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Bilateral native nephrectomy improves renal isograft function in rats

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Bilateral native nephrectomy improves renal isograft function in rats. Bilateral native nephrectomy has been suggested to improve renal allograft survival in man. This effect may be most prominent in patients experiencing acute tubular necrosis following transplantation. Thus, native kidneys may alter the course of ischemic acute tubular necrosis in the transplanted kidney. In the present studies, we utilized an experimental model of syngeneic transplantation in which rejection does not occur. We studied Lewis rat renal isografts transplanted into littermates following sham, unilateral or bilateral native nephrectomy. In a fourth group of rats, we evaluated the importance of native kidney excretory function by studying isografts transplanted into littermates with bilaterally obstructed native kidneys. Renal blood flow and excretory function were measured in vivo, eight days following transplantation. Renal excretory function of isografts transplanted into animals following bilateral native nephrectomy was similar to normal nontransplanted Lewis kidneys. The presence of either one or both functioning native kidneys significantly reduced isograft inulin clearance, PAH clearance, and blood flow. However, when isografts were transplanted into Lewis rats with bilaterally obstructed native kidneys, renal isograft inulin clearance and blood flow were not significantly impaired. Nontransplanted kidneys demonstrated "functional hypertrophy" following contralateral nephrectomy, with glomerular filtration rate and renal blood flow increasing by approximately 50%. In contrast, isograft glomerular filtration rate in animals following bilateral native nephrectomy was equivalent to that of single kidneys from normal animals with both kidneys in situ. However, renal blood flow of isografts from these animals increased to the same level as nontransplanted Lewis kidneys following contralateral nephrectomy. Histological examination of isografts from animals with functioning native kidneys in situ demonstrated extensive disruption of normal renal architecture with tubular and interstitial injury. This was in marked contrast to the appearance of Lewis–Brown Norway allografts, to isografts from animals following bilateral native nephrectomy, and to isografts from animals with bilaterally obstructed native kidneys. In Lewis–Brown Norway allografts, there was evidence of rejection with active inflammatory cell infiltration, arteriolitis and venulitis. In isografts from animals following bilateral native nephrectomy or with bilaterally obstructed native kidneys, renal architecture was normal. Thus, the detrimental effect of native kidneys on isograft function may be related to impaired recovery from ischemia or potentiation of ischemic injury which occurs during the transplantation procedure.

Bilateral native nephrectomy has been suggested to improve graft survival in renal transplant recipients [1–4]. In a recent multi-center analysis of 2,808 cadaveric renal transplants, allograft survival was increased in patients with bilateral native nephrectomy [1]. The improvement in graft survival was most striking in those patients with postoperative acute tubular necrosis. This suggests that native kidneys may directly affect graft function or may influence the outcome of ischemic acute renal failure in transplanted kidneys. In order to evaluate the potential relationship between native nephrectomy and graft function independent of rejection, we transplanted Lewis rat kidneys into littermates. In these animals with normal native kidneys, we evaluated the effects of sham, unilateral and bilateral native nephrectomy on isograft function. In other studies, we measured isograft excretory function and blood flow in the presence of nonfunctioning native kidneys. All studies were performed eight days after transplantation. We also compared isograft function with that of nontransplanted kidneys with and without contralateral nephrectomy. Finally, the histologic appearance of the isografts was examined and compared with that of rejecting Lewis kidneys which had been transplanted into Brown Norway rats.

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Methods

Study design

Seven groups of rats were studied. Four groups of Lewis rats received isografts from littermates:

Group 1. One group of rats ($N = 5$) underwent left native nephrectomy at the time of transplantation, followed by right native nephrectomy 48 hr later, leaving only the single transplanted kidney in situ (one kidney).

Group 2. The second group of rats ($N = 5$) underwent left native nephrectomy at the time of transplantation, followed by sham right native nephrectomy 48 hr later (two kidneys).

Group 3. The third group of rats ($N = 5$) underwent sham left native nephrectomy at the time of surgery, and sham right native nephrectomy 48 hr after transplantation. Thus, both native kidneys and the transplanted isograft remained (3 kidneys).

Group 4. The fourth group of rats ($N = 6$) underwent ligation of the left native ureter at the time of transplantation, followed by ligation of the right native ureter 48 hr later (3 kidneys).

