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# Transplantation of the Small Intestine: The Pathologist's Perspective

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Small-bowel transplantation is now ready for clinical trials. The surgical techniques and methods for immunosuppression and monitoring bowel status have been developed in animal models over the past 30 years. Several attempts at small-bowel transplantation in humans have already been reported. In the course of future trials, pathologists will be involved in the monitoring of the post-transplant course by mucosal biopsies and functional studies, including maltose and xylose absorption tests. The morphology of rejection has been studied in canine and rat models. Activated lymphocytes and plasma cells infiltrate the lamina propria and invade crypt epithelium, causing "cryptitis." Villous blunting ensues, resulting eventually in necrosis. Graft survival without immunosuppression is about 10 days. Under Cyclosporine immunosuppression, a lymphoplasmacytic infiltrate has been noted around nerves and vessels in the submucosa. The overlying mucosa may be relatively normal. End-stage bowel is characterized by a contracted, scarred mass. Due to the large amount of lymphoid tissue in the allograft, graft-versus-host disease is a significant problem in small-bowel transplantation.

**Key Words:** Small bowel—Transplantation—Rejection—Graft-versus-host-disease.

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After years of development in animal models, small-bowel transplantation is now approaching clinical application. Several attempts at small-intestine transplantation in humans have been reported (5,11,14), and the small bowel is included in multivisceral transplants (34,39). Surgical pathologists will become increasingly involved in monitoring the course of these patients, as they have in other transplant systems, because the morphologic evaluation of biopsy specimens is an important practical means for detecting rejection and distinguishing it from other modes of graft injury.

The indications for performing small-bowel transplantation have broadened as the techniques have become refined. More and more patients are being identified who may benefit from this procedure. The initial small-bowel transplants in humans were performed 20 years ago for massive intestinal infarction secondary to mesenteric vein thrombosis and as part of a pancreatic-duodenal-renal transplant for diabetes (19). More recently, patients with Gardner's syndrome, inflammatory bowel disease, postsurgery or postradiation short-bowel syndrome, and congenital anomalies have been considered eligible. As in kidney, liver, bone marrow, and heart transplantation, patients with small-bowel transplants will eventually be followed in their communities; therefore, pathologists in all types of practice will have to become familiar with the morphologic appearances of small-bowel biopsy specimens following transplantation.

## BACKGROUND

Techniques for small-bowel transplantation have been developed over the past 30 years. The successful canine small-bowel autografts with long-term survivors performed by Lillehei et al. (17) yielded valuable data about the surgical techniques,

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ischemia time, preservation methods, and rate of recovery of bowel function. These investigators subsequently noted that animals with small-bowel allografts given no immunosuppression died in 6–9 days. The animals showed systemic signs of wasting and enlarged mesenteric nodes but no cellular infiltrate in the graft. Lillehei et al. thereby recognized the potential for the development of graft-versus-host disease (GVHD), or "runting syndrome," after small-intestinal transplantation. If shorter bowel segments were transplanted and immunosuppression was added, the signs attributed to GVH decreased, and the bowel segments were eventually rejected (25).

During the 1960s and '70s, immunosuppression regimens, mainly Azathioprine and steroids, were tested to control GVH and rejection reactions (12,35). Mean survival was increased from 8 to 30 days. With the introduction of Cyclosporine (CyA) in the mid 1980s, survivals beyond 8 months were noted in rodent studies (15), and long-term survivors (over 1 year) were reported in canine models (7). Preoperative graft irradiation alone was less successful in bidirectional or large animal models (3). Later, preoperative graft irradiation at higher doses together with CyA produced long-term survivors (38).

The pioneering experiments of Monchik and Russell (23) showed that rejection and GVH reactions could be separated by using inbred strains of rats and their F1 hybrid offspring. Basically, transplanting tissues from one parental strain into another constitutes a fully allogeneic "bidirectional" model in which either rejection or GVHD can occur. Transplanting tissue from an F1 hybrid, which bears antigens from both parents, into a parental strain animal constitutes a semiallogeneic model in which only rejection can occur. Transplanting tissue from a parent strain animal into an F1 hybrid offspring constitutes a semiallogeneic GVHD model. These have become the classic models for experimental studies in small-bowel transplantation.

