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Morphology of intestinal allograft rejection and the inadequacy of mucosal biopsy in its recognition

P.R. Millard, A. Dennison, D.A. Hughes, Jack Collin and P.J. Morris
Nuffield Departments of Pathology and Surgery, John Radcliffe Hospital, Oxford

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Summary. Small intestinal segmental autografts and allografts in dogs were examined histologically to assess changes associated with the surgical technique, the effect of different luminal perfusates and for evidence of rejection. Some animals were immunosuppressed with Cyclosporin A. Specimens for examination were obtained by biopsy at regular intervals after transplantation, at death or when killed. Typical vascular changes of rejection were identified only within some allografts and in others the cause of graft failure remains conjectural. When there was rejection characteristic lesions were confined to the submucosa and muscle coats while changes in the mucosa were similar to those in the autografts. These mucosal features were affected by the nature of the perfusate and often appeared transiently after grafting. Mucosal biopsy as a way of monitoring intestinal allograft rejection neither reveals a sequential pattern of changes, nor provides a reliable method of recognition of the reaction. In contrast full thickness biopsies of the intestinal wall do appear to fulfil both of these requirements.

Keywords: intestinal allograft, intestinal autograft, rejection, biopsy

Transplantation of the small intestine has not achieved the success of other organ grafts either experimentally or in man. Difficulties with the surgical technique accounted for some failures but the main reason has been the immune responses envoked (Kirkman 1984; Ruiz *et al.* 1972). These have included graft versus host reactions (Garrido *et al.* 1970) as well as host versus graft reactions (Preston *et al.* 1965. The type of response is influenced by the amount of intestine transplanted (Deltz *et al.* 1981), irradiation of the graft before grafting (Cohen *et al.* 1976) and the mass of lymphoid tissue transplanted with the intestine (Thiede *et al.* 1982). Immunosuppression of various types can also affect these immune responses, although to date none has produced indefinite functional graft survival (Craddock *et al.* 1983) Recognition of the end stage of the immune reaction still relies upon the appearance of blood-stained secretions and engorgement of the graft's stoma by which time the reaction is irreversible and the tissue non-viable (Stamford & Hardy 1974). Morphological criteria consistent with graft rejection have been described in small intestinal transplants (Holmes 1973) and the use of biopsies to plot the progress of this reaction has been advocated (Cohen *et*

Correspondence:Peter R. Millard, E.M. Unit, Department of Histopathology, John Radcliffe Hospital, Oxford OX3 9DU, UK.

al. 1984). Universal agreement upon the changes found in these biopsies and rejected grafts has not been reached; nor has a constant sequence of events been described (Kunlin *et al.* 1971). Some of the discrepancies may be due in part to different transplantation techniques and immunosuppressive regimes but the variable morphological detail reported also makes comparison of results difficult. To resolve some of these problems and as part of a study of intestinal allografts (Dennison *et al.* 1986) canine segmental intestinal autografts and allografts – some of which were immunosuppressed with cyclosporin A, and all of which were luminally perfused with either distilled water or isotonic nutrient solutions – were routinely biopsied. Biopsies were taken at the end of the transplantation procedure and at regular intervals thereafter. The appearances of these biopsies were compared with those in the autopsy specimens. Changes ascribed to immune rejection in other organ transplants were looked for as well as a pattern of evolution of histological changes indicative of rejection.

Materials and methods

Unrelated mongrel dogs were used. Each small intestinal graft was a 100 cm Thiry-Vella fistula with orthotopic vascular anastomoses (Dennison *et al.* 1986). Autografts and allografts were performed (Groups A and B, Table 1) and Cyclosporin A was given orally to some dogs with allografts (Group C, Table 1) at 20 mg/kg/day. The lumen of each Thiry-Vella segment was regularly perfused with either distilled water or a solution of 100 mmol/l glucose, 90 mmol/l NaCl, 1 mmol/l L-alanine, 1 mmol/l lauric acid (dissolved in 10 ml 10% ox bile (dessicated ox bile:Oxoid Ltd:UIC)) and 0·5 mmol/l medium chain triglyceride (10% MCT B.Braun Mekungen Germany).