Two groups of nontransplanted Lewis rats and one group of Brown Norway rats that received allogenic Lewis kidney transplants served as controls:

Group 5. Four Lewis rats underwent sham transplantation and sham native nephrectomy, leaving both native kidneys intact.

Group 6. Four Lewis rats underwent sham transplantation and unilateral (right) nephrectomy, leaving a single native kidney intact.

Group 7. Five Brown Norway rats with native kidneys intact received single Lewis renal allografts. In these genetically dissimilar strains, we have previously shown that there is progressive inflammatory cell infiltration of the allograft which parallels a decline in renal function during the six days following transplantation [5].

In the four groups of animals with isografts and the two groups of nontransplanted controls, we measured the clearances of inulin and PAH and the excretion of sodium and solute by individual kidneys eight days following surgery. Renal blood flow (RBF) was measured in transplanted kidneys or in the left kidney from nontransplanted animals at the time of the clearance studies.

Transplantation

Kidneys from male Lewis rats weighing 200 to 300 g were transplanted into male littermates of similar wt using the technique described by Fabre, Lim and Morris [6]. In the genetically dissimilar control group, kidneys from male Lewis rats were transplanted into female Brown Norway recipients. The donor left kidney was prepared by freeing the ureter and bladder from all peritoneal attachments. Renal artery and aorta were separated from renal vein and inferior vena cava by blunt dissection. Small arteries not involved in renal circulation were ligated and cut. Heparin (1,000 U/kg, Upjohn, Kalamazoo, Michigan, USA) was infused intravenously and the aorta was ligated above the left renal artery. The donor kidney was then flushed with 20 ml of an iced solution containing 10% mannitol, 1 mg of chloramphenicol, and 100 U of heparin in half-normal saline. The kidney, ureter and bladder were removed en bloc, including the renal artery with a 3 mm aortic cuff and the renal vein with a 3 mm vena caval cuff. The kidney was placed into an iced solution of 10% mannitol and saline.

Recipients were prepared by carefully separating the aorta and vena cava between the origin of the renal vessels and the bifurcation of the iliacs. An anastomosis was created between the recipient's aorta and the donor's aortic cuff; the recipient's vena cava was anastomosed to the donor vena caval cuff. Donor and recipient bladders were attached dome to dome. Total ischemic time averaged 40 min. Surgical mortality of the recipients was less than 20%.

Renal clearance and hemodynamic studies

Animals were anesthetized with inactin and a polyurethane catheter (PE-240) was inserted into the trachea to facilitate spontaneous respiration. The right carotid artery was cannulated to permit periodic sampling of arterial blood and to measure arterial blood pressure (Statham Strain Guage, Statham Instruments, Oxnard, California, USA). The right jugular vein was cannulated to infuse carboxyl-^{14}C-inulin and glycyl-^{3}H-PAH (New England Nuclear, Boston, Massachusetts, USA) in a solution of 5% mannitol and 0.45% saline at a rate of 0.025 ml · 100μg^{-1} · min^{-1}. Transplant and native ureters were cannulated to measure function of individual kidneys. The renal vein of the transplanted kidney or the left native renal vein in nontransplanted animals was cannulated with a curved 0.965 mm O.D. teflon catheter (Bradford Scientific, Marblehead, Massachusetts, USA) to collect samples for the determination of renal venous PAH concentration.

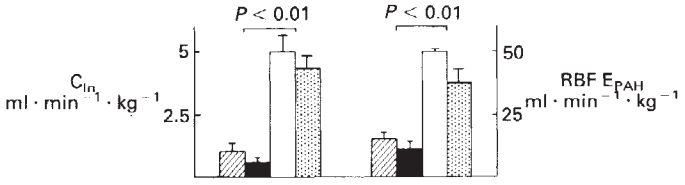

Fig. 1. *Lewis isograft GFR and RBF measured eight days after transplantation.* Bars indicated mean isograft RBF and C_{In} in animals with both native kidneys in situ (▨), with one native kidney in situ (■), following bilateral native nephrectomy (□), and following bilateral native ureteral obstruction (▩). Standard errors are indicated in the figure and *P* values are indicated where significant.

After a 45 min equilibration period, C_{In} and C_{PAH} were measured during two 30 min urine collections. Arterial and renal venous blood samples were obtained at the midpoint of each collection to determine renal PAH extraction. Sodium and potassium concentrations and osmolality were measured in blood and urine samples. Following renal clearance studies, all kidneys were excised, bivalved and fixed in buffered formalin for histologic evaluation. Three micron thick sections were prepared and stained with hematoxylin and eosin. Coded specimens were evaluated without knowledge of specimen source.