The introduction of functional tests for monitoring rejection in the bowel was another advance. Although morphologic assessment of small-bowel tissue specimens is still the gold standard for recognizing rejection in transplanted small intestine, this technique is not without flaws. Alternative means for monitoring graft function, such as maltose or xylose absorption studies, are being investigated. Although at present the results are variable and operator-dependent, these tests appear to offer a sensitive means to detect the mucosal damage that occurs early in rejection.

The ultimate refinement—namely, clinical trials—has already begun. In the trials reported to date, monitoring of graft function has been by clinical status and mucosal biopsy. However, there is now a need to develop sensitive and dependable laboratory techniques for monitoring the extended post-transplant course, to standardize the diagnostic criteria for rejection and GVHD, and to identify criteria that will distinguish the immunologic reactions from ischemic and infectious damage.

## TECHNIQUES

The portion of bowel to be transplanted is removed surgically, with its mesentery and vascular pedicle. The vessels and lumen of the bowel are flushed with cold Ringer's lactate or Eurocollin's solution. The maximum cold ischemia time, based on animal experiments (17), is 5 h. The bowel may be placed orthotopically, with end-to-end anastomosis to the residual host bowel, or heterotopically, auxilliary to the native bowel, with exteriorized ends (Fig. 1). The latter placement, in which the bowel is vascularized but not nutritionally functional, is a Thiry-Vella loop. The advantage of the Thiry-Vella loop is the easy access for absorption studies and biopsy; the disadvantage is that nutrition must be maintained by the native bowel, and the functional ability of the Thiry-Vella loop is difficult to ascertain. The vascular anastomoses are superior mesenteric artery or aorta (with or without an aortic cuff) and donor superior mesenteric or

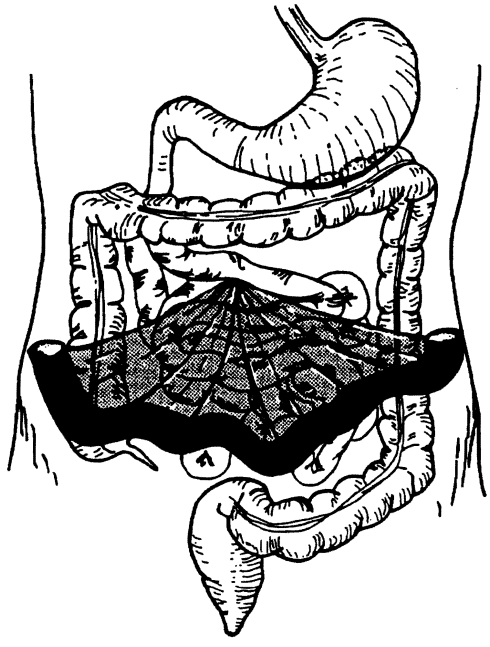

**FIG. 1.** Diagram of a Thiry-Vella loop.

portal vein to recipient portal vein or inferior vena cava. The lymphatics and nerves are not repaired.

Immunosuppression regimens include Azathioprine, Prednisone, CyA, and antilymphocyte serum in various combinations. Attempts have been made to ablate passenger lymphoid tissue by radiation (3,38) or surgical excision of mesenteric lymph nodes (6). Postoperatively, clinical signs such as weight loss, poor appetite, and diarrhea, as well as serum protein, triglyceride, and vitamin levels are determined as part of daily follow-up. Mucosal biopsy and absorption studies may also be performed.

## SURVIVAL AND COMPLICATIONS

Dogs undergoing intestinal autografts recover normal bowel function by 4 weeks (18,24). In the studies of Lillehei et al. (18), some animals were followed for 3 years. Histology and stool fat returned to normal in a few weeks, and lymphatics regenerated between 2 and 6 weeks, as determined by methylene blue injection studies.