A full thickness transverse section of the intestine was taken at the completion of the transplantation procedure. Subsequent biopsies from 6–8 cm inside the distal stoma were mucosal although 17 (four from Group C1, 11 from Group A2 and two from Group B2, Table 1) were full wall thickness biopsies. At death or killing (Table 1) full thickness sections of the graft were taken together with mesentery and most other organs. All tissues were fixed in 10% formalin and processed to paraffin wax. Paraffin sections were stained with haematoxylin and eosin and selected sections with Millers' elastin stain counterstained with Van Gieson for fibrous tissue. When either death of the animal or graft failure was clearly attributable to technical faults the tissues were not examined further (Table 2). In all other allografts evidence of an immune reaction was looked for including infiltrates of mononuclear cells, interstitial oedema and haemorrhage, and acute and chronic vascular rejection lesions (Table 3) as well as changes in small intestinal architecture.

Results

Distilled water perfusate

Autografts (Group A1). With one exception the initial biopsy from all dogs was comparable. The architecture of the bowel was normal with a mild degree of epithelial desquamation confined to the tips of the villi. Lacteal dilatation in these regions was also seen with minimal capillary congestion. A single biopsy included changes found in many later biopsies. The epithelium to the villi and in the crypts was flattened, basophilic and included a mild degree of pleomorphism amongst the cells. Mucosal cells were decreased in number and small zones of epithelium were absent. Within the lamina propria, in a patchy distribution, were groups of neutrophil polymorphs.

From day 2 onwards the tissue changes were neither consecutive nor consistent either overall or within any individual autotransplant. Only in one graft did the same pattern of reaction persist throughout all five biopsies taken between days 2 and 10. The tissue reactions described in the initial

Table 1. Summary of material examined

	Number of biopsies															Number autopsied	Average survival (days)	Cause of death
Day:	0	2	3	4	5	6	7	8	9	10	11	12	14	21	28			
Distilled water perfusate																		
A1 Autografts (12)	11	11	1	11	1	11	0	11	0	11	0	2	10	0	6	11	171.7 (50–196)	Killed
B1 Allografts (8)	8	8	4	8	5	6	0	1	0	1	0	0	1	0	0	7	9.9 (8–15)	Peritonitis
C1 Allografts + CyA (5)	5	5	0	5	0	4*	0	2	0	3*	0	2	4*	1	3	4	46.6 (19–117)	Obstruction peritonitis; pulmonary oedema; malnutrition
Isotonic nutrient perfusate																		
A2 Autografts (6)	6	6	0	0	0	6*	0	6*	0	6*	0	0	6	0	0	5	70 (70)	Killed
B2 Allografts (6)	6	6	4	6	4	6	4	5*	2	11	0	0	0	0	0	6	11.5 (9–14)	Peritonitis
C2 Allografts + CyA (6)	6	6	1	6	0	6	2	6	1	6	0	0	6	0	0	6	196.5 (28–814)	Peritonitis; malnutrition; pulmonary oedema; killed

* Some biopsies included full wall thickness.
CyA Cyclosporin A.

Table 2. Technical failures

Nos	Cause of failure	Survival (days)
1	Volvulus	3
2	Intussusception	7, 7
1	Haemorrhage	1
2	Venous-thrombosis	5, 1
2	Arterial thrombosis	1, 5
1	Technically impossible	—
1	Anaesthetic	—
4	Cyclosporin toxicity	9, 7, 10, 9

biopsies occurred, but in addition some biopsies also included necrotic debris infiltrated by acute inflammatory cells within which, in a few examples, were randomized clusters of mucosal epithelial cells.

At autopsy all but two autotransplants had slight-to-mild focal epithelial desquamation of the tips of some villi but were otherwise normal. Within parts of the mucosa of two grafts at 50 and 196 days there were also areas of ulceration associated with large numbers of neutrophil polymorphs which in the specimen at 196 days penetrated to the muscular layer. There were no vascular changes in the mesenteric vessels or in the vessels within the wall of any of the autografts.

Allografts without immunosuppression (Group B1). The initial biopsies in all grafts were similar to those of the autografts (A1) and these features were maintained in many subsequent biopsies. A few biopsies, however, also included necrotic inflammatory tissue near the tips of villi sometimes in association with small fragments of epithelium. Occasionally there was only a shadow architecture of the villi and lamina propria. In one dog surviving 14 days this reaction occurred most commonly and was evident on days 1, 4 and 14 with intervening appearances similar to day 0 on days 2, 6, 8 and 10.