Analytical techniques

Tritium and ^{14}C radioactivity were measured in plasma and urine with a dual channel Isocap 300 liquid scintillation system (Nuclear Chicago, Chicago, Illinois, USA). Sodium in plasma and urine was analyzed with a lithium internal standard flame photometer (Instrumentation Laboratories, Lexington, Massachusetts, USA), and U_{Osm} and P_{Osm} were determined with a vapor pressure osmometer (Wescor, Wescor, Utah, USA).

Calculations and statistics

RBF was calculated as: $C_{PAH}/[E_{PAH} \times (1\text{-Hct})]$. Data are presented as means ± SE. Statistical significance was assessed using analysis of variance and Dunnett's test.

Results

Inulin clearance and RBF of Lewis isografts measured eight days after transplantation are shown in Figure 1 and Table 1. Inulin clearance by isografts transplanted into animals with either one or both native kidneys in situ was significantly decreased when compared with isografts transplanted into animals with bilateral native nephrectomy or with both native kidneys totally obstructed. Isograft RBF was similarly affected by the presence of either one or both functioning native kidneys. Thus, blood flow to isografts in animals with functioning native kidneys was significantly less than that to isografts in animals with bilateral native nephrectomy or to isografts in animals with non-functioning native kidneys.

Table 1. Excretory function and blood flow of transplanted (TP) Lewis rat kidneys and native kidneys from nontransplanted Lewis rates (NonTP) 8 days following surgery

	BP *mm Hg*	C_{In} *ml/min/kg/kidney*	C_{PAH} *ml/min/kg/kidney*	RBF *ml/min/kg/kidney*	V *μl/min/kg*	C_{Osm} *μl/min/kg*	$U_{Na}V$ *μEq/min/kg*	$\%FE_{Na}$
TP+SNNX (5)	108 ± 6	1.0 ± 0.3**	3.2 ± 1.1**	15.0 ± 2.9**	19 ± 2**	19 ± 4**	0.3 ± 0.1	0.6 ± 0.2
TP+UNNX (5)	107 ± 3	0.6 ± 0.1**	1.9 ± 0.5**	11.0 ± 3.0**	25 ± 6**	40 ± 10**	0.6 ± 0.2	0.6 ± 0.2
TP+BNNX (5)	107 ± 6	5.0 ± 0.7	17.8 ± 3.4	46.1 ± 3.4	238 ± 45	427 ± 58	5.1 ± 2.0	1.1 ± 0.5
TP+BNUO (6)	101 ± 4	4.3 ± 0.3	14.0 ± 1.6	38.3 ± 7.8	61 ± 18**	407 ± 102	0.4 ± 0.1	0.1 ± 0.1*
NonTP (4)	102 ± 8	5.3 ± 0.3	13.9 ± 1.2	31.6 ± 3.8*	72 ± 18**	227 ± 36	7.2 ± 3.2	0.9 ± 0.5
NonTP+UNNX (4)	113 ± 5	7.4 ± 0.5*	21.9 ± 1.0	41.5 ± 3.4	127 ± 32	390 ± 51	8.8 ± 4.6	0.8 ± 0.5

Symbols are: * $P < 0.05$, and ** $P < 0.01$ compared with TP+BNNX. Abbreviations are: SNNX, sham native nephrectomy; UNNX, unilateral native nephrectomy; BNNX, bilateral native nephrectomy; BNUO, bilateral native ureteral obstruction.

As demonstrated in Table 1, the clearances of inulin and PAH by Lewis isografts in animals with bilateral native nephrectomy were similar to that of nontransplanted kidneys and isografts in animals with hydronephrotic native kidneys. Isografts in animals with either one or both native kidneys had significantly decreased PAH clearance, urine flow rate, and osmolar clearance when compared with isografts from animals with bilateral native nephrectomy. In animals with hydronephrotic native kidneys, isografts had significantly lower urine flow rate and fractional excretion of sodium than isografts following bilateral native nephrectomy. Mean arterial pressure was essentially the same in all groups.

