Rejection of multivisceral allografts in rats: A sequential analysis with comparison to isolated orthotopic small-bowel and liver grafts

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Multivisceral isografts and allografts were transplanted to Lewis rats, and the histopathologic changes were studied in the liver, intestine, and other constituent organs. Rats receiving isografts had indefinite survival with maintenance of weight. With multivisceral allografts (from Brown-Norway donors), the intestinal component was rejected more severely than the companion liver and with about the same severity as when intestinal transplantation was performed alone. Intestinal rejection in either circumstance was a lethal event, causing death in 10 to 12 days. The earliest (by day 4) and most intense cellular rejection was in the Peyer's patches and mesenteric lymph nodes. This was associated with or followed by cryptitis, epithelial cell necrosis, focal abscess formation, mural necrosis, and eventual perforation. Liver allografts transplanted alone or as part of multivisceral grafts also had histopathologic evidence of rejection, but this was self-limiting and spontaneously reversible when the liver was transplanted alone. Thus the Achille's heel of multivisceral grafts is the intestinal component that is not protected by the presence of the liver in the organ complex. Better immunosuppression should permit successful experimental and clinical transplantation of such grafts. (SURGERY 1990;108:880-9.)

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MULTIVISCERAL ALLOGRAFTS THAT include the liver, pancreas, omentum, stomach, small intestine, and colon have been transplanted in the dog,[1] pig,[2] and human.[2, 3] We report here the feasibility of using the rat to study this complex procedure. As a result, many basic questions can now be addressed. We have started with morphologic studies of the different organs in multivisceral grafts, to see if there was organ-specific susceptibility to rejection. The findings were compared with those in multiorgan isografts and those in isolated orthotopic small-bowel and orthotopic liver allografts.

Supported by research grants from the Veterans Administration and project grant No. DK 29961 from the National Institutes of Health, Bethesda, Md.

Accepted for publication Feb. 1, 1990.

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11/56/20716

MATERIAL AND METHODS

Animals. Normal healthy male Lewis rats ($RT1^l$) weighing 200 to 300 gm and 250 to 350 gm were used as donors and recipients, respectively, for isografts. For allograft procedures, the Lewis rats were used as recipients and Brown-Norway rats ($RT1^n$) were used as donors. The animals were obtained from Harlan Sprague Dawley, Inc., Indianapolis, Ind. Multivisceral recipients were maintained under standard conditions, with water and regular rat food provided ad libitum. Their donors were given 25 mg/day oral neomycin sulfate for 5 days; the donors were fasted for 2 days before operation, during which time the donor rats were given free access to 50 calories/day of sugar to avoid loss of body weight. All surgical procedures were performed in a clean but not sterile fashion. Open drop methoxyflurane anesthetic was used, with oxygen supplied over the face mask. Animals that died within 4 days after transplantation were excluded from further analyses.

Table I. Histologic data

Postoperative days	No. of animals			
	MVTX (isograft)	MVTX (allograft)	SBTX	LTX
3-5	2	3	2	1
7-9	2	4	4	2
10-14	1	5	6	3

MVTX, Multivisceral transplant; *SBTX*, small-bowel transplant; *LTX*, liver transplant.

Operations

Multivisceral procedures. The multivisceral graft, including liver, pancreas, stomach, omentum, small intestine, and colon, was based on the donor abdominal aorta. Venous outflow was into a segment of donor vena cava that was interposed in the recipient vena cava (Fig. 1), with 7-0 Novafil (D & G Monofil Inc., Manati, Puerto Rico) suture used for the upper anastomosis and a cuff for the lower anastomosis. Aortic reconstruction was accomplished as shown in Fig 1. An aortic homograft from another Lewis donor was first anastomosed to the side of the recipient aorta. This was later connected to the aorta of the multivisceral speciment with a cuff. Gastrointestinal continuity was reestablished by end-to-end anastomosis at the stomach and rectum (Fig. 1).

Liver transplantation. Orthotopic liver transplantation with aortic reconstruction was performed with modifications of Kamada's methods.[4] The most important modification was arterial reconstruction by the same principle as shown in Fig. 1 for the multivisceral operation.

Small-bowel transplantation. The entire donor small bowel from the ligament of Treitz to the ileocecal valve was isolated on a vascular pedicle consisting of the superior mesenteric artery connected to a segment of aorta and the portal vein. After the donor was given 300 units heparin intravenously, the intestine was removed and perfused through the superior mesenteric artery with 10 ml cold lactated Ringer's solution. After the bowel lumen was flushed with cold 0.5% neomycin sulfate solution, the graft was placed in an ice bath.

In the recipient the infrarenal aorta and inferior vena cava were isolated and an end-to-side, aorta-to-aorta, and portal vein–to–inferior vena cava anastomosis was performed with 10-0 Novafil suture. After reperfusion of the graft, the entire recipient small bowel was resected, including mesenteric lymph nodes. Intestinal continuity was restored by proximal and distal end-to-end anastomoses with 6-0 silk suture. All animals were housed in individual cages and given regular rat food after surgery.