In only one autopsy specimen (8 days post-transplant), was there unequivocal evidence of rejection. Some mesenteric vessels included focal fibrinoid necrosis and others subintimal mononuclear cells and vacuolated cells (Fig. 1). Most of these vessels and others were cuffed and infiltrated by mononuclear cells and a few veins were partly narrowed by recent thrombus. A much smaller number of vessels within the muscle coat and submucosa included similar features but in most there was only mononuclear cell cuffing. There was no diffuse or focal increase in mononuclear cells in the lamina propria although there was some margination of these cells at the junction with the muscularis mucosa. The villous and crypt architecture remained normal. The epithelium included a few crypt abscesses but with no alteration amongst the epithelial cell

Table 3. Number of allografts with vascular lesions

	Immunosuppression			
	None		Cyclosporin A	
Perfusate group*:	B1	B2	C1	C2
(Number of grafts):	(8)	(6)	(5)	(6)
Recent thrombus	3	4	0	1
Mononuclear cell cuffing	1	0	1	2
Fibrinoid necrosis	1	0	2	2
Fractured internal lamina	0	0	0	1
Obliterative end-arteritis	0	0	2	1

* See text and Table 1.

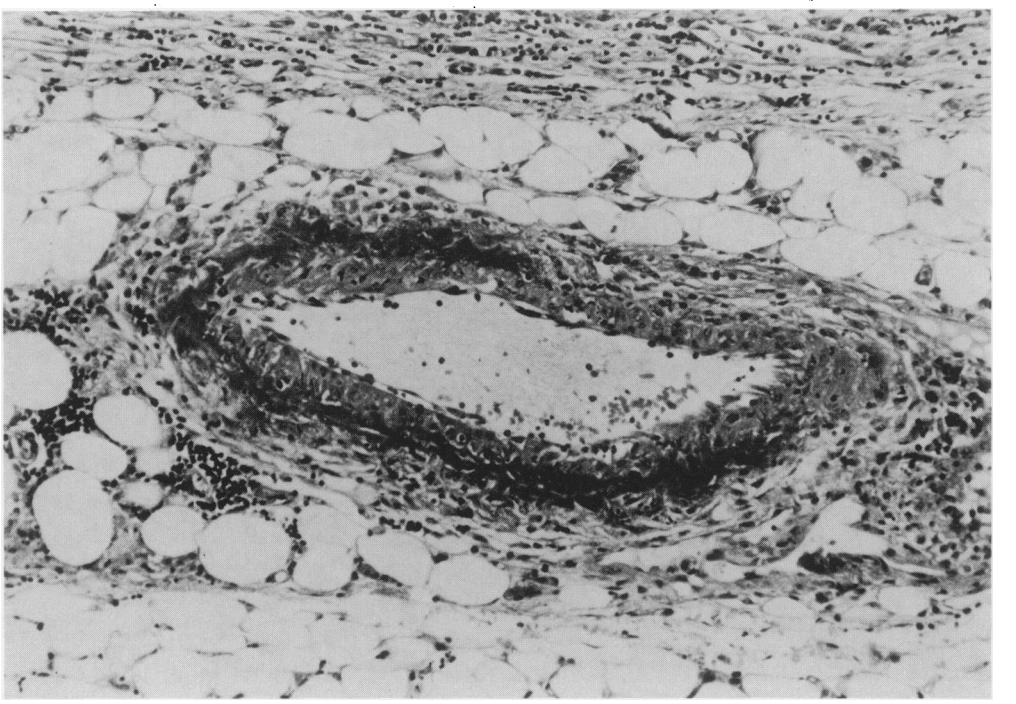

Fig. 1. Allografted intestine perfused with distilled water and without immunosuppression. Mesenteric vessel with fibrinoid necrosis eight days after transplantation. H & E × 180.

types or their distribution. All the other grafts were necrotic and congested with a preserved architecture. They were either devoid of any cellular infiltrate or associated with a massive focal infiltrate of neutrophil polymorphs throughout the wall and mesentery. There were a few very recent thrombi but no other vascular lesions within the graft wall or mesenteric vessels. The animals' own small intestine had none of these features.

