**Letter and Reply**

**Is diagnosis and treatment of renovascular stenosis cost efficient?**

Sir,

The recent invited opinion on ‘Diagnosis and treatment of renovascular stenosis (RVS)—a cost-benefit analysis’ [1] raises some topical and important issues. Few would argue that an increased awareness of costs is necessary in all those practising medicine in the 1990s. However, many clinicians have an inherent uneasiness about combining economics and health care.

In recent years systematic literature reviews have helped highlight strengths and weaknesses in clinical research. The increasing demands on clinical trials’ methodology must be matched by similar demands on published economic evaluations. Both contribute to the evidence base for policy makers and guideline committees. Therefore when health economics is used, particularly by non-economists, the methods must be sound. It has recently been shown that this may not always be the case [2].

The evidence for economic evaluations should be sought systematically and weighted according to quality. Methods must be made explicit, and assumptions should always be accompanied by ‘sensitivity analyses’ to demonstrate how a variation in that assumption might have affected the results.

From the information given by Radermacher and Brunkhorst evidence was not systematically sought or weighted according to quality. Assumptions are acknowledged, but no attempt has been made to apply sensitivity analysis to them. For example, a figure of 2.6% is calculated as the percentage of patients with RVS who progress to ESRD. To calculate this requires knowledge of the number of patients with RVS in Germany and the proportion of incident ESRD patients with RVS. However, the authors use the proportion of prevalent ESRD patients with RVS when calculating the value 2.6%. This is clearly inappropriate. Patients with vascular disease have a much lower survival than those without. They therefore form a higher proportion of the incident compared to the prevalent population of patients with ESRD. Also, the denominator is based on the approximation that 20% of the German general population (80 million) have hypertension and 1% of such patients will have RVS. An absolute variation of 0.5% in the latter assumption could mean variation from 80,000 to 240,000 people—a three-fold difference. This has obvious implications for intervention costs, numbers progressing to ESRD and therefore overall conclusions.

Quantifying the uncertainty of such assumptions, and the impact that fluctuations in these assumptions have on results, is essential to inform decision-making. If we, as non-economists, chose to include economic evaluations in our work we must use the validated methods that already exist.

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**Reply**

Sir,

Dr Caskey correctly states, that the incidence rate of patients with renovascular disease requiring renal replacement therapy rather than the prevalence rate should be used to calculate the percentage of patients suffering from renal artery stenosis who will eventually proceed to end-stage renal disease. We actually used incidence data which were extracted from an US publication (Mailloux (1994) AJKD; 24 pp. 622) which is cited in the paper and reports an incidence rate of 10–15%. Unfortunately, incidence data are not available for the German population, as we have once more confirmed with ‘Quasi-Niere’, the German registry for patients with end-stage renal disease.

We agree with Dr Caskey that one should try to quantify the uncertainty of one’s assumptions. However, if the reported data show too great a variation, no conclusion regarding cost benefits could be drawn from them. We therefore think that an educated guess as to the ‘true’ numbers better serves the purpose of our review. We calculated the prevalence of patients with RAS in Germany assuming that 20% of the overall population suffer from hypertension and 1% of this number suffered from renal artery stenosis. There are five large studies reporting on the prevalence of RAS in a hypertensive population. The possible variation is actually larger than the one suggested by Dr Caskey, prevalence rates of renal artery stenosis in the hypertensive population ranging from 0.2 to 4% have been reported. Using this wide range of prevalence rates of renal artery stenosis in unselected hypertensive populations and assuming an incidence of renal artery stenosis in patients with end-stage renal disease ranging from 10 to 15%, a range of 0.6–19.4% of patients with RAS proceeding to end-stage renal disease could be calculated. This would amount to possible cost savings (reduced need for renal replacement therapy) in this patient group ranging from DM 2400 to DM 77600. Pick your choice.