In nontransplanted animals, unilateral nephrectomy produced a 40% increase in C_{In} by the single remaining kidney (Table 1). However, C_{In} was not increased in isografts in animals with bilateral native nephrectomy when compared to nontransplanted controls with both kidneys intact. In contrast to GFR, RBF increased to isografts in animals with bilateral native nephrectomy and was similar to that of kidneys of nontransplanted animals following contralateral nephrectomy. Thus, inulin clearance by isografts in animals with bilateral native nephrectomy failed to demonstrate "functional hypertrophy" despite increased renal blood flow.

The clearances of inulin and PAH by the right native kidney in transplanted and nontransplanted animals is indicated in Figure 2. Excretory function of the right native kidney was not significantly altered by the addition of a single isograft. Unilateral nephrectomy produced a significant increase in both inulin and PAH clearance by the contralateral kidney. This "functional hypertrophy" of inulin and PAH clearance occurred despite the addition of a second transplanted kidney. Thus, the addition of a Lewis isograft did not prevent the increase in C_{In} and C_{PAH} observed after contralateral native nephrectomy.

Whole animal clearances of inulin and PAH by Lewis control rats and Lewis rats that received renal isografts are indicated in Table 2. Inulin clearance by animals that received a renal isograft (total of three kidneys) was not significantly different from Lewis rat kidneys that did not receive an extra kidney. The clearance of PAH by three kidney animals was also equivalent to that of two kidney animals. In nontransplanted animals subjected to contralateral nephrectomy, total inulin and

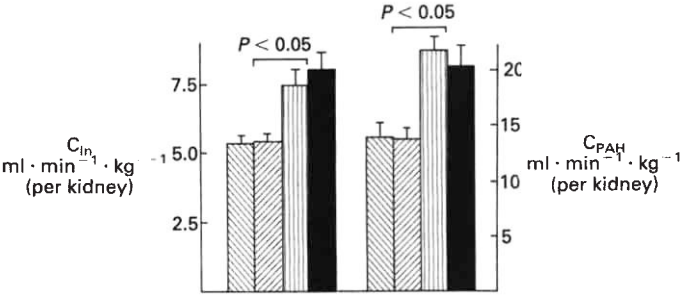

Fig. 2. *Inulin and PAH clearances by native right kidneys eight days following surgery.* Symbols are: control animals with both kidneys in situ ▨; transplanted animals with both native kidneys in situ ▨; control animals following contralateral nephrectomy ▥; and transplanted animals following contralateral native nephrectomy (■). Standard errors are indicated in the figure and *P* values are indicated where significant.

PAH clearances were reduced only to 75%, not 50%, of the level of nontransplanted animals with both kidneys intact. This occurred as a result of "functional hypertrophy" of the single remaining kidney. In contrast, animals with a single isograft and bilateral native nephrectomy had total inulin clearances that were 50% of normal with no evidence of "functional hypertrophy" of GFR.

Figures 3 and 4 are representative samples of isograft histology eight days following transplantation into littermates with functioning native kidneys in situ (Fig. 3) and following bilateral native nephrectomy (Fig. 4). As shown in Figures 3A and 3B, renal isografts from animals with functioning native kidneys in situ demonstrated a marked disruption of the renal architecture with evidence of diffuse tubular injury, patchy cortical necrosis, calcinosis and giant cell formation. However, isografts from animals following bilateral native nephrectomy (Figs. 4A and 4B) demonstrated preservation of normal renal architecture with no evidence of cellular infiltration. The morphologic appearance of isografts from animals with hydronephrotic native kidneys was similar to that of isografts from animals with bilateral native nephrectomy. In contrast, Lewis rat kidneys transplanted into genetically incompatible Brown Norway recipients (Figs. 5A and 5B) demonstrated histologic evidence of rejection with extensive interstitial infiltration by inflammatory

Table 2. Total excretory function of transplanted (TP) and nontransplanted (NonTP) Lewis rats 8 days following surgery

	C_{In} *ml/min/kg/animal*	C_{PAH} *ml/min/kg/animal*	$\dot{V}$ *μl/min/kg*	$\%FE_{Na}$	$U_{Na}V$ *μEq/min/kg*
TP+SNNX (5)	11.7 ± 0.5**	30.7 ± 1.8*	182 ± 43	0.6 ± 0.2	10.3 ± 4.5
TP+UNNX (5)	8.6 ± 0.8*	22.2 ± 2.3	190 ± 24	0.3 ± 0.1	4.5 ± 0.8
TP+BNNX (5)	5.0 ± 0.7	17.8 ± 3.4	238 ± 45	1.1 ± 0.5	5.1 ± 2.0
NonTP (4)	10.7 ± 0.6*	27.9 ± 2.4	144 ± 36	0.9 ± 0.4	14.4 ± 6.4
NonTP+UNNX (4)	7.4 ± 0.5*	21.9 ± 1.0	127 ± 32	0.9 ± 0.5	8.8 ± 4.6

Symbols and abbreviations are the same as Table 1.