Allografts with cyclosporin A immunosuppression (Group C1). The initial and many of the subsequent biopsies were similar to those in the initial autograft biopsies (A1) and these appearances were also maintained in the autopsy tissues in two grafts 24 and 34 days after transplantation. The biopsies from two other grafts at 39 and 117 days had in addition fragments of necrotic inflammatory tissue some of which were associated with a recognizable villous pattern although without any viable epithelium. The third allograft, surviving 19 days, in which there were full thickness biopsies, had at days 6 and 10, a few arteries within the muscle coat with subintimal vacuolated cells. In the day 10 biopsy there were also similar vascular features in the mesentery and submucosa where a very few arteries also included focal fibrinoid necrosis. Only small numbers of perivascular mononuclear cells were seen. The day 12 and 14 biopsies from this graft included some of these vascular lesions and had an intact epithelium and lamina propria.

The autopsy specimens from the dogs surviving 39 and 117 days included subintimal vacuolated cells in vessels in the muscle coat, submucosa and mesentery (Fig. 2). A single mesenteric vessel in the 39 day survivor manifested fibrinoid necrosis, but only in the other specimen were there small focal mononuclear cell infiltrates. The mucosa of the former animal was acutely ulcerated and

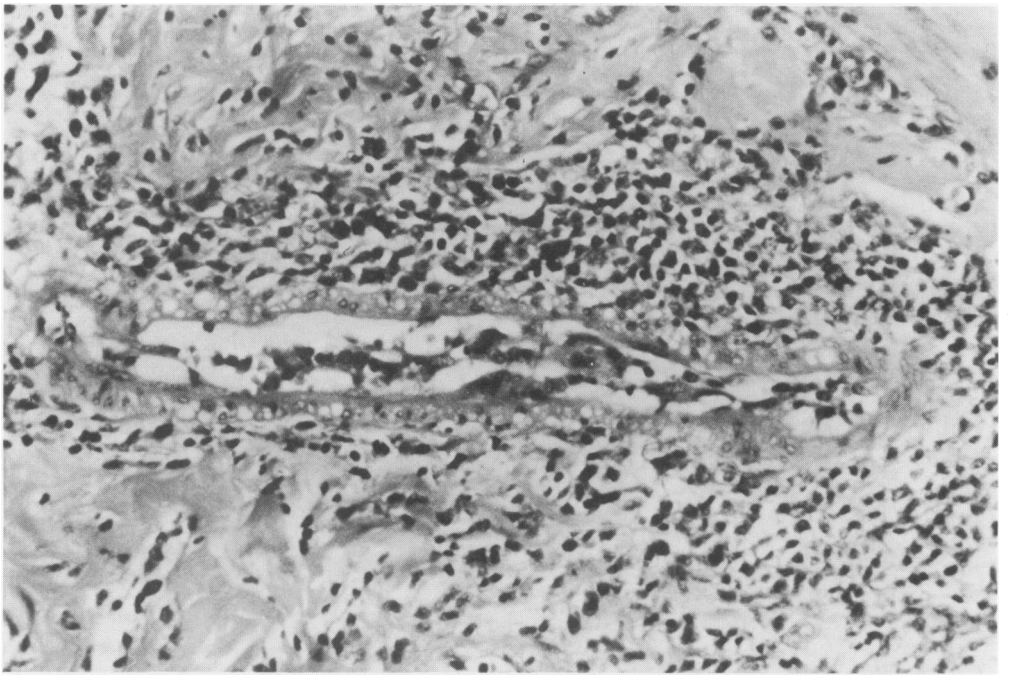

Fig. 2. Allografted intestine perfused with distilled water and associated with cyclosporin A 28 days after transplantation. A vessel within the submucosa with narrowing of the lumen from subintimal vacuolated mononuclear cells and infiltrating mononuclear cells. Similar mononuclear cells surround the vessel. H & E × 200.

covered with pus while that of the dog dying at 117 days was replaced by granulation tissue.

Isotonic nutrient solution perfusate

Autografts (Group A2). Specimens including only mucosa invariably had dilated lacteals and some vascular engorgement with interstitial haemorrhage and oedema. There was no loss of mucous cells or villus or crypt deformity. The features were strikingly uniform between specimens irrespective of the time after transplantation.