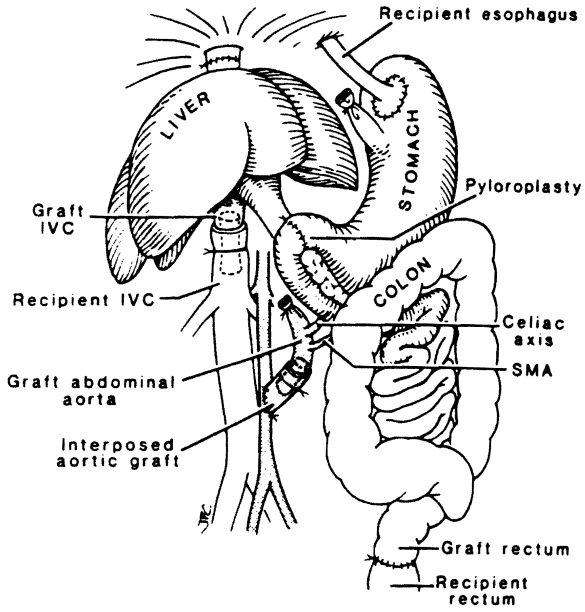

Fig. 1. Technique of multivisceral transplantation. *IVC*, Inferior vena cava; *SMA*, superior mesenteric artery.

Postoperative care. The multivisceral recipients routinely were given 2 to 3 ml whole blood transfusions or lactated Ringer's solution with 10% dextrose. Oral sugar and 10% dextrose were given freely for the first 4 postoperative days, after which regular rat food was given ad libitum. Cefamandole nafate (20 mg/day) was given intramuscularly for 5 days. No immunosuppressive treatment was given.

Histopathologic studies. In the rats that received multivisceral grafts, the following tissues from the graft were sampled for histopathologic analysis: distal esophagus, stomach, duodenum, small intestine with Peyer's patches, cecum, ascending colon, pancreas, liver, and mesenteric lymph nodes. The recipient tissues sampled were thymus, thoracic lymph nodes, bone marrow, ear skin, tongue, lung, kidney, esophagus, colon, and heart.

In animals that received intestinal transplantation alone, the recipient liver, spleen, kidney, lung, heart, bone marrow, skin, tongue, and pancreas were sampled. Sections were obtained of the graft including the anastomoses, Peyer's patches, intestine, and mesenteric lymph nodes.

A complete autopsy was performed at the time of death in all groups and the tissues were examined microscopically. In addition to these animals, additional rats from the various groups were either killed or underwent an open wedge biopsy as shown in Table I to obtain tissue for sequential histologic studies.

All the tissues were immersion fixed in neutral buffered formalin at the time of death to prevent autolytic

Table II. Survival after multivisceral transplantation, small bowel transplantation, or liver transplantation, without immunosuppressive treatment

	Strain combination					
Procedure	*Donor*	*Recipient*	*n*	*Survival (days)*	*MST (days)*	*p Value**
MVTX	Lewis	Lewis	8	7,† 72,‡ 81,‡ >100 × 5	>100	—
MVTX	BN	Lewis	5	10, 10, 10, 10, 13	10.0	—
SBTX	BN	Lewis	7	9, 10, 11, 12, 13, 13, 14	12.0	NS
LTX	BN	Lewis	6	>100 × 6	>100	0.0001

MST, Median survival time; *MVTX*, multivisceral transplantation; *BN*, Brown-Norway; *SBTX*, small-bowel transplantation; *LTX*, liver transplantation.
*p Values versus MVTX allografts (Student *t* test).
†Cause of death: technical complication.
‡Killed in healthy state after 72 and 81 days as part of a colony depopulation program.

changes of the intestinal mucosa. Thereafter the fixed tissue was embedded in paraffin, sectioned at 6 μm, and routinely stained with hematoxylin and eosin stain.

RESULTS

Survival data. Animals from each transplant group were followed up until death or long term (>100 days) in those that did not have rejection of the grafts (Table II). Seven of the eight rats with multivisceral isografts had long survival, two were killed after 72 and 81 days in a population-control program, and five lived more than 100 days (Table II).

All of the Lewis recipients of Brown-Norway isolated liver grafts had long-term survival without immunosuppression, which was not unexpected because this strain combination has been shown to be nonrejecting for livers.[4] By contrast, the median survival time of the Brown-Norway to Lewis, multivisceral, or isolated small-bowel recipient was 10 and 12 days, respectively (difference not significant; Table II).