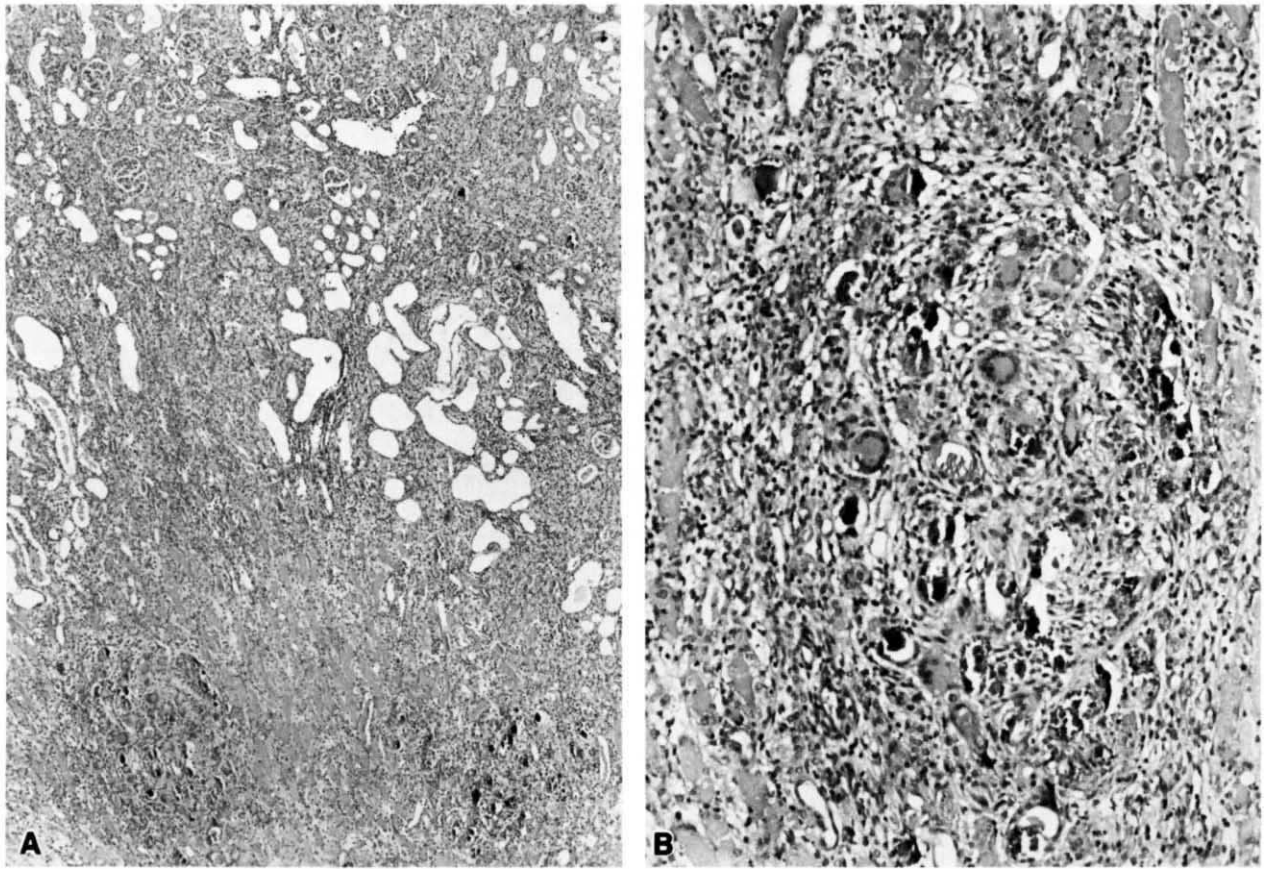

Fig. 3. *A Lewis rat renal isograft eight days following transplantation into a littermate with native kidneys intact.* There is disruption of the normal renal architecture with cortical necrosis, tubular injury and calcinosis with giant cell formation. (3 micron thick sections stained with hematoxylin and eosin; **A**, 40×; **B**, 130×).

cells, arteriolitis and venulitis. In these rejecting kidneys, RBF and GFR were negligible.