Biopsies that included the full thickness of the bowel wall had virtually absent lacteal dilatation. There was some shedding of the epithelium over the tips of the villi and within these there was a greater number of mononuclear cells than in those biopsies with only mucosa. There was also a mild degree of submucosal oedema but no vascular changes in any part (Fig. 3).

Allografts without immunosuppression (Group B2). The biopsies from day 0 to day 5 were similar to those of the autografts (A2). From day 6 the epithelium was either absent or severely disrupted with mucus, epithelial cells and neutrophil polymorphs mushrooming into the lumen of the bowel. There were neutrophil polymorphs within the lamina propria but no marked increase in the mononuclear cells. Lacteal dilatation was often marked and in some specimens capillaries were engorged. A few biopsies included muscle which in one animal was infiltrated diffusely by mononuclear cells at day 11. A dog surviving 9 days had at days 6 and 9 the mucosal changes above but at day 7 only the features found in the autografts (A2).

The autopsy specimens were all necrotic

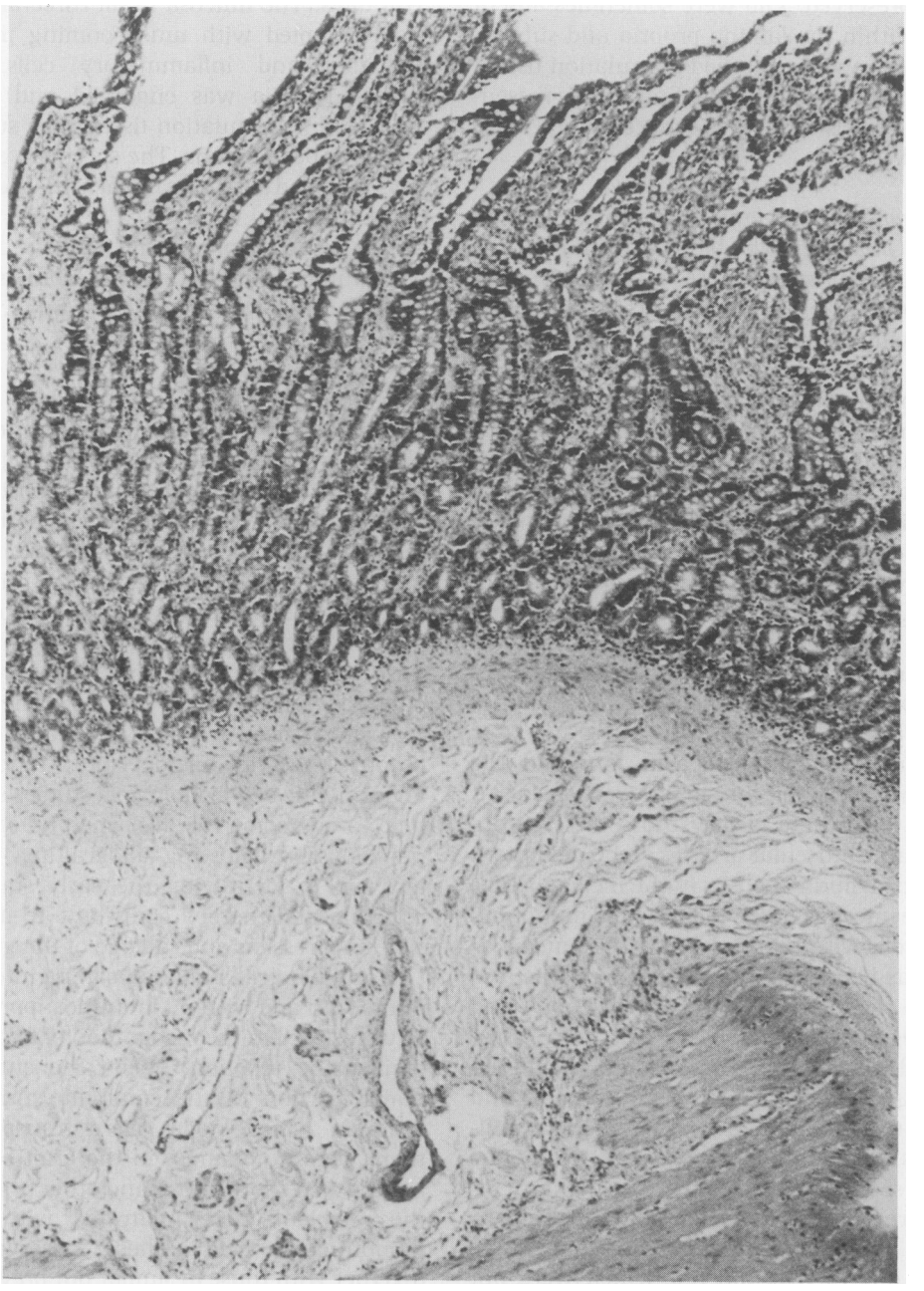

Fig. 3. Autografted intestine perfused with isotonic nutrient after 6 days. The villi are long and no architectural abnormality is present. Within the submucosal and muscle coats there is neither a mononuclear cell infiltrate nor vascular changes. H & E × 50.

although the dog's own small intestine was well preserved. Villi were sometimes absent and within the lamina propria and submucosa there was engorged granulation tissue. Vascular lesions were confined to the mesenteric vessels where recent thrombi were found.

Allografts with cyclosporin A immunosuppression (Group C2). The biopsies from day 0 to day 14 mirrored those of the autograft mucosal biopsies (A1) apart from a dog surviving 142 days and with the addition in some later biopsies in three dogs of small fragments of crushed epithelium associated with mucus. The mucosal biopsies from the dog surviving 142 days, at day 7, 10 and 14 included no viable mucosa. In the two early biopsies there was only fibrin, necrotic tissue and acute inflammatory cells and in the final biopsy (day 14) no epithelium was recognized. The villous architecture remained and there were plugs of fibrin and red cells in lacteals and a widespread infiltrate of neutrophil polymorphs together with some mononuclear cells.