Recalculating our data of cost differences between the different apparative screening tests, using the extreme ranges of these prevalence data, would alter the total cost to detect renal artery stenosis and perform angioplasty on a single patient as follows (data reported as ranges): Renovasography: DM 19818–34068; Spiral CT DM 15959–30209; NMR-Angiography DM 21792–36042; Colour duplex sonography DM 13773–28023; Captopril-enhanced scintigraphy DM 14719–28969. Prevalence rate after clinical screening however, has the greatest influence on total cost. Recalculating our data for a prevalence rate of renal artery stenosis after clinical screening ranging from 1% (i.e. no screening was performed) to 20%, the cost of colour duplex sonographic screening to detect and treat a single patient with renal artery stenosis would range from DM 28023 to 69356 and for a more costly apparative screening method...
like NMR-angiography it would range from DM 36042 to 22972.

We thank Dr Caskey for the opportunity to reemphasize the necessity of careful clinical screening as a first step in establishing the diagnosis of renal artery stenosis.

Letters

Increased plasma GDNF levels in patients with chronic renal diseases

Sir, Glial cell-line-derived neurotrophic factor (GDNF) is a member of the transforming growth factor (TGF) superfamily and is considered to be a physiological trophic factor for neurons [1]. During fetal development, GDNF is highly expressed in metanephric kidneys, as well as in the nervous system [2,3], and GDNF-deficient mice completely lack kidneys [4–6]. GDNF signalling is mediated through the c-ret proto-oncogene [7]. During kidney morphogenesis, c-ret and GDNF are expressed by abutting cellular population [9]. Ret mRNA is localized in the epithelial cells of the branching ureteric bud, whereas GDNF is produced by the surrounding metanephric mesenchymal cells [7]. Moreover, GDNF has been shown to be a growth factor for mesangial cells and thus has been implicated to be a player in the genesis of progressive renal damage [8]. However, little is known about GDNFs behaviour in the presence of renal dysfunction. We report here that chronic renal failure patients have very high plasma GDNF level.

Patients and methods. The plasma GDNF levels of 15 normal individuals who had normal routine biochemical values, and of 45 chronic renal failure (CRF) patients on regular haemodialysis (from 3 months to 15 years) were evaluated (mean age ± standard error of the mean (SEM), 60.2 ± 1.97 years). Of the CRF patients, 18 suffered from diabetic nephropathy (mean ± SEM, 65.8 ± 4.24 years), 11 from nephrosclerosis (mean ± SEM, 66.5 ± 4.52 years), and 16 from chronic glomerulonephritis (mean ± SEM, 56.3 ± 2.63 years). No acute disorders were present during the 1 month prior to the study. Blood samples of CRF patients were taken immediately before haemodialysis. Blood samples of normal subjects were taken at 9 am. The plasma was kept frozen at −80°C until assayed. GDNF was measured with a sandwich ELISA kit (Promega, USA) that detects human GDNF but not TGF-beta or nerve growth factor (NGF). The detection limit of GDNF assay was 2 pg/ml. TGF-beta-1 levels were quantified using ELISA (R&D systems, USA). Overall differences between the groups were analysed with the Mann–Whitney’s U test. Correlation coefficients between variables were calculated by Spearman’s non-parametric correlation analysis.

Results. Table 1 summarizes the plasma level of GDNF in control and CRF groups. GDNF was not detected in plasma from any of the healthy controls. Although we tried to detect the plasma GDNF using a concentrating membrane filter system (Amicon Centricup, USA), which increases the detection limit of GDNF assay to 0.5 pg/ml, we failed to detect a significant level of GDNF in any of the control samples studied. In contrast, tests of plasma from CRF patients showed that GDNF was present in 53% (24/45) of samples studied, with a range of 2–38 pg/ml (average 7.8 pg/ml).