Discussion

The presence of native kidneys has been suggested to adversely affect renal graft survival but the mechanism for this phenomenon is unknown [1–4]. In a recent clinical study, bilateral native nephrectomy was associated with a highly significant increase in overall graft survival in first time recipients of cadaveric renal transplants [1]. This increase was most marked in patients who experienced acute tubular necrosis after transplantation, suggesting that native nephrectomy may influence the course of ischemic acute tubular necrosis in man.

Beneficial effects of nephrectomy have been described in other models of acute renal failure. In the unilateral cross–clamp model of ischemic renal failure, several studies have demonstrated that removal of the contralateral kidney results in enhanced recovery of function following ischemic damage [7–10]. Finn has reported that contralateral nephrectomy performed two weeks after ischemic injury results in increased GFR and renal plasma flow, and improves the histologic appearance of the post-ischemic kidney [8]. Fried, et al have

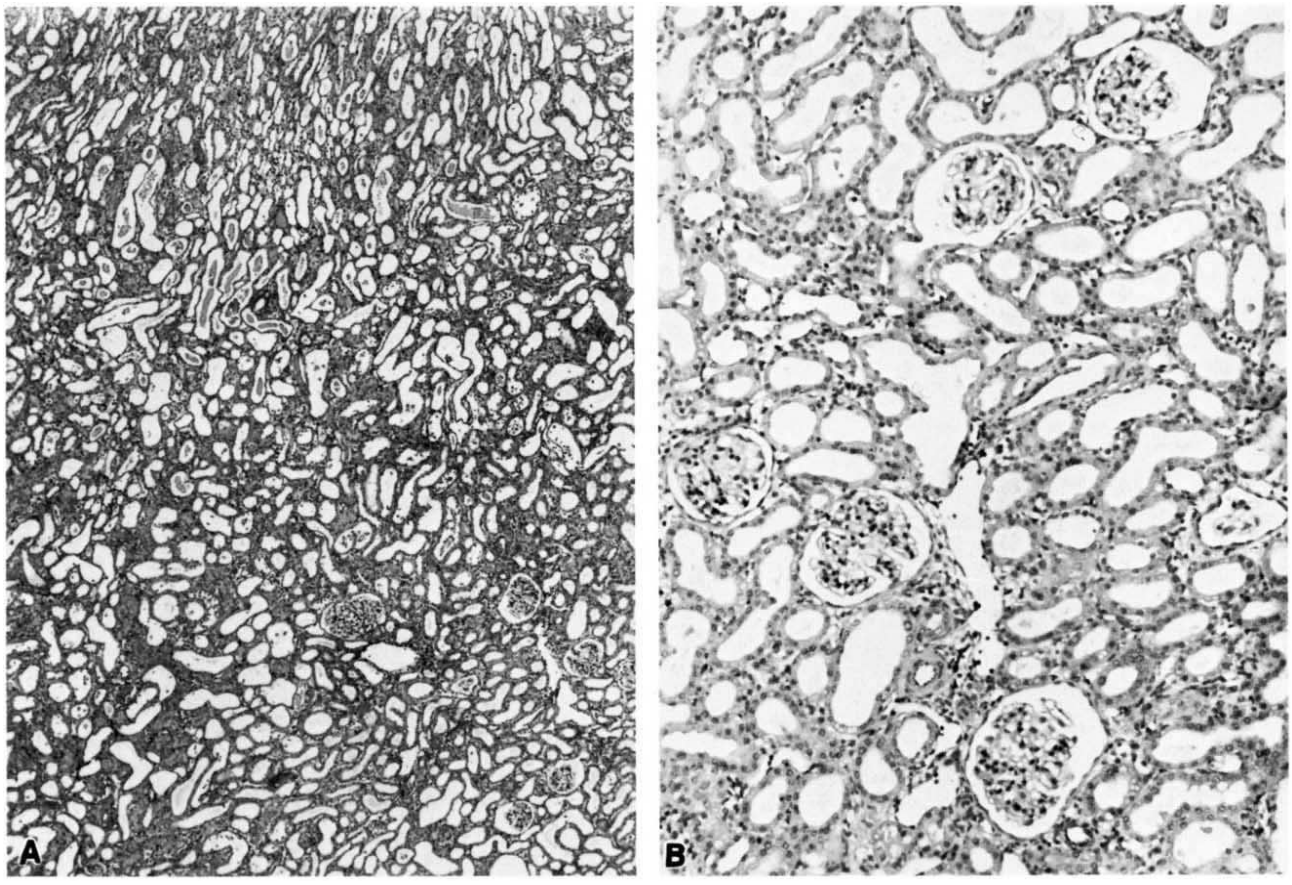

Fig. 4. *A Lewis rat renal isograft eight days following transplantation into a littermate with bilateral native nephrectomy.* The renal architecture is well preserved. (3 micron thick sections stained with hematoxylin and eosin, **A**, 40×; **B**, 130×).

