro-Collins solution may be the best preservation fluid for the canine small bowel, as compared to University of Wisconsin (UW) solution or Ringer's lactate [40], but in rats UW solution seems to be the most effective preservation solution [129]. The mucosa of the small bowel is very susceptible to ischemia and reperfusion injury [99]. Vascular and luminal perfusion of the graft alone without cold ischemia leads to mucosal injury in rats that is completely healed 24 h after transplantation. After 5 h of cold ischemia at 4 °C using UW or Sacks' solution, the mucosa of the graft was significantly injured, but 24 h after transplantation there was complete healing of the mucosa. However, 18 h of cold ischemia led to severe injury that was still present 24 h after transplantation [98].

The pathophysiology of reperfusion injury involves the formation of oxygen-derived free radicals [99]. It has been shown that the addition of free radical scavengers, such as superoxide dismutase, to the preservation fluid may be beneficial to the small bowel graft [74, 139].

In a recent series of successful clinical SBT, a simple preservation method proved to be appropriate: simple core cooling of the graft with UW solution without extensive flushing of the capillary bed, followed by immersion in an ice bath. Even intraluminal washing was omitted, leaving the succes entericus in the graft, with no consequent infection from this practive [145]. Using UW solution, satisfactory preservation for up to 16 h has been reported in humans [21].

Small bowel transplantation in humans

Before CyA became available, attempts at clinical SBT were invariably unsuccessful. Failures were due to technical complications, rejection, GVHD, and sepsis [57]. These discouraging results, and the availability of TPN, led to a diminished interest in SBT.

Several successful SBT have been reported since CyA was introduced. Deltz et al. [24] reported a case of successful SBT using a 60-cm segment of jejunum and ileum harvested from the sister of the recipient. Although this graft was not rejected, the patient had severe diarrhea. The graft donor also developed chronic diarrhea. Nine attempts at SBT in seven children have resulted in one successful case in which the recipient is alive more than 3 years after grafting. In all of the other patients the grafts had to be removed because of necrosis or because rejection was uncontrollable [33]. The combined European experience in SBT was recently reported by Schroeder et al. [126]: from March 1987 until July 1990, 15 SBT were performed in 12 patients. Four grafts are presently functioning, with patients independent of TPN. Immunosuppression in these patients was with CyA and prednisone, usually supplemented with azathioprine and ALS. In one patient transient GVHD was encountered. Recently, a successful case of multiorgan transplantation including liver, pancreas, stomach, and small bowel was reported by Margreiter et al. [78]. Two minor rejection episodes of the bowel were encountered. Six months postoperatively all grafted organs functioned normally.

McAlister et al. [83] performed isolated SBT, as well as combined small bowel-liver transplantation and abdominal cluster transplantation; the isolated small bowel transplant had to be removed 15 days post-transplantation because of uncontrollable rejection. Two of three patients with small bowel-liver transplantation are alive on CyA therapy, whereas the other died from a nonimmunological cause. One of two patients given an abdominal cluster transplant is well 7 months post-operatively, whereas the other died of a lymphoma. Todo et al. [145] reported on eight isolated SBT and eight small bowel-liver transplantations using FK 506 as the main immunosuppressant. Seven of the eight isolated small bowel transplants are functioning, and all patients who have their graft for more than 2 months are free of TPN. Of the eight small bowel-liver graft recipients, one died of sepsis and GVHD 23 days post-transplantation. The other seven have grafts functioning from 7 to 23 months post-transplantation and are free of TPN.

In all clinical cases, intestinal continuity was restored in stages. During the first operation, the proximal and distal ends, or the distal end of the graft only, were brought out as enterostomies. This allowed for macroscopic inspection and graft biopsy in order to monitor graft rejection. Moreover, early alimentation of the graft or decompression in the case of ileus are possible. In a second operation some weeks later, intestinal continuity was restored, after which oral feedings could be instituted [24, 36, 145]. It should be noted, however, that pediatric patients had an aversion to food and preferred tube feedings.

Although in most of the cases reported the postoperative course was stormy, these successful cases suggest that SBT has become a clinical reality.

Future prospects

The reasons why the small bowel graft is particularly vulnerable to rejection are now being delineated. The high rate of sepsis after SBT [37, 126] has several causes. Immunosupression given to the recipient compromises the

immunological barrier function of the bowel wall. Ischemia and rejection increase the permeability of the graft by compromising the physical barrier. This has been shown to lead to bacterial translocation to the host [7, 37]. Leakage of toxins also occurs in this phase. This may be aggravated by the bacterial overgrowth in the graft encountered after SBT [7, 143].

