Hypertension after renal transplantation in patients treated with cyclosporin and azathioprine

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Abstract

The incidence of hypertension was sought in 102 children who had undergone renal transplantation. Fifty five were being treated with cyclosporin and 47 with azathioprine, and they were followed up for a maximum of five years. After one year 35 of those receiving cyclosporin (64%) and 34 of those receiving azathioprine (72%) were hypertensive; after five years the figures were 5/6 (83%) and 25/35 (71%), respectively. Recipients of grafts from living related donors had a lower incidence of hypertension than recipients of cadaveric grafts. The incidence of hypertension was higher in patients with acquired original kidney disease than in children with congenital or familial diseases. In both groups creatinine clearance and the frequency of acute rejection episodes did not differ between normotensive and hypertensive patients. When the lowest concentrations of cyclosporin in whole blood were more than 400 ng/ml the incidence of hypertension one year after transplantation was higher. The incidence of hypertension after renal transplantation in children is higher than that reported in adults. Acquired original disease, transplantation of cadaveric grafts, and nephrotoxicity of cyclosporin are all contributory factors.

Hypertension after renal transplantation poses a considerable therapeutic problem to the nephrologist. Transient hypertension immediately after the transplant is found in almost all cases.[1] The main concern, however, is persistent hypertension with cardiovascular and cerebrovascular complications, and increased mortality and morbidity.[2 3] The aim of the present study was to investigate the incidence and possible causes of hypertension after transplantation in children and adolescents, and to compare two different treatment regimens—cyclosporin and azathioprine.

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Patients and methods

One hundred and two patients who received transplants between 1973 and 1987 were studied. Patients with grafts that had been functioning for less than a year were excluded. Seventy two patients who received transplants between 1982 and 1987 were given cyclosporin, but 10 lost their grafts because of irreversible rejection, and surgical and other complications, and seven patients were lost for follow up or received three drugs for immunosuppression (a combination of cyclosporin, azathioprine, and low dose prednisolone). Thus 55 patients could be evaluated in the cyclosporin study group. Ninety seven recipients were treated with azathioprine alone, and 62 grafts functioned for more than a year. Thirty five organs were lost because of irreversible rejection, thrombosis and recurrence of oxalosis, and 15 patients were lost to follow up. Thus 47 patients receiving conventional immunosuppression with azathioprine and high dose prednisolone could be evaluated.

Our treatment regimens for azathioprine and cyclosporin have been described elsewhere.[4 5] The mean (SD) age at the time of renal transplantation was 11·7 (3·4) years in the azathioprine group and 12·4 (4·0) years in the cyclosporin group. Histories were obtained from the case notes, and included information about hypertension before transplantation, and previous treatment with steroids. Hypertension was defined as persistent blood pressure readings above the 95th percentile (according to Horan *et al*[6]) that required antihypertensive treatment. Severe hypertension was defined as blood pressure readings necessitating treatment with three or more antihypertensive drugs in maximum or near maximum dosage.

Antihypertensive regimens varied, and the following drugs were used in a 'stepped care' approach: propranolol (dose range: 0·8–5·8 mg/kg/day), hydralazine (dose range: 0·9–5·9 mg/kg/day), nifedipine (dose range: 0·2–1·8 mg/kg/day), and α-methyldopa (dose range: 9–52 mg/kg/day). Two patients in each group were also given captopril (dosage range: 0·5–2·1 mg/kg/day). One patient with a membranoproliferative glomerulonephritis had a decreased glomerular filtration rate, but none of the others showed deterioration of renal function after taking captopril. Most of the patients received additional frusemide (dose range after the initial period of six weeks after transplantation: 0·9–6·2 mg/kg/day). Chest radiographs, electrocardiograms, and ophthalmic examinations were assessed for symptoms suggestive of hypertension.

Serum creatinine and sodium concentrations were measured by standard procedures, and urinary sodium excretion was calculated and correlated with body weight. Creatinine clearance was calculated by the method of Schwartz *et al*,[7] which is appropriate for children who have received transplants.[8] Cumulative doses of predinisolone were documented for each patient for each observation interval.

The Mann-Whitney U test, Student's *t* test, and Fisher's exact test were used to assess the significance of differences between and within groups. Values are given as mean (SD), or median and 95% confidence interval (CI).