Body weight change and clinical course. Body weight changes after the various transplantation procedures are summarized in Fig. 2. For the first 5 to 6 days the clinical course of animals that received multivisceral allografts was similar to that of those given isografts. On the seventh or eighth postoperative day, animals that had undergone allografting had palpable abdominal masses, which were identified as enlarged mesenteric lymph nodes by laparotomy. Thereafter the rats given allografts had diarrhea and progressively lost weight, whereas the animals that received isografts returned to their pretransplant weight (Fig. 2) and began to grow. Harbingers of death at 10 to 12 days in those given allografts were ruffled hair, rapid respiration, hunched posture, and apparent chills. At autopsy all vascular anastomoses for the multivisceral procedures were intact and patent. All of the animals that had received allografts had peritonitis with purulent ascites and interintestinal adhesions. Patchy areas of necrosis were noted throughout the small and large intestines. Mesenteric lymph nodes were markedly enlarged and tan-red. The livers were slightly enlarged. There were no significant gross pancreatic abnormalities. No hair loss or dermatitis (i.e., signs of graft-versus-host disease) was observed.

Weight loss after isolated small intestinal allotransplantation was not as severe as in the rats given multivisceral allografts, but the postoperative clinical course was similar. The rats that received isolated liver allografts briefly lost weight but were back to normal by 2 weeks (Fig. 2) No significant clinical abnormalities were noted in this group.

Histopathologic studies

Multivisceral isografts. Five animals were killed 3, 5, 7, 8, and 13 days after multivisceral isografting. There were no specific alterations in the intestines except for a very mild focal neutrophilic and eosinophilic cryptitis in the stomach, mild peritonitis, and inflammation at the sites of anastomoses. The livers showed mild regenerative change and mild nonspecific reactive hapatitis, with a slight increase in sinusoidal neutrophils. Mild interstitial (septal) edema was noted in the pancreas. The mesenteric lymph nodes showed sinusoidal red blood cell congestion at 3 days, which had cleared by the fifth day.

Isolated small-bowel allografts. Two animals each were killed at 4, 7, and 9 days. In addition, six animals were killed or died between 10 and 13 days after transplantation. Particular attention was given to the Peyer's patches, the areas between these lymphoid deposits, and the mesenteric lymph nodes.

By day 4 there was already a marked difference in the small bowel from the multivisceral isografts and the isolated small bowel allografts. The principal change in the allografts was an expansion and change in the composition of the T-cell–dependent areas of the Peyer's patches. In the multivisceral isografts these areas were populated by small, round, dark (inactive) lymphoid

