Abstract
Reflux nephropathy, renal scarring after urine infection, typically occurs in infancy. Although vesicoureteric reflux occurs commonly in kidney allografts, grafts have not previously been regarded as likely to be affected by reflux nephropathy, perhaps because older kidneys are considered to have matured out of the risk. Evidence that adult pigs remain at risk of reflux nephropathy challenges that assumption. We therefore reviewed the pathological findings in allograft nephrectomy specimens to look for evidence of reflux nephropathy, and sought evidence of focal transplant renal scarring in paediatric recipients who had a urine infection and vesicoureteric reflux. Consecutive allograft nephrectomy specimens (146) that had been removed between 1990 and 1999 were examined for evidence of reflux nephropathy, and relevant case notes were reviewed. Also, children with a renal transplant who had a urine infection were investigated for focal scarring by dimercaptosuccinic acid (DMSA) scanning and for reflux with a cystogram. Four transplanted kidneys from adult donors that were removed from adult recipients had developed changes consistent with reflux nephropathy. Of these, 3 also had definite evidence and 1 probable evidence of a glomerulopathy associated with hyperfiltration due to reduced renal mass. All 4 patients had had recurrent urine infection and the 2 assessed had had vesicoureteric reflux. Two children with renal transplants that also had urine infections and vesicoureteric reflux to their graft were shown to have sustained focal damage on DMSA scan, confirmed as reflux nephropathy scarring on biopsy in 1 case. The grafts were aged 14.4 years and over 16 years at the time of scarring. Reflux nephropathy can occur in previously healthy adult human kidneys after transplantation. Previous studies of the effect of vesicoureteric reflux on renal allografts were not designed to assess the possibility of mild or focal scarring.

Keywords
Urinary tract infection · Kidney transplant · Renal scarring · Reflux nephropathy · Vesicoureteric reflux

Introduction
Vesicoureteric reflux into renal allografts is common whether simple ureteroneocystotomies or anti-reflux anastomoses are used [1, 2, 3, 4, 5, 6, 7]. Avoidance of early leakage and late obstruction has been a greater consideration than prevention of reflux when ureteric anastomoses are fashioned [3, 6, 7]. Although there has been dispute whether vesicoureteric reflux into a transplanted kidney increases the risk of urine infection [3, 5, 7] or pyelonephritis [7, 8, 9], and whether it leads to hypertension [2] or loss of graft function [1, 3, 4, 5, 6, 7], little attention has been paid to the possibility that grafts with reflux may develop areas of inflammation or scarring with urine infection, i.e., reflux nephropathy, in the same way as the kidneys of young children [10]. Studies of reflux in allografts have been designed to look for changes in overall kidney function rather than for scars. None has used sensitive dimercaptosuccinic acid (DMSA) scanning, and few have looked systematically for scars in nephrectomy specimens [11]. It could be assumed that human kidneys mature out of their early vulnerability to develop scars when exposed to urine infections and vesicoureteric reflux, partly be-
cause of the clinical evidence that new scars are initiated only in young children [10, 12], and partly because a model that helps to explain the mechanism of scarring is based on vulnerable young animals, namely piglets [13]. At least some studies in allograft recipients have been designed with the assumption that mature donor kidneys are no longer at this risk [11].

We have shown that adult pigs are equally vulnerable to reflux nephropathy as piglets [14]. This makes it unlikely that adult human kidneys have matured out of the risk of developing reflux nephropathy. Since vesicoureteric reflux occurs in only about 1% of babies [15], 99% of transplanted kidneys are likely to be from donors without prior exposure to reflux. Therefore, if the recipient has a urine infection and the transplanted ureter refluxes, this is likely to be the first time that the graft kidney has been exposed to the set of conditions that are known to damage infant kidneys within a few days. We have therefore looked to see if typical reflux nephropathy does occur. First, we have undertaken a pathological review of allograft nephrectomy specimens, and second we have used DMSA scanning to screen transplanted children after urine infections.

Materials and methods

Allograft nephrectomy specimens

All specimens from one transplant unit between 1990 and 1999 inclusive were reviewed. Sections were examined for evidence of complications of abnormal urine drainage from the graft. These complications were hydronephrosis, acute pyelonephritis, and reflux nephropathy [16, 17]. Hydronephrosis was identified by uniform dilatation of the pelvis with flattening of medullary papillae and uniform chronic damage in the cortex. Acute pyelonephritis was identified by pus in tubules with a radial distribution through medulla and cortex. Reflux nephropathy was identified by radial areas in medulla and cortex of chronic inflammation and tubular atrophy, particularly seen as thyroidisation, with dilatation of tubules that contained casts. Clinical notes of patients with reflux nephropathy were reviewed.

Paediatric transplant cases

Children had either a DMSA or a diethylenetriaminepenta-acetic acid (DTPA) isotope scan within 10 days of receiving their kidney transplant. Children that later had a urine infection had a subsequent DMSA scan after a 3-month infection-free interval. Those cases where this indicated focal scarring then had a cystogram to evaluate whether there was vesicoureteric reflux. A percutaneous transplant biopsy was undertaken in 1 child to determine the cause of reduced renal function.

Results

Allograft nephrectomy specimens

In the 10 years studied there were 146 specimens. Drainage complications were identified in 18. Hydronephrosis was the commonest problem, seen in a pure form in 12. One other specimen had acute pyelonephritis and 1 kidney had areas of scarring related to obstruction of the lower ureter without clinical evidence of urine infection. Four specimens showed changes of reflux nephropathy and these are the basis of this study.

Clinical details are given in Table 1. All 4 patients were adult recipients of adult kidneys, all had repeated urinary tract infections, and all lost graft function before nephrectomy. One was shown to have vesicoureteric reflux on a cystogram and 1 was known to have had reflux for the 1st year post transplant since there had been a ureteric stent in place. The other 2 did not have cystography.

Pathological findings are given in Table 2. All had evidence of structural changes of reflux nephropathy in the nephrectomy specimen, with various other features of disorders of drainage (Fig. 1). The extent of changes within kidneys could not be assessed from sections. At

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex, age at transplant</th>
<th>Own disease</th>
<th>Sex, age, and cause of death of donor</th>
<th>Clinical course</th>
<th>Interval from transplant to nephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F 18 years</td>
<td>Subendothelial membranoproliferative glomerulonephritis</td>
<td>M 26 years accident</td>
<td>Repeated UTI, mostly E. coli; graft failed at 5 years</td>
<td>5 years 4 months</td>
</tr>
<tr>
<td>2</td>
<td>M 19 years</td>
<td>Megalocystis, megaloureter, reflux nephropathy</td>
<td>M 17 years road traffic accident&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Repeated Salmonella UTI; reflux on cystogram; graft failed at 13 years 6 months</td>
<td>14 years 2 months</td>
</tr>
<tr>
<td>3</td>
<td>F 35 years</td>
<td>Subendothelial membranoproliferative glomerulonephritis</td>
<td>M 17 years road traffic accident&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Repeated UTI, mostly E. coli; graft failed at 12 years 5 months</td>
<td>12 years 10 months</td>
</tr>
<tr>
<td>4</td>
<td>M 51 years</td>
<td>IgA nephropathy</td>
<td>F 48 years intra-cerebral haemorrhage</td>
<td>Ureteric stent at transplant; repeated UTI for 1 year; stent removed, well 7 years; then obstructed by stone; stone removed and given nephrostomy; nephrectomy at time of removal of empyema of gall bladder</td>
<td>8 years 7 months</td>
</tr>
</tbody>
</table>

<sup>(UTI urinary tract infection)</sup>

<sup><sup>a</sup> Not the same donor</sup>