Table 1 Original diseases in recipients of renal transplants

	Patients treated with cyclosporin (n=55)	*Patients treated with azathioprine (n=47)*
No (%) with congenital or familial renal disease:	38 (69)	31 (66)
Renal dysplasia or hypoplasia	14	10
Familial juvenile nephronophthisis	8	5
Oxalosis	0	1
Cystinosis	5	9
Obstructive uropathy	8	1
Familial nephritis	2	4
Infantile polycystic kidney	1	1
No (%) with acquired renal disease:	17 (31)	16 (34)
Proliferative glomerulonephritis	3	3
Focal segmental glomerulosclerosis	3	2
Haemolytic uraemic syndrome	4	6
Miscellaneous	7	5

Results

The distribution of original kidney diseases in the study groups is shown in table 1. About two thirds of the patients had congenital or familial diseases; there were no differences between the two treatment groups. The overall incidence of hypertension after transplantation is shown in table 2; there was no significant difference between the study groups. No change of incidence was seen in the azathioprine group during the five years of observation, whereas in the cyclosporin group the percentage apparently increased slightly. The difference between the first and fifth year, however, was not significant.

The incidence of severe hypertension requiring treatment with at least three antihypertensive drugs was higher among those receiving cyclosporin than among those taking azathioprine (table 3). In the azathioprine group there was only one patient who required more than two hypotensive drugs during the period two to four years after transplantation, but the difference was not significant.

Ten patients receiving cyclosporin and 17 receiving azathioprine received allografts from living related donors, the remainder receiving cadaveric grafts. Hypertension was significantly more common in recipients of cadaveric grafts who were taking azathioprine during the first two years after transplantation, and during the first three years in those taking cyclosporin (table 4). The difference persists during the following years, but seems to level off.

Bilateral nephrectomy was not routinely performed in our patients, but in a few (six taking cyclosporin and three taking azathioprine) bilateral nephrectomy was done before transplantation because of obstructive uropathy (n=4), infantile polycystic disease (n=2), or severe hypertension (n=3). In some other cases nephrectomy was done after transplantation, mainly because of severe hypertension. The incidence of hypertension in the small group of patients after bilateral nephrectomy is shown in table 5. Most of the patients remained hypertensive.

The role of the original disease that lead to endstage renal failure in causing hypertension after transplantation is shown in table 6. Acquired original kidney diseases were associated with hypertension more often than congenital or familial diseases. The difference was significant in the first year in children treated with azathioprine (table 6).

The cumulative prednisolone dose received by each patient each year is shown in fig 1. The mean dose in the azathioprine group was about

Table 2 Overall incidence hypertension in the two groups before, and up to five years after, transplantation*

	Before transplantation	*Years after transplantation*				
		1	*2*	*3*	*4*	*5*
Patients receiving cyclosporin	39/55 (71)	35/55 (64)	25/36 (69)	16/25 (64)	11/15 (73)	5/6 (83)
Patients receiving azathioprine	34/47 (72)	34/47 (72)	32/44 (73)	32/42 (73)	30/39 (77)	25/35 (71)

*No with hypertension/total No of patients.

Table 3 Incidence of severe hypertension in the two groups up to five years after transplantation*

	Years after transplantation				
	1	*2*	*3*	*4*	*5*
Patients receiving cyclosporin	4/55	3/36	2/25	2/15	1/6
Patients receiving azathioprine	0/47	1/44	1/42	1/39	0/35

*No with severe hypertension/total No of patients.
The results were not significant.

Table 5 Incidence of hypertension in patients who underwent bilateral nephrectomy before investigation*

	Years after transplantation				
	1	*2*	*3*	*4*	*5*
Patients receiving cyclosporin	3/6	3/5	1/3	1/2	1/2
Patients receiving azathioprine	3/3	2/3	2/3	2/3	—

*No with hypertension/total No of patients.

Table 4 Incidence of hypertension in patients with cadaveric kidneys compared with that among patients with kidneys from living related donors*

	Years after transplantation				
	1	*2*	*3*	*4*	*5*
Patients receiving cyclosporin:					
No (%) with cadaveric kidneys	33/45 (73)	24/30 (80)	15/20 (75)	9/12 (75)	3/3 (100)
No (%) with kidneys from living related donors	2/10 (20)	1/6 (17)	1/5 (20)	2/3 (67)	2/3 (67)
p Value	<0·01	<0·01	<0·05	1·0	1·0
Patients receiving azathioprine:					
No (%) with cadaveric kidneys	25/30 (83)	23/27 (85)	22/26 (85)	20/24 (83)	17/22 (77)
No (%) with kidneys from living related donors	9/17 (53)	9/17 (53)	10/16 (63)	10/15 (67)	8/13 (62)
p Value	<0·05	<0·05	0·2	0·4	0·5

*No with hypertension/total No of patients.