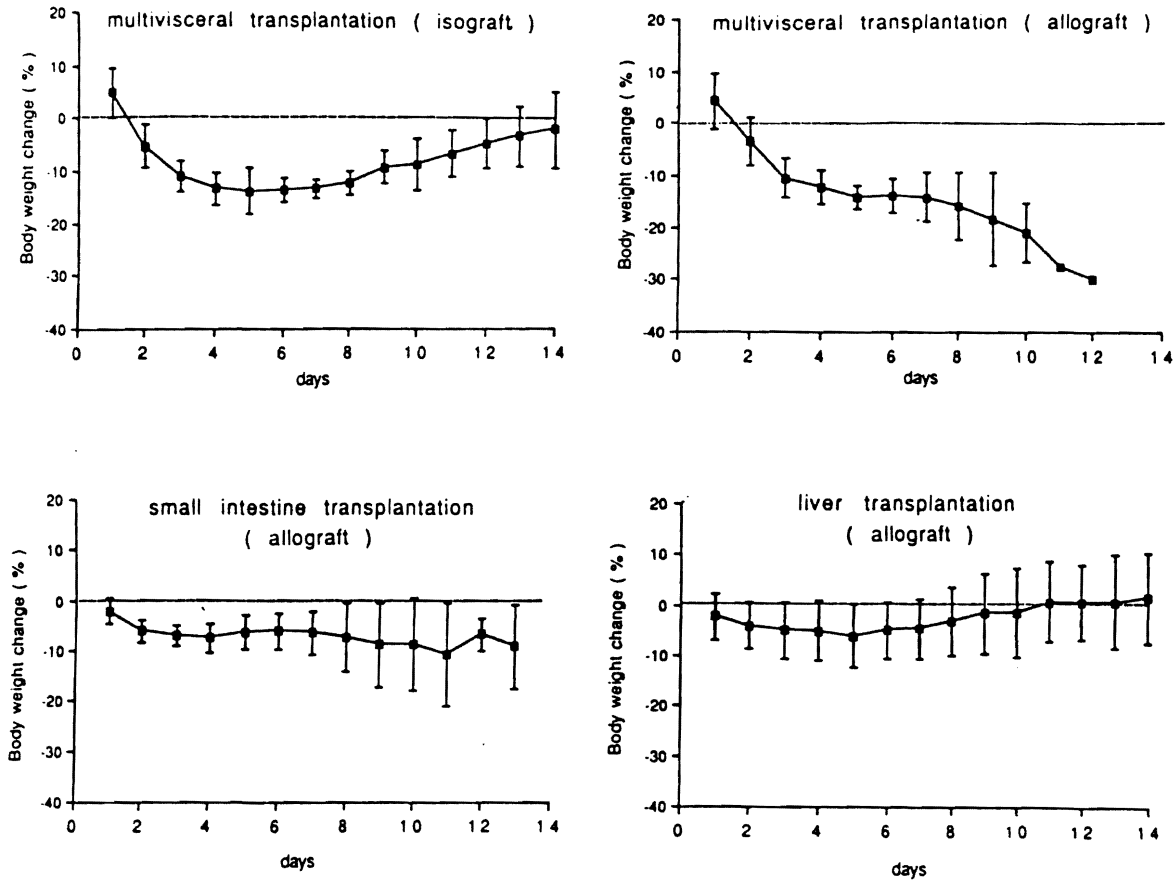

Fig. 2. Body weight (mean ± SD) after transplantation for each of the operative procedures.

cells (Fig. 3). By contrast, the same areas in the small bowel allografts were expanded and marked reactivity of the nascent lymphoid cells was seen; the small round cells mentioned above had been replaced by blastic lymphoid cells, which contained enlarged nuclei and centrally placed nucleoli (Fig. 4). Mitotic figures were abundant. The M-type epithelial cells overlying the Peyer's patches were focally disrupted. The lymphatic spaces in the lamina propria were dilated and an increase in margination of lymphoid cells was seen in the vein walls of the deep lamina propria.

Alterations in the mesenteric nodes were similar to those observed in the Peyer's patches. The T-cell zones (paracortex and interfollicular regions) were markedly expanded by the proliferating population of blastic lymphoid cells as in the Peyer's patches. Increased margination and probably emigration of lymphoid cells through the paracortical high endothelial venules were also seen. Secondary follicle formation was not detected and small areas of necrosis and replacement were seen of the paracortical architecture by eosinophilic histocytic and spindle-shaped cells.

By 6 to 7 days the T-cell zones of the Peyer's patches (Fig. 5, *A*) and mesenteric lymph nodes were infiltrated by eosinophilic histiocytic and spindle-shaped cells, intermixed with immunoblasts replacing large areas of the T-cell-dependent zones of the lymphoid tissue (Fig. 5, *B*). Typically there was edema of the lamina propria and dilatation of lymphatics (Fig. 5, *C*). Within a day or so the Peyer's patches were almost totally replaced with histiocytes (Fig. 6, *A*), and focal areas of mild lymphocytic cryptitis could now be observed in the intestinal mucosa away from the Peyer's patches (Fig. 6, *B*). It was characterized by a minimal lymphocytic periglandular infiltrate in the lamina propria, associated with necrosis and karyorrhexis of individual epithelial cells (Fig 6, *B*). By 7 to 8 days, focal areas of peritonitis were seen overlying partially or completely destroyed Payer's patches. The mucosa overlying the Peyer's patches became necrotic, which resulted in leakeage of intestinal contents into the muscular wall, focal abscess formation, extension of the mural necrosis, and eventual gut perforation (Fig. 7). By this time the cryptitis was more severe and congestion and hemorrhage appeared in the lamina propria.