Without immunosuppression, bowel allograft survival is about 6–12 days in all species studied (8,26,35). Azathioprine with or without Prednisone prolongs survival to an average of 21–42 days (13,35). CyA with or without Prednisone regimens, now more or less standard, have longer survivals; some studies have reported long-term survivors (8,15,17,26,38).

In animals, causes of death in the immediate posttransplant period are infarction of the graft due to arterial or venous thrombosis (26,28,38) and mechanical problems such as volvulus and intussusception (24,28,38). Acute rejection with graft necrosis, perforation, or peritonitis (7,15,28), or pneumonia (26,38) is seen approximately 1 week posttransplantation. Causes of death in long-term survivors with CyA immunosuppression include inanition attributed to rejection and graft failure (7,8,26,28,38), pneumonia (26), and mechanical factors such as intestinal obstruction (26,28,38). Systemic infection is rare, except for bacterial sepsis secondary to bowel perforation. In Williams's study of 27 dogs under CyA immunosuppression after orthotopic transplant, fatal histoplasmosis occurred in two cases, and incidental giardiasis in five (38). Neither posttransplant lymphoproliferative disorder nor CyA toxicity has been described in the animal models.

Twelve cases of small-bowel transplant in humans have been reported. Survivals range from 0 to 205 days (5,11,14,34,39). Most of the initial cases failed in the early posttransplant period because of technical reasons; one failed due to rejection, and another due to sepsis (14). The longest survivor (11) died with hepatorenal failure and *Candida* sepsis. The other two long-term survivors (34,39) died with posttransplant lymphoproliferative disorder at 4–6 months posttransplant. Although the morphologic and physiologic effects of CyA on small bowel are not known, Goulet et al. (11) suggest that CyA toxicity may have contributed to the renal insufficiency that was a major contributing factor in their patient's demise.

## BOWEL FUNCTION POSTTRANSPLANT

Changes in bowel mucosa during the immediate posttransplant period were studied by Madara and Kirkman (20) using electrophysiologic and ultrastructural techniques in a heterotopic rat model. They demonstrated that the earliest evidence of damage is in endothelial and crypt epithelial cells at 3 days. Transepithelial resistance and spontaneous electrical potential difference decreased in both graft and host bowel at 3 days; host bowel recovered, graft bowel did not. Crypt cell secretory function decreased by day 6; absorptive cell function was normal until day 9. The authors concluded that there is primary injury to endothelial and crypt cells after transplant and that absorptive cells are damaged later, possibly due to ischemia.

Most studies have focused on long-term bowel function, usually in animals under CyA immunosuppression. Clinically, the animals exhibit diarrhea and a 30% weight loss, both of which are reversible over several weeks to months (7,15,24,26,31). Serum proteins and triglycerides remain normal (15,26). Absorption of various substances has been extensively investigated with the aim of developing a relatively noninvasive means for following mucosal function posttransplant. Although assessment of the morphologic changes in tissue has been the gold standard for detecting rejection, mucosal biopsies are invasive and prone to sampling error, artifact, and interference from inflammation around a stoma. These biopsies do not sample deeper layers of the wall where significant changes of rejection may be occurring while the overlying mucosa is relatively normal, particularly in long-term survivors (1,9,22).

Thus, absorption of tracer substances presents an attractive solution to these problems. The absorption of D-xylose, C14-glucose (24,26), and short- and long-chain fatty acids (33) decreases as rejection develops. Unfortunately, Cyclosporine absorption also appears to be decreased during rejection (24); this decrease has obvious therapeutic implications. Absorption of maltose and lactose depends

on intact brush border enzymes in absorptive cells and appears to decrease before histologic evidence of rejection is present (2). This may be the most sensitive test for monitoring rejection. Long-term survivors with good nutritional status have normal maltose absorption (15).