Table 6 Incidence of hypertension in patients with acquired kidney disease compared with that among patients with congenital or familial kidney disease*

	Years after transplantation				
	1	*2*	*3*	*4*	*5*
Patients receiving cyclosporin:					
No (%) with acquired kidney disease	12/17 (71)	10/13 (77)	6/8 (75)	4/5 (80)	1/1 (100)
No (%) with congenital kidney disease	23/38 (61)	15/23 (65)	10/17 (59)	7/10 (70)	4/5 (80)
p Value	0·7	0·7	0·7	1·0	1·0
Patients receiving azathioprine:					
No (%) with acquired kidney disease	15/16 (94)	13/15 (87)	13/15 (87)	12/14 (86)	10/13 (77)
No (%) with congenital kidney disease	19/31 (61)	19/29 (66)	19/27 (70)	18/25 (72)	15/22 (68)
p Value	<0·05	0·3	0·4	0·6	0·9

*No with hypertension/total No of patients.

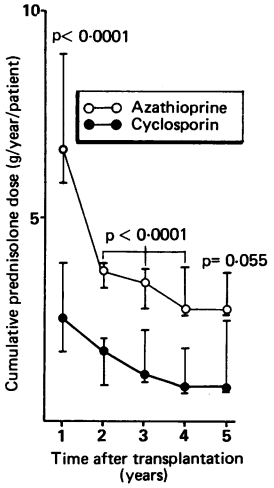

Figure 1 Cumulative prednisolone doses in patients receiving treatment with azathioprine and cyclosporin. Values are given as median and 95% confidence intervals.

twice as high as that received by the cyclosporin group. This difference is highly significant during the first four years. Comparing hypertensive and normotensive patients in each group separately, however, there was no correlation between hypertension with dose of prednisolone.

Graft function was assessed by calculation of the creatinine clearance from plasma creatinine concentration and body length. The creatinine clearance declined in both groups over the five years, but was significantly lower in the cyclosporin group compared with the azathioprine group (fig 2). Patients in the two groups were compared, measurements of glomerular filtration rate below 30 ml/min/1·73m^2 were associated with higher rates of hypertension (table 7).

The influence of cyclosporin on the development of hypertension was assessed by studying the concentrations of cyclosporin in the blood of both normotensive and hypertensive patients (fig 3); the mean concentrations were slightly higher in the hypertensive patients, but the difference was not significant. High concentrations of cyclosporin in blood were associated with a higher incidence of hypertension a year after transplantation (table 8).

The incidence of abnormal findings on chest radiography, ophthalmoscopy, and electrocardiography in recipients of transplants is shown in table 9. Retinal and electrocardiographic features of hypertension were consistently seen in 40–60% of patients. Radiological signs (vascular congestion and increased transverse cardiac diameter) decreased over the first two years and by five years were seen in only 16% of patients. There were no significant differences between normotensive and hypertensive patients within each group concerning daily urinary sodium excretion, urinary volume, and the number of acute episodes of rejection.

Hyper-reninism or complications of the graft's vascular anastomosis, or both, were found in four patients of the cyclosporin group and five patients of the azathioprine group. They were not serious and no specific measures were taken to correct the stenosis. Two children treated with cyclosporin and one treated with azathioprine experienced recurrence of original disease (membranoproliferative glomerulonephritis); all three were hypertensive.

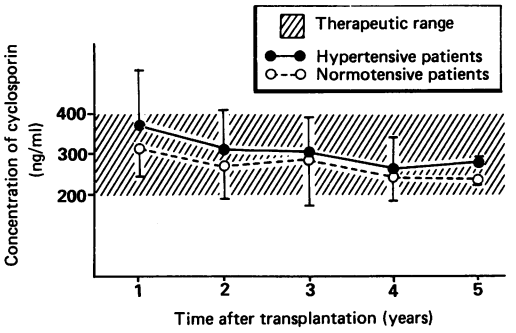

Figure 3 Cyclosporin concentrations in whole blood in normotensive and hypertensive patients projected on to the therapeutic range. Values are given as mean (SD).