The final stages of rejection of the small bowel began

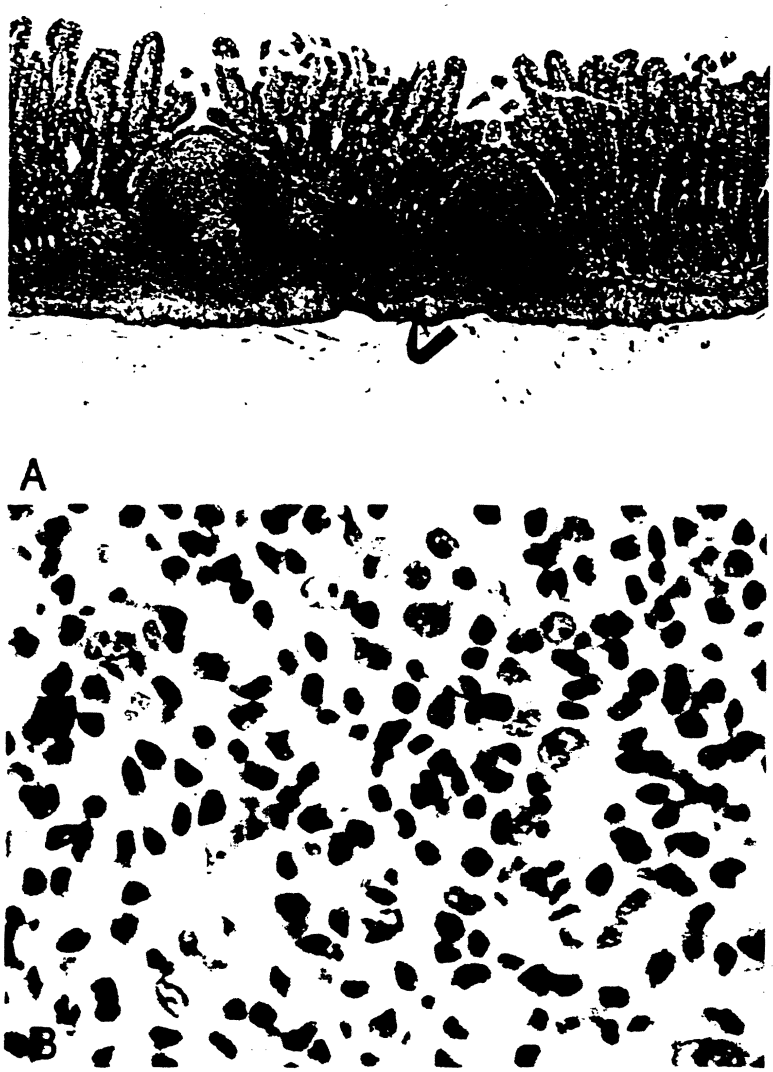

Fig. 3. Small intestine from a multivisceral isograft. **A,** Peyer's patch on day 5; note intact villi and normal-appearing lymphoid tissue. (Hematoxylin and eosin stain; original magnification ×100.) **B,** High-power view of **A** shows small inactive lymphoid cells in the interfollicular T-cell zone (see *arrow* in **A**). The isografts remained normal thereafter. (Hematoxylin and eosin stain; original magnification ×1000.)

at 9 to 10 days, when focal areas of transmural necrosis were observed, interspersed with more viable regions that demonstrated marked congestion, focal hemorrhage, and fibrin thrombi in the veins of the deep lamina propria. Extensive transmural necrosis and death quickly followed in the next several days.

Isolated orthotopic liver allografts. A brisk mononuclear portal infiltrate was detectable by 3 days and increased in intensity during the next 4 to 5 days, at which time the portal tracts were expanded by lymphohistiocytic inflammation, associated with subendothelial localization of the cells beneath the portal veins and mild cholangiolar proliferation. Very few if any inflammatory cells invaded the lobules and no areas of zonal necrosis of hepatocytes were seen. By day 12 the portal infiltrates had begun to wane and the liver was returning to normal, which was the last day of early histologic observations in this experiment.

Multivisceral allograft. Changes in the Peyer's patches of the small intestine, the lymphoid aggregates in the cecum, and the mesenteric nodes were not noticeably different from those described for the isolated small bowel allograft. However, the subsequent appearance of cryptitis in the intestinal mucosa, away from the Peyer's patches, was delayed by several days. Many of the animals had severe peritonitis with focal areas of intes-

Fig. 4. Small intestine from a small-bowel allograft. **A**, Peyer's patch on day 4 with mild expansion of the T-cell zone *(arrow)*. (Hematoxylin and eosin stain; original magnification ×40.) **B**, High-power view of T- cell zone shown in **A**. Note the blastic transformation and compare with isograft in Fig. 3, *B*.

tinal perforation associated near the Peyer's patches, as seen in the isolated intestinal allografts. Focal intestinal perforation and subsequent sepsis was thought to be the primary cause of death in these animals.

In the livers the appearance of portal inflammatory cells was delayed by 3 to 4 days compared with the isolated liver allograft. In addition, when the infiltrate finally appeared, it was comprised of a greater percentage of markedly blastic lymphoid and histiocytic cells compared with the isolated liver allograft. The infiltrate never reached the intensity of the isolated liver allograft, although late in the course (13 days) several of the rats demonstrated small hepatic infarcts that were presumably related to sepsis or agonal hypotension.

Little if any evidence of rejection was noted in the pancreas until 7 to 8 days, when focal mild perivenular lymphocytic infiltrates appeared. This was followed by acinar and duct infiltration and damage and subsequent architectural distortion by 10 to 12 days.

Recipient tissues. Recipient tissues were examined in animals with multivisceral isografts and allografts and in recipients of small-bowel allografts. The thymus glands were severely depleted; it was even difficult to identify thymic tissue in the mediastinum. On the other