One caveat in all of these absorption studies is that bowel absorption of a number of substances has been shown to be dependent on an intact nerve and lymphatic supply. In the study of Ruiz et al., absorption of D-xylose dropped in nontransplanted bowels after interruption of nerves and lymphatics (28). Watson et al. (37) showed that the absorption of water and sodium, but not glucose, is reduced in transplanted bowel and denervated nontransplanted controls. These changes were not related to rejection or ischemia in the allografts. The implication was that the absorption of sodium and water is dependent on an intact autonomic nerve supply. Another caveat in monitoring rejection by absorption studies is that the cellular targets in rejection have not been entirely elucidated. Madara and Kirkman's study implicated endothelial and crypt cells. In our own studies of small-bowel transplantation in a rat model, crypt damage seems to precede changes in the villous cell population. Thus, functional tests such as maltose absorption, which reflect villous cell function, may not pick up the earliest changes of rejection. In summary, the ideal functional test agent has yet to be developed. It need not be cell specific, but it should be sensitive to early mucosal damage and not to changes induced by denervation or lymph stasis.

Physiologic studies of motor function in canine heterotopic segmental jejunal transplants by Schiller et al. (29) showed spasmodic uncoordinated electrical activity and vigorous peristalsis on interruption of blood supply, decreased motility during cold ischemia, and increased activity and tone on reperfusion. Except for this study, bowel motility after small-bowel transplant has not been investigated. Motility disorders are a potential problem in long-term survivors. Muscle hypertrophy and poor motility were the major contributors to inanition in the study of canine long-term survivors after orthotopic transplant by Williams et al. (38).

## PATHOLOGY OF SMALL-BOWEL ALLOGRAFTS

### Ischemic Damage

There are numerous studies of ischemia in small bowel after vascular ligation. Lillehei's group (17) showed that canine bowel could tolerate 3 h of clamping of the superior mesenteric artery; with hypothermia the tolerance extended to 5 h. Similar studies in rat bowel (10,36) showed reversible damage to villous epithelium progressing from tip to base with increasing degrees of ischemia. Damage occurred with as little as 15 min ischemia time and was irreversible with ischemia beyond a duration of 2 h. Regeneration began as early as 12 h and was complete by 8 days. Lillehei's group also provided some of the initial data about methods to preserve bowel. With their techniques of perfusion and cold storage, mucosal damage was reduced (21). Holmes et al.'s classic description of the pathology of canine allografts notes congestion and necrosis of villous tips during the first 24 h (13). These changes were reversible by 3 days. The donor bowels had been prepared by vascular perfusion with cold Ringer's lactate. Rosemurgy and Schraut noted similar reversible changes in rat allografts (27).

Vascular thrombosis has been a major complication and a cause of early postoperative death in small-intestinal transplantation, especially in large animal models (26,28,38). This complication has decreased with refinement of technique (J.W. Williams, unpublished data).

### Acute Cellular Rejection

The morphologic features of acute cellular rejection have been studied in canine (1,4,9,13) and rat (27) models of small-intestinal transplanation. Cellular rejection appears to begin at 3–6 days, with infiltration of the mucosa by activated lymphocytes and plasma cells. There is corresponding mucosal edema, dilatation of lacteals, and blunting of villi. Inflammation increases and involves deeper layers of the wall. Eventually the entire bowel becomes necrotic, and the mucosa sloughs, usually by 10–12 days. Bacterial superinfection may hasten this process (13). In the case reported by Goulet et al. (11), there was an increase of T helper cells, cells bearing IL2 receptors, and HLA-DR expression by crypt epithelial cells in mucosal biopsy specimens during rejection. Other than this report, however, there has not been a systematic study of the lymphocyte subpopulations infiltrating the small bowel during rejection.