A range of changes was found in the autopsy specimens but in only one dog at 28 days were these clearly those of rejection. The large muscular arteries of the mesentery had focal fibrin deposits in the media, breaks in the internal elastic lamina, and mononuclear cells within the adventitia and media as well as beneath the intima. There was also some endothelial cell proliferation and aggregates of vacuolated cells were associated with marked narrowing of the lumen (Fig. 4). Some vessels in the muscle coat and submucosa had small focal perivascular infiltrates of mononuclear cells but no lesions were seen in the mucosa.

Three grafts (one each at 28, 108 and 142 days) included changes which may have been due to rejection but which were not unequivocally so. There was fibrinoid necrosis in the mesenteric vessels in the specimen at 28 days. Subendothelial mononuclear cells were seen in vessels in the intestine wall together with foci of similar cells in all parts of the wall in the specimen at 108 days. The mucosa in all three animals was disrupted with mushrooming mucus, epithelial and inflammatory cells. The lamina propria was engorged and partly replaced by granulation tissue. The submucosa was oedematous. The specimen at 142 days included abscesses replacing large areas of the intestinal wall.

The grafts examined at 59 and 814 days were autolysed more than the animals' own intestine, but were otherwise normal.

Discussion

The morphology of some of these intestinal allografts demonstrates clearly that rejection occurred. Nevertheless, in many biopsies and even some autopsy specimens no definite morphological evidence of rejection was apparent. Rejection is cited as the principal cause for the failure of small bowel allotransplants (Garrido *et al.* 1970; Preston *et al.* 1965; Ruiz *et al.* 1972) but the reaction is often diagnosed either because the graft recipient is dead with no obvious cause or because the graft has developed functional abnormalities. Morphological studies should help to overcome the dilemma and sequential biopsies, following allografting, might also aid in identifying the early stages of rejection and thereby contribute to its possible suppression and salvage of the graft.

Morphological studies of canine intestinal grafts with and without immunosuppression have resulted in the recognition of two types of immune reaction. When the entire or major portion of the small intestine and draining lymph nodes were transplanted there were no changes in the graft but the animal died shortly after and other organs of the recipient were infiltrated with graft mononuclear cells. These observations, together with those in similar but previously irradiated grafts (Cohen *et al.* 1976), as well as grafts freed of mesenteric lymph nodes and grafts associated with immunosuppression (Cohen *et al.* 1984) led to the acceptance that there was a graft versus host reaction.