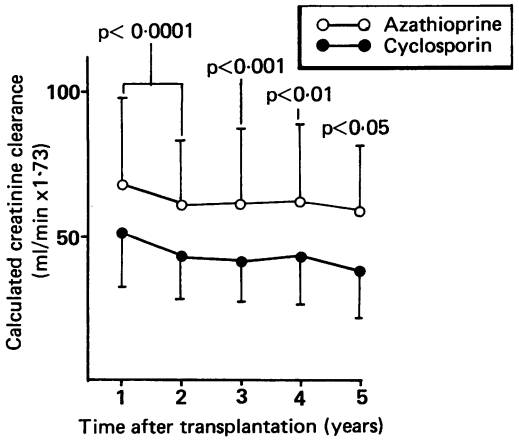

Figure 2 Graft function expressed as creatinine clearance in the two groups. Values are given as mean (SD).

Discussion

The incidence of hypertension after renal transplantation is generally reported to be higher in children and adolescents than in adults. Almost all the children who received renal transplants became hypertensive in the first few weeks after

Table 7 Incidence of hypertension in patients with glomerular filtration rate above and below creatinine clearance of 30 ml/min/1·73 m^2*

	Years after transplantation				
	1	*2*	*3*	*4*	*5*
No (%) with glomerular filtration rate ≤30	8/9 (89)	8/9 (89)	7/10 (70)	9/9 (100)	4/4 (100)
No (%) with glomerular filtration rate >30	61/93 (66)	49/71 (69)	41/57 (72)	32/45 (71)	26/37 (70)

*No with hypertension/total No of patients. The results were not significant.

Table 8 Incidence of hypertension in patients treated with cyclosporin. Those with high concentrations in whole blood (>400 ng/ml) are compared with those with low concentrations (<400 ng/ml)*

	Years after transplantation				
	1	2	3	4	5
No (%) with concentrations <400 ng/ml	25/44 (57)	19/29 (66)	14/22 (64)	10/14 (71)	4/5 (80)
No (%) with concentrations >400 ng/ml	10/11 (91)	6/7 (86)	2/3 (67)	1/1 (100)	1/1 (100)
p Value	<0·05	0·6	1·0	1·0	1·0

*No with hypertension/total No of patients.

Table 9 Incidence of other findings indicating past or present hypertension in recipients of renal transplants*

	Years after transplantation				
	1	2	3	4	5
No (%) with electrocardiographic changes	43/71 (61)	22/55 (40)	26/49 (53)	15/36 (42)	11/28 (39)
No (%) with radiological changes	18/61 (30)	9/52 (17)	10/53 (19)	7/36 (19)	4/25 (16)
No (%) with retinal changes	22/53 (42)	14/34 (41)	12/30 (40)	12/21 (57)	10/24 (42)

*No of abnormal findings/total No of examinations.

transplantation,[1] whereas hypertension in the same period in adults occurs in about 80%.[9] Persistence of hypertension in adult patients occurs in about half.[2 9] In a large series of children undergoing transplantation and treated with azathioprine Broyer *et al* found an incidence of late hypertension of 65%,[10] and sustained hypertension in children has been reported in up to 86%.[3] Our data confirm these findings (table 2). A slight but not significant increase in the development of hypertension over the years can be noted in the cyclosporin group. The incidence in the azathioprine group remained within the range 72–77%. The incidence of hypertension was higher in patients who received cadaveric grafts than in those who received grafts from living related donors in both study groups (table 4), particularly among those in the cyclosporin group during the first three years after transplantation. These findings accord with those of other investigators.[9–11] The beneficial effect of organs from living related donors could be related to fewer immunological injuries at vascular and parenchymal sites, or to shorter ischaemic time of the graft, or both.[12]

The results of investigation of the influence of original disease on hypertension after transplantation are conflicting. Though some authors have reported a similar incidence of hypertension in congenital and glomerular diseases,[9 10 12] others have found a stronger association between hypertension and glomerular diseases.[1 3] We classified our cases as congenital or familial, and acquired, diseases. Our findings support the idea that acquired diseases, assuming that they were associated with pathoimmunological mechanisms, are more often followed by hypertension after transplantation (table 6). Most of these patients had received steroids before transplantation. Recurrence of the original disease was the cause of the hypertension in three children.