At the University of Pittsburgh, we have been using rat hybrid models to study the effects of various immunosuppressive regimens and immunodepletion techniques on rejection and GVH reactions. Histologic changes in the graft bowels in the semiallogeneic rejection model included necrosis, villous blunting, cryptitis, and inflammation of lamina propria first seen in and around the thin-walled vas-

cular channels (A. Hoffman et al., unpublished data) (Fig. 2). Larger vessels appeared spared initially. Host bowels from the semiallogeneic GVH group showed similar cryptitis and inflammation. These findings were identical to those described in GVH reactions in human bowel in bone marrow transplant patients by Snover et al. (32). Host bowels from the rejection group, donor bowels from the GVH group, and donor and host bowels from the syngeneic groups showed only occasional single-cell necrosis without inflammatory response in crypts. Cryptitis and infiltration of the lamina propria by mononuclear cells appear to represent the morphologic expression of both cellular rejection and GVH reaction in the bowel. These findings are comparable to those in kidney and liver, where the pathogenesis of rejection involves infiltration by activated lymphocytes and associated destruction of epithelial structures.

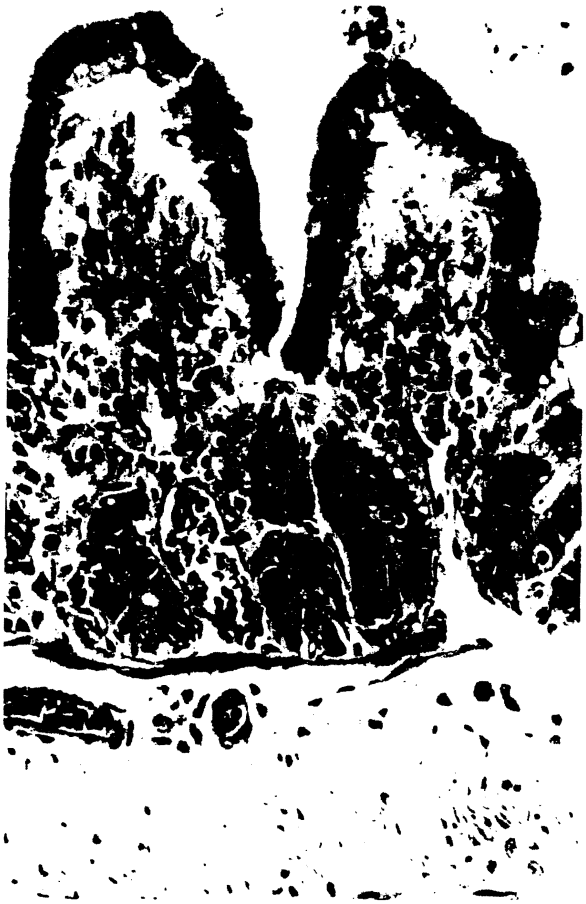

**FIG. 2.** Acute cellular rejection at 9 days in a semiallogeneic (ACI-Lewis) F1 hybrid to Lewis rat model. Note villous blunting, single-cell necrosis in the crypts (arrow), and inflammatory infiltrates in the lamina propria.

### Chronic Rejection

Although the pathologic features of chronic rejection have not yet been established for bowel as they have in other organ systems, certain features that have been noted in long-term survivors of small-bowel transplants are believed to represent a rejection reaction. In dogs with orthotopic allografts immunosuppressed with Cyclosporine (7) or Cyclosporine plus pretransplant graft irradiation (1), a lymphoplasmacytic infiltrate around nerves, ganglia, and vessels in submucosa and muscle has been described (Fig. 3). In one study (1), this inflammatory reaction persisted for months deep in the wall, while the overlying mucosa was normal. Eventually, most dogs in this study developed graft fibrosis and inanition.

Millard et al. (22) described pathologic changes in mucosal biopsy specimens and full-thickness sections from heterotopic accessory small-bowel allografts. Perivascular mononuclear cell infiltrates or fibrinoid necrosis were noted in and around submucosal vessels. This finding was noted in full-thickness sections of bowel but not in mucosal biopsy specimens. The authors stress that mucosal biopsy specimens are not a reliable way to monitor chronic rejection, because they do not show significant changes occurring in the submucosa.