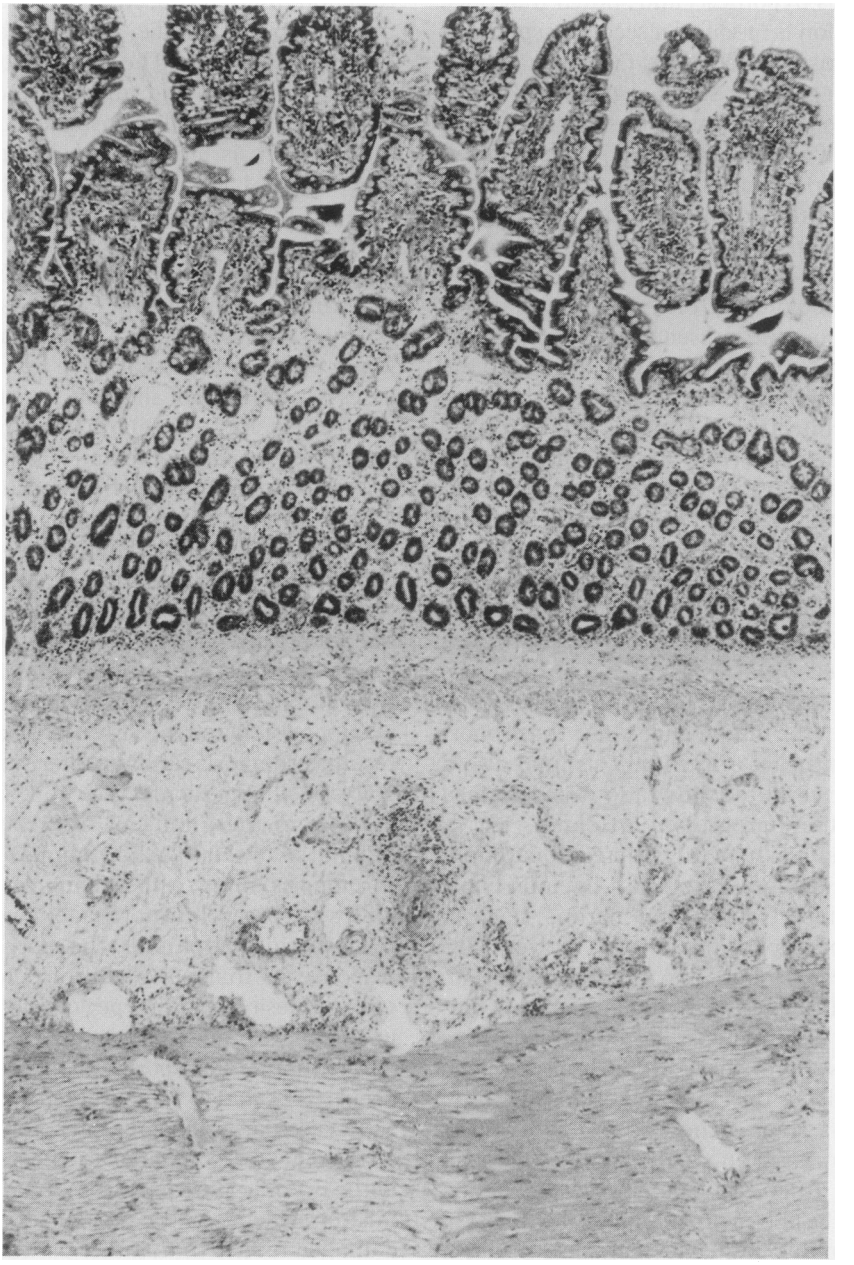

Fig. 4. Allografted intestine perfused with isotonic nutrient and associated with Cyclosporin A 28 days after transplantation. No architectural changes are evident. Adjacent to some vessels in the submucosa are small collections of mononuclear cells. H & E × 50.

Subsequent studies in rodents have supported this hypothesis and shown that once this reaction is modified a second response of host versus graft develops (Monchik & Russell, 1971). When small segments of intestine were transplanted host versus graft rejection was the invariable response (Cohen *et al.* 1969). Immunosuppression in various forms attenuated either form of response (Garrido *et al.* 1970; Thiede *et al.* 1982).