demonstrated that this enhanced recovery from ischemia also occurs if contralateral nephrectomy is performed either 14 days before or immediately prior to renal artery occlusion [10].

In the present study, we examined renal isograft function in the presence of functioning or hydronephrotic native kidneys and after unilateral or bilateral native nephrectomy. Transplants were performed between littermates of a highly inbred strain of rats so that observed effects on transplant function would be independent of graft rejection. In this model, the presence of one or both functioning native kidneys was equally detrimental to isograft function. However, bilateral native nephrectomy preserved isograft GFR and RBF. Isograft function was similarly preserved in animals with total ureteral obstruction of native kidneys. Morphologically, isografts from animals with functioning native kidneys demonstrated extensive tubular and interstitial changes which were most consistent with chronic ischemic injury. Unlike rejecting allografts, there was no evidence of active inflammatory cell infiltration, arteriolitis, or venulitis. Thus, the detrimental effect of functioning native kidneys on renal isograft function may be mediated by potentiation of the severity of ischemic injury or impairment in recovery from ischemia. The effect appears to require normal native kidney function for its full expression.

A similar phenomenon has been observed by Klein and Gittes in a model of transplantation in rats [11]. They have previously reported that Lewis rat renal isografts, transplanted into recipients with functioning native kidneys undergo a significant reduction in size and weight, although graft function was not measured in their study. This effect was ascribed to the theory of renal counterbalance (proposed by Hinman) which suggested that the extent of recovery of injured renal tissue was dependent upon the total amount of residual functioning tissue [12]. Klein and Gittes suggested that the magnitude of reduction in isograft size was related to the amount of normal renal mass present in the recipient [11]. However, in the present study, the presence of one native kidney was equally detrimental to isograft renal function as the presence of both native kidneys.

In animals with obstructed native kidneys, isograft GFR and RBF were equivalent to values measured in isografts from animals with bilateral native nephrectomy. However, urine flow rate and fractional excretion of sodium were significantly lower in the animals with hydronephrotic native kidneys. The mechanism of this effect is not apparent from these studies. A variety of hormonal systems which can affect sodium excretion are stimulated by ureteral obstruction and may play a role in the observed antinatriuresis [13].

In the present studies, isografts functioned "normally" in the absence of native kidneys but did not behave like endogenous kidneys following contralateral nephrectomy. The GFR of isografts in animals with bilateral native nephrectomy was equivalent to that of nontransplanted controls with both kidneys intact. However, GFR did not increase to the same extent