Our data do not show clearly the beneficial effect of bilateral nephrectomy on the development of hypertension because there were too few cases for statistical evaluation (table 5). The effect of removal of the kidneys has, however, been thoroughly studied. Curtis *et al* investigated six patients before, and a mean (SD) of 4·5 (1·5) months after, bilateral nephrectomy.[13] They found that blood pressure fell and renal vascular resistance dropped. Renal plasma flow of the graft rose 77% at the same time. Other authors have confirmed these results.[9 14 15] Renin hypersecretion of the patients' own remaining kidneys is thought to be the main mechanism.[9 14 15] This is in accord with the observation that patients with uncontrollable hypertension on haemodialysis respond to nephrectomy.[16]

Hypertension as a result of long term steroid treatment is a well known feature. Some studies have shown a significant drop in blood pressure after switching to taking them on alternate days, the total dose remaining the same.[10 17 18] Patients taking conventional immunosuppression with azathioprine and high dose prednisolone are particularly at risk of developing steroid associated hypertension. As shown in fig 1, patients treated with azathioprine received significantly more steroids. We therefore regard treatment with steroids as an important contributory factor to the development of hypertension in conventional immunosuppression. Considering each study group separately, the hypertensive patients did not receive significantly higher cumulative doses of prednisolone.

It has been reported that normotensive recipients of grafts increase their blood pressure when put on a high sodium diet.[14] Thus the intake of sodium may also be a contributory factor. The daily sodium intake (as assessed by the daily urinary sodium excretion) was not higher in our hypertensive patients. With an assumed sodium intake of 3–5 mmol/kg/day, our patients were receiving a normal amount of sodium.

Renal artery stenosis can be the result of endothelial damage, atheromatous plaques, trauma during harvest and transplantation, disturbed haemodynamics during the end to side anastomosis, and immunological damage.[16] Broyer *et al* found a total incidence of 43/334 (13%) of appreciable stenoses in children who had received transplants, and 20% in grafts in hypertensive patients.[10] Henrikson *et al* detected 22/367 (6%) in a series of adult patients; nine of the 22 were normotensive.[19] In

our series four cases had mild to moderate renal artery stenosis.

The effects of cyclosporin on renal function have been the subject of numerous investigations. Continuous cyclosporin treatment leads to chronic vasoconstriction of the renal microvasculature.[9 20] This is partly mediated through increased sympathetic nerve activity and inhibited renal prostaglandin synthesis, and partly through stimulation of the renin angiotensin system.[21] Renal vascular resistance and arterial blood pressure are increased in consequence. In cardiac graft recipients receiving cyclosporin for more than 12 months, these effects are rarely reversible and potentially progressive.[20] Switching from cyclosporin to azathioprine after a certain period has been reported to cause a fall in renal vascular resistance and arterial blood pressure.[9 22] More recent data indicate that hypertension in patients treated with cyclosporin may be associated with a defect in renal sodium excretion.[23 24] The effect of dietary sodium restriction and antihypertensive treatment may thus be more pronounced in hypertension associated with cyclosporin. As an obvious sign of the influence of cyclosporin on the renal microvasculature, creatinine clearance was significantly compromised in the cyclosporin group (fig 2). The decline in renal function over five years, however, was parallel in the two groups. This indicates the existence of other factors in the azathioprine group. Figure 3 shows that hypertensive patients had slightly higher cyclosporin concentrations, although there was no significant difference. A higher percentage of patients with cyclosporin concentrations of more than 400 ng/ml were hypertensive (table 8). As doses of cyclosporin were reduced, the number of concentrations over 400 ng/ml decreased. There were therefore too few data to evaluate the influence of high cyclosporin concentrations after three years. The percentage of severe hypertension was higher in recipients treated with cyclosporin, indicating that cyclosporin has a role in the pathogenesis of hypertension (table 3).

Chronic rejection has been reported as a cause of hypertension in renal recipients of allografts in about 15% of adults,[19] and 59% in children.[10] Ingelfinger *et al* found a positive correlation between blood pressure, renal function, and the number of antihypertensive agents administered. They interpreted these results as an effect of chronic rejection.[1] In our study the creatinine clearance was not significantly lower in hypertensive patients than in normotensive patients. Glomerular filtration rate declined in both treatment groups, however. It may be that chronic rejection leading to progressive impairment of graft function could also be a cause of hypertension.

The long term outcome of renal transplantation depends on the control of hypertension. Strict observation on consistent treatment of the patients are therefore necessary. Our antihypertensive regimen varied; nowadays we start with frusemide because the renal function is usually reduced. If necessary, we then add nifedipine as a vasodilatator. If there is tachycardia, β-adrenergic antagonists (for example, propranolol) are considered. We may then give an additional vasodilatating agent (for example, hydralazine). Converting enzyme inhibitors (such as captopril) are used in refractory hypertension if renal function remains stable after an initial dose. Subsequent doses and intervals between them are adjusted according to the renal function.