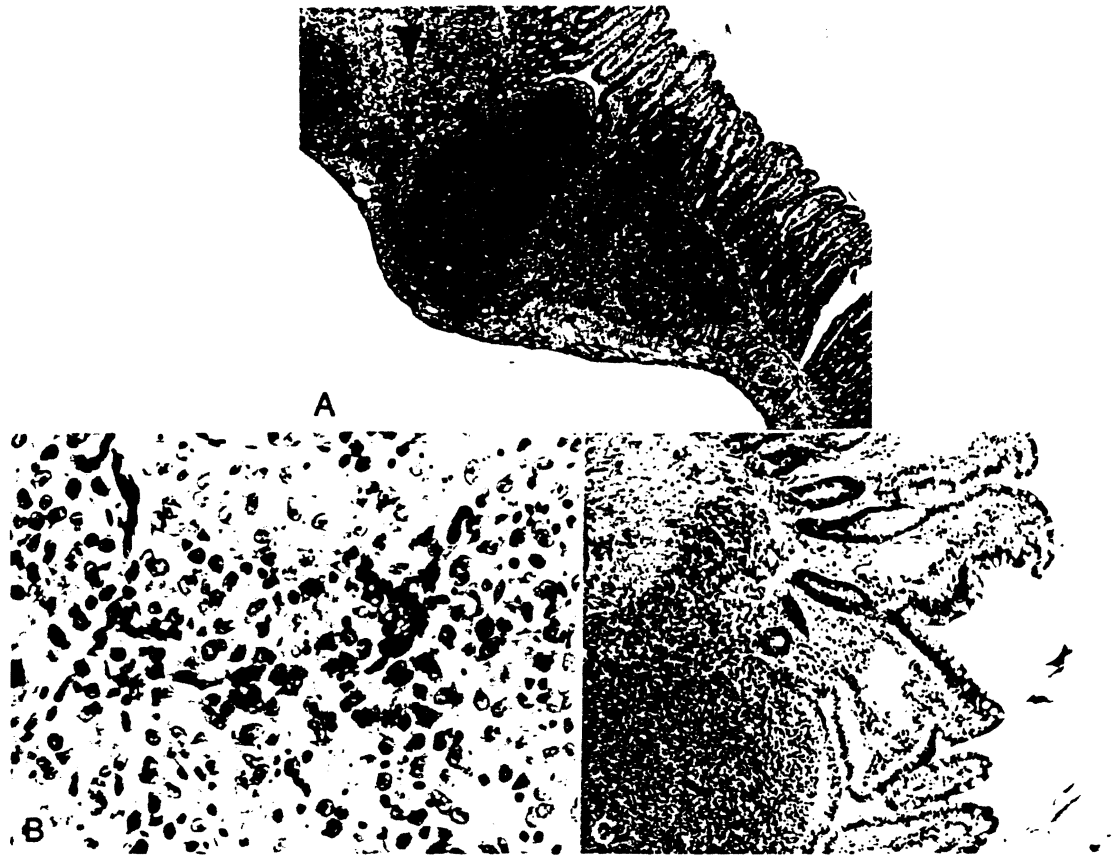

Fig. 5. Small intestine from a small-bowel allograft. **A,** Peyer's patch region on day 7. Note the marked expantion of T-cell zones *(arrowheads)*. (Hematoxylin and eosin stain; original magnification ×40.) **B,** High-power view of T-cell zone in **A** demonstrates immunoblastic and histocytic cells. (Hematoxylin and eosin stain; original magnification ×400.) **C,** The lymphatics in the lamina propria also became dilated on day 7 in allografts. (Hematoxylin and eosin stain; original magnification ×100).

hand, mediastinal lymph nodes were enlarged and demonstrated paracortical reactivity and secondary follicle formation. Eosinophilic histiocytes, similar to those described in the grafted tissues, appeared transiently in the paracortical regions but were gradually replaced by normal lymphoid elements.

No specific abnormalities were seen in the hearts or kidneys other than occasional areas of necrosis of the proximal tubules. Several of the animals had a mild acute bronchopneumonia. No evidence of graft-versus-host disease was seen in any animal when sections of the tongue or skin of the ear were examined.

DISCUSSION

The intestinal portion of the multivisceral allograft was shown in these studies to be the "Achilles heel" of the procedure. The survival of the animals that received the multivisceral allografts was not significantly different from that of animals that received intestinal allografts alone. In contrast, the rat recipients of isolated liver allografts had long-term survival without immunosuppression. The pathologic changes in the tissues supported the clinical observations in that the timing, histologic appearance, and ultimate morphologic consequences of uncontrolled rejection in the region of the Peyer's patches, the mesenteric lymph nodes, and ultimately the entire intestine were almost identical in the multivisceral and isolated intestinal allografts. The only hint that the presence of the liver might have mitigated rejection in the intestine was the delayed onset of cryptitis in the recipients of multivisceral grafts compared with the recipients of isolated intestinal grafts. The appearance of rejection in the liver of the multivisceral allografts was slightly delayed compared with that of the isolated liver allografts.