Fujiwara et al. (9) also described fibrinoid necrosis and inflammation in small submucosal arteries in 21.4% of the dogs with orthotopic small-bowel transplants from both the treated and nontreated groups. Thus, it seems that histopathologic changes occur throughout the wall after small-bowel transplantation. These histopathologic changes are not those usually seen with injury due to ischemia or infection; they appear to represent the pathologic process of rejection.

Some studies (1,9) suggest that significant morphologic changes may occur without functional abnormalities for a while, but eventually there is a slow progression to an end stage of fibrosis of the graft, followed by death of the animal due to inanition. One may speculate that inflammation or vascular compromise deep in the wall, particularly in muscle, contributes to the motility problems noted frequently in long-term survivors (38). These problems may parallel the functional changes seen in other organs with graft failure due to chronic rejection.

## GRAFT-VERSUS-HOST DISEASE

Because of the large volume of lymphoid tissue associated with the bowel, GVHD presents a major

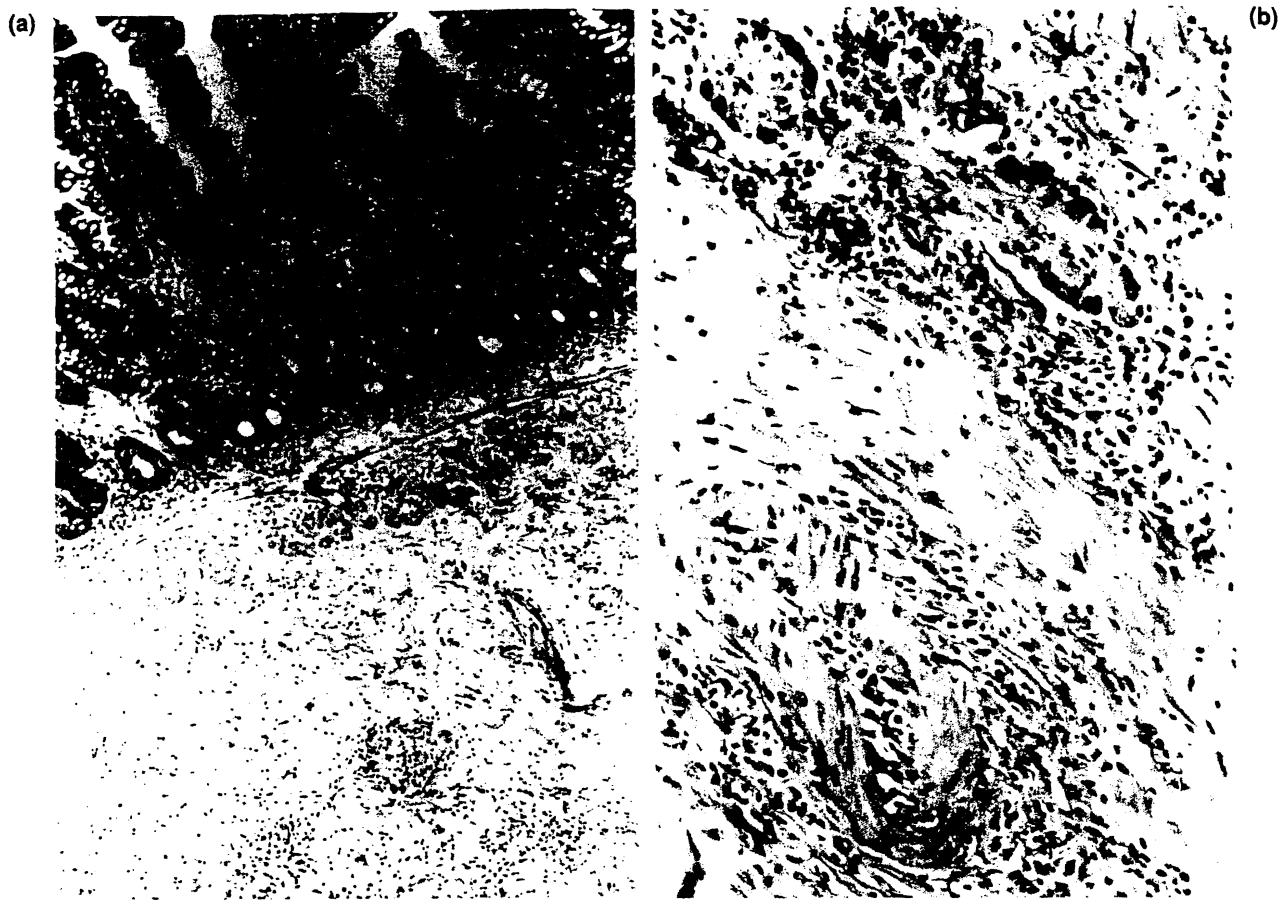


**FIG. 3.** Chronic cellular rejection at 3 months in a canine allograft immunosuppressed by Cyclosporine and pretransplant graft irradiation. **(a)** Low power showing concentration of inflammation in submucosa, with intact mucosa. **(b)** Higher power showing lymphoplasmacytic infiltrate in nerves and vessels in submucosa.

problem in small-bowel transplantation. There may be species differences in susceptibility to GVHD, and the potential for bowel allografts to mount such a response in humans is currently unknown. Also, development of GVHD may relate to whether proximal or distal bowel is transplanted and to the amount of bowel (and lymphoid tissue) transplanted.

Lillehei et al. (16,18) were the first to recognize that GVHD could cause morbidity and death after small-bowel transplantation, although GVHD was not known as such at that time. Their dogs with homografts died within the time frame expected for rejection, but the grafts showed no evidence of rejection at autopsy, leading to the conclusion that the homograft was, in some manner, rejecting the host. Monchik and Russell (23) offered the first descriptions