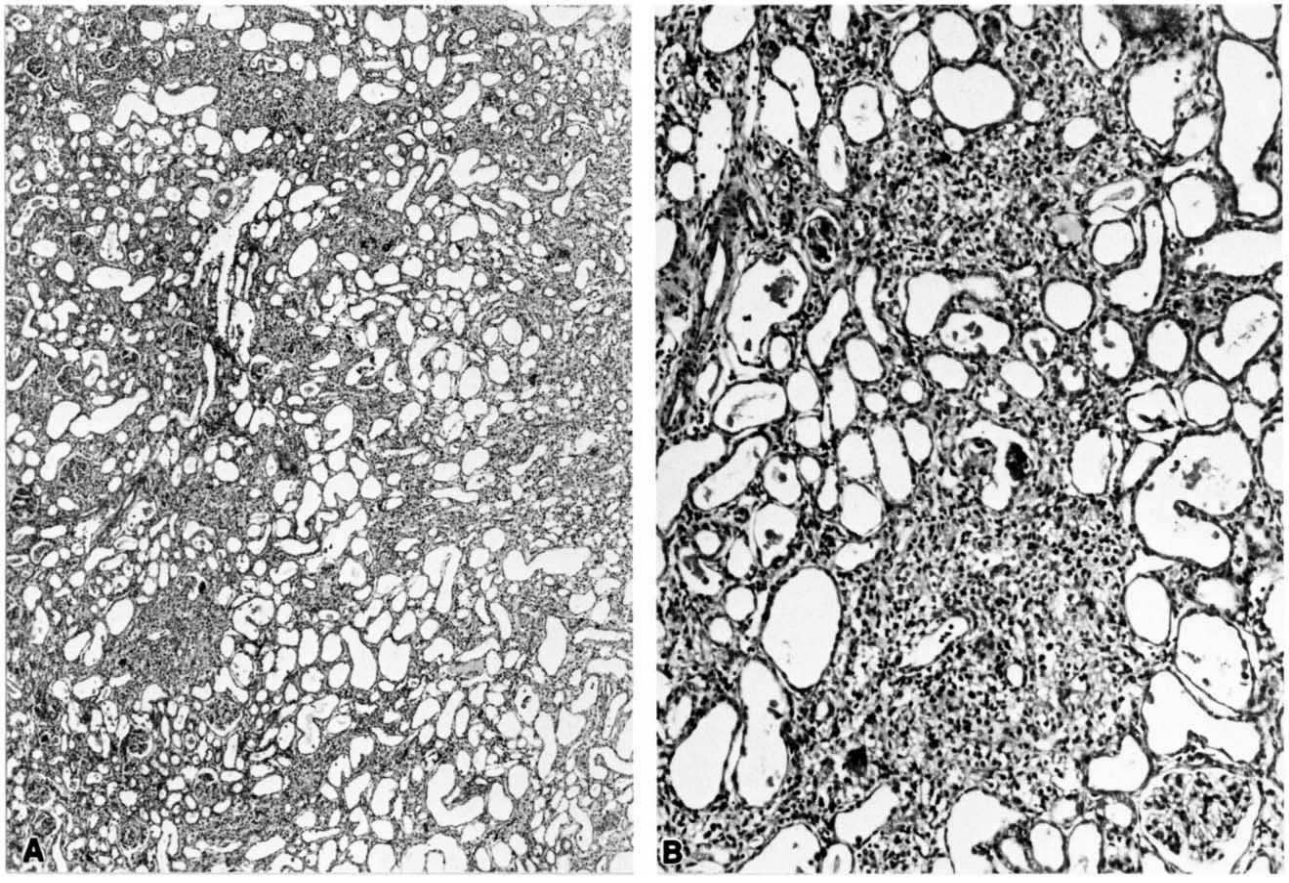

Fig. 5. *A Lewis rat kidney eight days following transplantation into a genetically dissimilar strain (Brown Norway) with native kidneys intact.* There is evidence of rejection with extensive interstitial infiltration by inflammatory cells, arteriolitis, and venulitis. (3 micron thick sections stained with hematoxylin and eosin; **A**, 40×; **B**, 130×).

as in nontransplanted kidneys following contralateral nephrectomy. Provoost, et al found a similar lack of "compensatory hypertrophy" of GFR by isografts [14]. In our study, this failure of GFR to increase occurred despite a significant increase in RBF. The mechanism which produces these alterations in renal and possibly glomerular hemodynamics is unknown.

The relevance of the present study to the clinical studies which show beneficial effects of native nephrectomy on human allograft survival is unclear. In our study, the detrimental effect of native kidneys on recovery from ischemia required the presence of native excretory renal function. However, the decrease in sodium excretion by animals with bilateral native ureteral obstruction demonstrates the importance of diseased native kidneys in influencing excretory function of the transplanted kidney. Other potential effects of native kidneys on immunologic function which might affect graft survival were not addressed in these studies.

In summary, the presence of functioning native kidneys had a significant detrimental effect on isogeneic rat renal transplants. This adverse effect occurred in the presence of either one or both functioning native kidneys. The morphologic appearance of these kidneys was consistent with chronic ischemic changes and did not suggest rejection. Thus, the detrimental effect of native kidneys on isograft function may have been related to potentiation of ischemic injury or inhibition of recovery from ischemia. Isografts in animals with bilateral nephrectomy or hydronephrotic native kidneys had "normal" renal function, similiar to that in nontransplanted animals with both kidneys in situ. However, isografts in animals with bilateral native nephrectomy failed to exhibit the "compensatory" increase in GFR typical of native kidneys following contralateral nephrectomy despite equivalent increases in RBF.

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