Emphasis has been laid for the morphological recognition of intestinal allograft rejection on the presence of mononuclear cell infiltrates confined almost entirely to the lamina propria, recent vascular thrombosis and architectural changes within the mucosa (Holmes *et al.* 1971*a*). Surprisingly the more characteristic fibrinoid necrosis, mononuclear cell infiltration and luminal obliteration of vessels, of the type encountered in the unequivocally rejected grafts (Table 3) have not been reported. The architectural changes ranged from blunting of villi with eventual total flattening to decrease and total loss of epithelial mucous cells. An increase in the mitotic index (i.e., the proportion of epithelial cells in mitosis) and also a fall in the crypt to villus ratio was described as rejection progressed (Holmes 1973; Holmes *et al.* 1971*a*). Lacteal dilatation, mucosal congestion and haemorrhage, muscle hypertrophy, and fibrous replacement of parts of or the entire wall were also recognised (Holmes 1973; Holmes *et al.* 1971*a*). Progressive epithelial necrosis culminating in total loss accompanied these lesions. None of these architectural lesions are specific for rejection and, as in this study and others, some of these occur in autografts (Ballinger *et al.* 1962). Denervation (Elliott *et al.* 1967; Ruiz & Lillehei 1972), ischaemia (Kilgore Barnett, 1965) and as in this study some luminal perfusates can also produce similar changes. Autografts in this study showed changes that were more frequent when the perfusate was distilled water than an isotonic nutrient solution. Since the final common pathway is probably ischaemia which is also an inevitable sequel of the vascular lesions characteristic of allograft rejection, there has been an understandable temptation to ascribe these architectural features to rejection. The results, particularly when the biopsy and autopsy findings are compared, clearly demonstrated that such an approach is all too often inappropriate. The emphasis by others on architectural changes rather than on mononuclear cell infiltrates and vascular lesions is further in striking contrast to the features of rejection in other organs where most structural changes are regarded as a late phenomenon. Many of the criteria that have been used for assessing intestinal allograft rejection thus lack specificity and this may in part have contributed to an overdiagnosis of allograft rejection. A graft versus host reaction modified by immunosuppression may, nevertheless, conceivably underlie these morphological findings as well as their differences from the usual patterns of allograft rejection, but the results provided no clear answer to this possibility. Necrosis of the entire intestinal wall in allografts performed without immunosuppression and the very high incidence of recent thrombosis raises an alternative possibility of a hyperacute rejection. However, aside from the timing of the reaction, the hallmarks of this reaction namely capillary thrombosis, neutrophil polymorph infiltates and widespread haemorrhage were absent. Cyclosporin A attenuated the morphological response in that early chronic obliterative vascular lesions of the type commonly found in chronic human rejection appeared, whereas without Cyclosporin A these had not occurred (Table 3). The greater incidence of such vascular lesions in grafts perfused with distilled water compared to those perfused with isotonic nutrient solutions provides further evidence of the greater propensity of damaged tissues than intact tissues to rejection but the vascular changes with either perfusate are typical of allograft rejection.

The features in the mucosal biopsies in these experiments provide no clear cut evidence that their basis was rejection or that there was a sequential pattern of changes.

Biopsy appearances reverted to the base line pattern of the initial biopsy even though intervening biopsies had included a number of abnormal features. Similar observations have been made by others although some workers claim that sequential changes culminating in rejection are identifiable (Holmes 1973; Holmes *et al.* 1971*a*; Lossing *et al.* 1982). The disparity amongst these results may come from the use of multiple or single biopsies combined with the patchy nature of the rejection process although the observations on the morphological diagnosis of intestine allograft rejection already made show that biopsies confined to the mucosa are unsuitable for this purpose. In this series allograft rejection was unequivocally evident morphologically only when all parts of the intestinal wall were available for study. Only then were vessels other than capillaries included and only then could mononuclear cells be clearly identified as abnormal since they were in the submucosal and muscle coats. Increases in mononuclear cells within the lamina propria are difficult to assess against the normal background population of the intestinal mucosa, especially if the biopsy includes parts of lymphoid follicles. Mitotic counts do not provide specific evidence of the nature of the mononuclear cells although increased mitotic indices have been reported in rejection reactions (Holmes *et al.* 1971*b*). Demonstration of changes in either T-cell subpopulations with monoclonal antibodies or immunoglobulin distribution might provide some indication of the onset and prognosis of rejection but neither has provided conclusive evidence of rejection in other organ allografts. Until more specific mucosal changes are recognized full thickness biopsies of the wall of intestinal allografts should be made if morphology is to be used to monitor rejection.

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