These clinical and pathologic findings in untreated rats were similar to those reported in humans under cyclosporine-steroid therapy.[2, 5] In clinical trials conducted so far, the morbidity associated with multivisceral allografts was overwhelming, [2, 3, 5] with intestinal

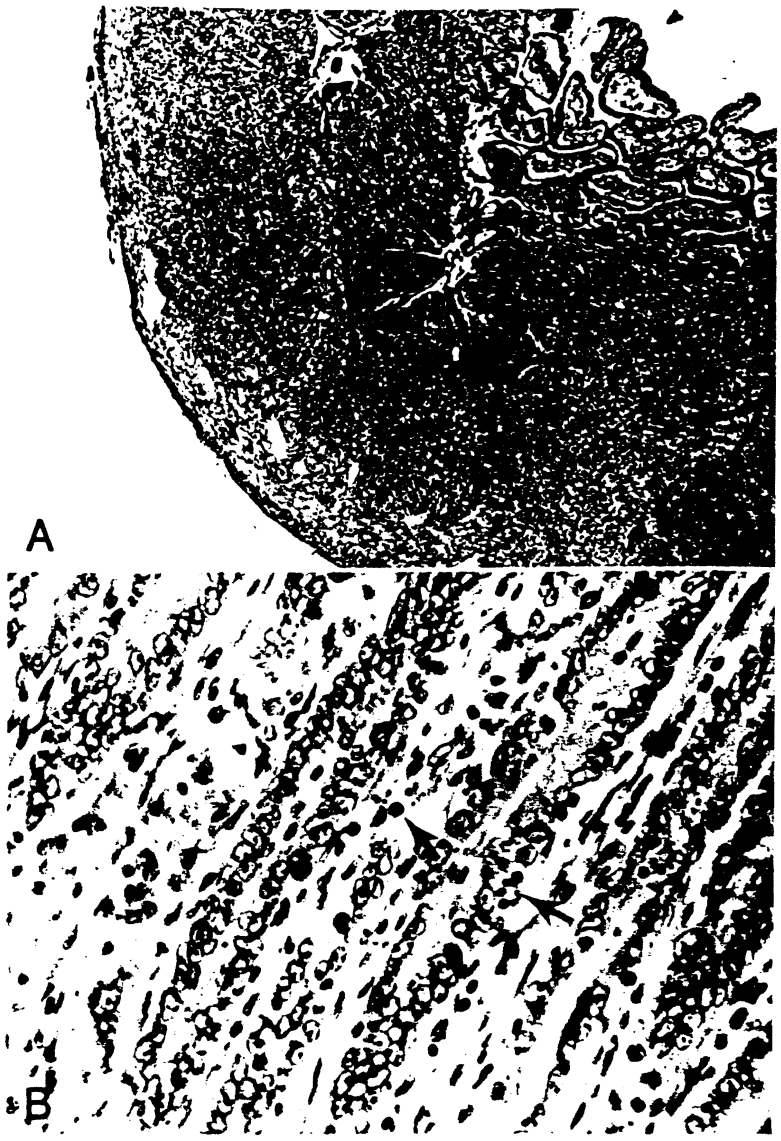

Fig. 6. Small intestine on day 9 from a small-bowel allograft. **A,** By day 9 the Peyer's patches were largely replaced with histiocytes. Focal and mucosal breakdown of the epithelium overlying the Peyer's patches was evident. The cellular population shown in Fig. 5, *B* is typical for this time. (Hematoxylin and eosin stain; original magnification ×100.) **B,** Cryptitis is seen in the allograft small-intestine epithelium, away from the Peyer's patches *(arrows)*. (Hematoxylin and eosin stain; original magnification ×400).

perforation, widespread musocal denudation from rejection, and the development of lymphoproliferative lesions. Even with pancreaticoduodenal-jejunal splenic transplantation, inclusion of a significant segment of jejunum led to mucosal destruction and a protein-losing enteropathy. At the same time the pancreas was functioning perfectly.[6] Although the findings were puzzling at the time, in retrospect this was an example of selective small bowel rejection. In contrase, "cluster" allografts that consist essentially of the multivisceral organs minus the intestine have been tolerated routinely.[7]

Perhaps it is inappropriate to attempt such comparisons between humans under immunosuppression and untreated rats. Further studies are in progress with the powerful new innumosuppressive agent FK 506 (Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan), which specifically inhibits T-lymphocyte helper cells[8]; at the time of reporting, no pure intestinal grafts had been performed, and the maximum survival of a multivisceral recipient was 72 days. Since then maximum survival with 14 current long-term multivisceral graft recipients is 130 days (unpublished observations). Similar survival