of GVHD in their semiallogeneic models. Two notable current studies are those of Schraut et al. (30) and Deltz et al. (6). Schraut et al. described GVHD after orthotopic and heterotopic transplantation in a Lewis to (Lewis × Brown Norway) F1 semiallogeneic (GVH) hybrid rat model. Clinically, dermatitis and weight loss appeared over days 9–11, and death resulted by day 14. Histologically, host bowel displayed inflammation while graft bowel was normal. Lymphoid tissue displayed progressive lymphocyte depletion after day 5.

Deltz et al. studied the effects of various types of immunodepletion on reducing GVHD in Brown Norway to (Lewis × Brown Norway) F1 accessory heterotopic small-bowel transplants in the rat. Animals treated with Cyclosporine, irradiation, or mesenteric lymphadenectomy lived 120–150 days and had no GVHD or in vitro T-lymphocytotoxic antihost activity. It is of note that GVHD has not been a significant complication in the human cases reported thus far.

## SUMMARY

Small-bowel transplantation has reached the level of clinical application; the indications have been defined, and the techniques have been developed. The immunosuppression regimens are being formulated. A major area of current investigation is to find accurate, yet relatively noninvasive ways to monitor the posttransplant course and to detect rejection and GVHD. At present, musocal biopsies and maltose absorption tests are preferred. Because infiltration of the lamina propria by activated lymphocytes and cryptitis are the early manifestations of acute cellular rejection, biopsies are useful initially. However, in long-term survivors under CyA immunosuppression, the mucosa may appear normal, and the only manifestation of rejection may be a lymphoplasmacytic infiltrate in the submucosa. The next steps in understanding the pathogenesis of rejection in small-bowel allografts will include (a) the immunophenotypic characterization of the infiltrating cells as to donor or host origin, (b) the better delineation of the morphologic changes due to drug toxicity and perfusion injury, and (c) correlation of histology with absorptive function over time to determine the sensitivity of noninvasive functional tests and their ability to predict long-term bowel function. □


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