Measures that maintain the gut barrier function after SBT will improve its outcome. Better immunosuppressive drugs, like RAPA, may have a higher therapeutic index than CyA, although some believe that CyA, as the mainstay of immunosuppressive therapy, will provide satisfactory immunosuppression [78, 126].

Several authors suggest that there may be an advantage to combined small bowel-liver transplantation, and this has been supported by recently performed successful clinical small bowel-liver transplantation [36]. In rats, SBT performed 17 days after orthotopic liver transplantation led to long-term survival of the small bowel graft without any immunosuppression, whereas isolated small bowel grafts were rejected in 6–9 days [117]. Similar results were reported by Zhong et al. [160]. In a series of clinical small bowel and small bowel-liver transplantations, however, the incidence of graft rejection in the first 2 months after isolated SBT was lower than after combined small bowel-liver transplantation. The greater ease and safety of isolated SBT in this series indicates that combined small bowel-liver grafting should only be reserved for patients with coexisting liver failure [145].

Early institution of feeding of the graft helps to prevent disuse atrophy [72, 109], and antibiotics reduce the bacterial load of the gut. Other options that one may wish to experiment with include the administration of hormones trophic to the gut, such as epidermal growth factor and prostaglandin E_2, or the use of nutrients that are essential to the gut. One such nutrient that, in our opinion, deserves special attention is the amino acid L-glutamine. Several studies have demonstrated that glutamine is the principal fuel for enterocytes [134, 152]. There is only limited evidence that glutamine is essential for maintenance of normal intestinal function [134]. However, the stress of a major operative procedure, combined with general anesthesia, is followed by a decrease in circulating and muscle glutamine concentrations [133]. During injury or stress, glutamine may be a necessary dietary component to maintain gut structure and function. This is possibly due to the fact that glutamine is essential for nucleic acid biosynthesis and might be especially important during critical illness when the mucosal barrier becomes susceptible to breakdown [134]. It has been shown, for instance, that glutamine consumption by the intestinal tract is increased by 75% after laparotomy [134]. It has also been shown that glutamine reduces bacterial translocation from the gut to the mesenteric lymph nodes following abdominal irradiation [135]. Moreover, glutamine supplementation of standard TPN solutions decreases the villous atrophy associated with long-term i.v. feeding [95], and bacterial translocation following TPN administration is attenuated when glutamine is added to the mixture. This diminished translocation was associated with a normalization of sIgA levels and a decrease in bacterial adherence to enterocytes, suggesting that adding glutamine to the TPN solution enhances gut immune function [2, 13]. Preliminary results also indicate that glutamine is able to prevent the mucosal atrophy seen after heterotopic SBT [128]. Taken together, these findings indicate that glutamine could have important applications after SBT that are worth investigating.

Early detection of rejection is of vital importance in preserving barrier function and may benefit long-term graft function since it could delay and/or reduce fibrosis and chronic rejection. Several serum and urinary markers are now available which, in conjunction with histology, allow early recognition and treatment of rejection, and new markers are still being sought. For example, the enzyme diamino-oxidase is a potentially interesting marker for both rejection and long-term graft function [112]. This enzyme, which is involved in the regulation of polyamine metabolism and probably also the regulation of mucosal growth, is produced mainly by mature enterocytes in the villus tip [111]. It may have elevated levels in serum during acute ischemic injury of the small bowel mucosa [153] and, hence, may be useful in detecting acute rejection. Normally, after i.v. heparin administration, a rapid increase in plasma diamino-oxidase is seen [60, 75]. These postheparin plasma diamino-oxidase levels are lowered in small bowel mucosal damage [20] and could prove to be a marker for graft function, something which deserves further study.

Denervation, an inevitable consequence of SBT, causes hypersecretion from the crypts and diarrhea in the early stages after transplantation [86, 150]. It is thought that long-term impaired motility as a result of denervation, although not hindering the passage of food, is associated with bacterial overgrowth. Increased chloride secretion [86, 150], steatorrhea [107, 122, 143], and increased fecal water content [143] are all thought to be long-term consequences of extrinsic denervation of the graft.

Because these obstacles have now been traced and either removed or resolved, and because the first successful clinical cases are being reported, there is reason to be optimistic about the future of clinical SBT.

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