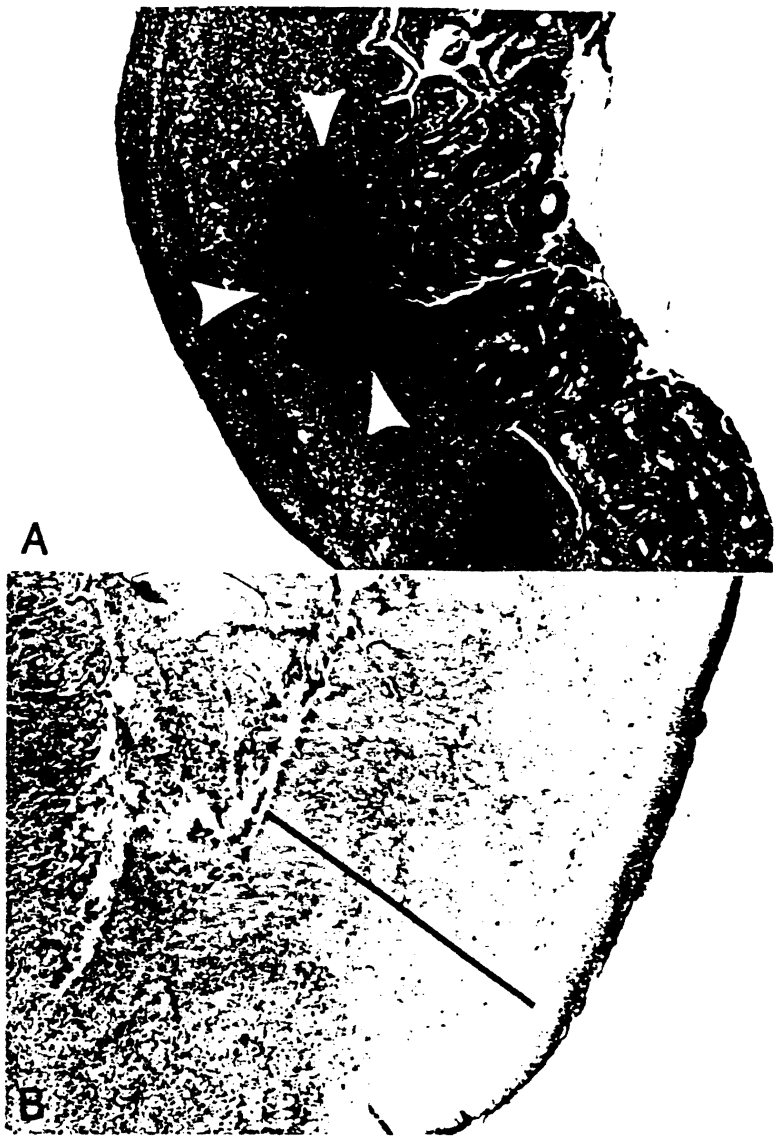

Fig. 7. Intestine from a small-bowel allograft. **A,** By day 9, mucosal breakdown with leakage of intestinal contents and intramural abscess formation were evident *(arrows)*. (Hematoxylin and eosin stain; original magnification ×40.) **B,** This was followed 2 to 3 days later by transmural necrosis *(bar)*. (Hematoxylin and eosin stain; original magnification ×100.)

with FK 506 has been accomplished with the isolated intestine in 15 animals but with greater difficulty (unpublished observations). We are not prepared to consider this seeming unbalance in difficulty as more than a tentative observation.

The lymphoid deposits in the intestine of either isolated intestinal or multivisceral grafts represent a special cause for concern because of early and preferential involvement of the Peyer's patches and other gut-associated lymphoid tissue compared with the remainder of the intestine. This has never been mentioned in the literature. However, most of these previous studies relied on methods such as serial intestinal biopsies or examination at or near the time of death, which could have easily missed the earlier development of these lymphoid lesions.[9-23]

Our own histologic observations on intestinal rejection after 6 to 7 days were essentially identical to those reported in the literature for intestinal rejection.[9-23] By this time the Peyer's patches were either partially or completely destroyed. With the studies reported earlier, the preferential involvement of Peyer's patches could be seen, which probably proceeded to focal mucosal breakdown, leakage of intestinal contents, focal intramural abscess formation, sepsis, and eventual transmural necrosis with perforation. We suggest that this focal mural

damage could explain the mysteriously high incidence of early deaths associated with intestinal transplantation even when no evidence of intestinal rejection is found.[17] The immediate cause of death in all of our animals was thought to be local or generalized peritonitis.

The early and preferential changes observed in the Peyer's patches and mesenteric lymph nodes could be caused by high immunogenicity of this part of the graft. The most potent stimulators of the mixed lymphocyte reaction and therefore the alloreaction are from the dendritic reticulum cell lineage.[24] The T-cell–dependent zone of the Peyer's patches and mesenteric lymph nodes are rich in interdigitating reticulum cells,[25] which belong to this family. Also, T cells that are the first to proliferate in response to alloantigens may preferentially "home" to these areas. An analogous situation may exist with bronchial associated lymphoid tissue in rat lung allografts.[26] No matter where the grafted lymphoid tissue is located, successful immunosuppression and sparing of the lymphoid tissue could theoretically lead to graft-versus-host disease. However, graft-versus-host disease was not observed in any animal in our study.

Our results also suggest that immunologic monitoring may continue to be a problem in the clinical application of multivisceral transplantation. The only portion of the graft that would be readily accessible to biopsy evaluation in humans with current procedures in the liver. However, in our animals, just as in a recent human case,[5] the changes in the liver were relatively mild and did not occur until several days after the changes in the intestine, particularly in the gut-associated lymphoid tissue, were already advanced. Because the intestine was the major target organ of rejection, attention must be focused here for routine monitoring. The problem of focality and sampling errors will have to be addressed.

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