The Statistical Package for the Social Sciences (x) software was supplied by SPSS Inc.

1 Ingelfinger JR. Hypertension in children with endstage renal disease. In: Fine RN, Gruskin AB, eds. *End stage renal disease in children*. Philadelphia: Saunders, 1984:340–58.
2 Kirkmann RL, Strom TB, Weir MR, Tilney NL. Late mortality and morbity in recipients of long-term renal allografts. *Transplantation* 1982;**34**:347–51.
3 Tejani A. Post-transplant hypertension and hypertensive encephalopathy in renal allograft recipients. *Nephron* 1983;**34**:73–8.
4 Offner G, Brandis M, Brodehl J, Krohn HP, Pichlmayr R, Tidow G. Nierentransplantation bei Kindern in Hannover 1970–1977. *Dtsch Med Wochenschr* 1979;**104**:393–401.
5 Hoyer PF, Offner G, Wonigeit K, Brodehl J, Pichlmayr R. Dosage of cyclosporin A in children with renal transplants. *Clin Nephrol* 1984;**22**:68–71.
6 Horan MJ, Falkner B, Kimm SYS, *et al*. Task force on blood pressure control in children. Report of the second task force on blood pressure control in children–1987. *Pediatrics* 1987;**79**:1–25.
7 Schwartz GJ, Haycock GB, Edelmann CM, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976;**58**:259–63.
8 Hoyer PF, Krohn HP, Offner G, *et al*. Renal function after kidney transplantation in children. A comparison of conventional immunosuppression with cyclosporine. *Transplantation* 1987;**43**:489–93.
9 Luke RG. Hypertension in renal transplant recipients. *Kidney Int* 1987;**31**:1024–37.
10 Broyer M, Guest G, Gagnadoux MF, Beurton D. Hypertension following renal transplantation in children. *Pediatric Nephrology* 1987;**1**:16–21.
11 Rikot S, Byrd L. Post-renal transplant hypertension. *N Engl J Med* 1976;**294**:342–8.
12 Jacquot C, Idatte IM, Bedrossian I, Weiss Y, Safar M, Bariety I. Long-term blood pressure changes in renal homotransplantation. *Arch Intern Med* 1978;**138**:233–6.
13 Curtis JJ, Luke RG, Diethelm AG, Jones P. Benefits of removal of native kidneys in hypertension after renal transplantation. *Lancet* 1985;**ii**:739–42.
14 Curtis JJ, Lukw RG, Jones P, Diethelm AG, Whelchel JD. Hypertension after successful renal transplantation. *Am J Med* 1985;**79**:193–200.
15 McHugh MI, Tanboga H, Marcen R, Liano F, Robson V, Wilkinson R. Hypertension following renal transplantation: the role of the host's kidneys. *Q J Med* 1980;**196**:395–403.
16 Waltzer WC, Turner S, Frohnert P, Rapaport FT. Etiology and pathogenesis of hypertension following renal transplantation. *Nephron* 1986;**42**:102–9.
17 Luke RG, Curtis JJ, Jones P, Whelchel JD, Diethelm AG. Mechanisms of post-transplant hypertension. *Am J Kidney Dis* 1985;**5**:A79–84.
18 McHugh MI, Tanbog H, Wilkinson R. Alternate-day steroids in blood pressure control after renal transplantation. *Proceedings of the European Dialysis and Transplant Association* 1980;**17**:496–501.
19 Henrikson C, Nilson AE, Thoren OK. Artery stenosis in renal transplantation. *Scand J Urol Nephrol* 1975;**29**:89–90.
20 Myers BD, Sibley R, Newton I, *et al*. The long-term course of cyclosporin-associated chronic nephropathy. *Kidney Int* 1988;**33**:590–600.
21 Siegel H, Ryffel B, Petric R. Cyclosporin, the renin angiotensin aldosteron system, and renal adverse reactions. *Transplant Proc* 1983;**15**(suppl 1):2719–21.
22 Chapman JR, Marcen R, Arias M, Raine AEG, Dunnil MS, Morris PJ. Hypertension after renal transplantation. *Transplantation* 1987;**43**:860–4.
23 Curtis JJ, Luke RG, Jones P, Diethelm AG. Hypertension in cyclosporine-treated renal transplant recipients is sodium dependent. *Am J Med* 1988;**85**:134–8.
24 Bennett WM, Porter GA. Cyclosporine-associated hypertension. *Am J Med* 1988;**85**:131–3.