<table>
<thead>
<tr>
<th>Condition</th>
<th>GDNF (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>(n=15)</td>
</tr>
<tr>
<td>Chronic renal failure; total</td>
<td>(n=45)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>(n=18)</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>(n=11)</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>(n=16)</td>
</tr>
</tbody>
</table>

Fig. 1. Correlations of plasma GDNF concentration with plasma TGFbeta-1 level in patients with CRF from diabetic nephropathy.
Continuous veno-venous haemofiltration versus continuous veno-venous haemodialysis in severe lithium self-poisoning: a toxicokinetics study in an intensive care unit

Sirs, Continuous haemodiafiltration in an intensive care unit (ICU) has been proposed for the treatment of acute lithium poisoning [1]. There is still no agreement concerning the usefulness of continuous veno-venous therapy (CVVT) with dialysis or filtration or intermittent haemodialysis (IHD) in lithium poisoning [2]. There may be haemodynamic consequences such as severe lithium poisoning collapse. Therefore, extracorporeal renal replacement therapy may be poorly tolerated [3]. We report a case of such intoxication treated with continuous veno-venous haemodiafiltration (CVVHDF) in which dialysis and filtration could be analysed.

Case. A 49-year-old woman under long-term treatment with lithium carbonate was admitted to the ICU for acute lithium self-poisoning. On admission she had cerebellar ataxia, temporal and spatial disorientation, agitation, myoclonic seizures, hypothermia, parkinsonian movements or electroencephalographic abnormalities. Serum biochemical showed: sodium 135 mmol/l, potassium 6.3 mEq/l, urea 13.6, creatinine 212 mmol/l, PaO₂ 83 mmHg, PaCO₂ 37 mmHg, pH 7.37 and bicarbonate 21.3. Serum lithium concentration was 4.14 mEq/l.

A total of 3000 ml 0.9% saline was infused for fluid expansion but 3 h later no clinical improvement had occurred despite a decrease in serum lithium concentration to 3.0 mEq/l. CVVHDF was performed. The blood circuit was connected to a polycrylonitrile haemofilter (Prisma M60 preSet-AN69 HF hollow fiber haemofilter/dialyser). The haemo-pump was a Prisma CPM-Hospal control unit (Cobe laboratories Inc). Pre-dilution replacement therapy and continuous infusion of 45000 IU calcium nadroparine per 24 h were performed. The filtration and dialysate regimens are shown in Table 1. The first hour’s regimen was a filtration therapy consisting of a blood flow rate of 150 ml/min and a replacement flow rate of 1000 ml/h without dialysate (CVVHF). The second hour’s regimen was a dia-


Comments. We evaluated plasma GDNF level from normal individuals and from CRF patients on regular haemodialysis. GDNF was not detected in plasma from any of the healthy controls. In contrast, tests of plasma from CRF patients showed that GDNF was present in approximately half the samples. The plasma GDNF levels in diabetic nephropathy, nephrosclerosis, and chronic glomerulonephritis were not significantly different. The levels of GDNF in the patient with moderate renal dysfunction and in CRF patients were similar (data not shown). We observed no significant correlation between plasma GDNF levels and renal, cardiac, or hepatic damage or plasma creatinine, BUN, or electrolytes (data not shown). Further lithium carbonate was administered to the ICU for acute lithium self-poisoning: a toxicokinetics study in an intensive care unit

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Table 1. Toxicokinetics of lithium self-poisoning treated by continuous veno-venous haemodiafiltration

<table>
<thead>
<tr>
<th>Time and regimens</th>
<th>Lithium concentration (mEq/l)</th>
<th>Urine output (ml/min)</th>
<th>Effluent output (ml/min)</th>
<th>Regimen clearances (ml/min)</th>
<th>Regimen lithium removal (mEq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>serum</td>
<td>urine</td>
<td>effluent (†1)</td>
<td>renal</td>
<td>CVVT</td>
</tr>
<tr>
<td>Admission</td>
<td>4.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid challenge</td>
<td>3.00</td>
<td>5.46</td>
<td>4.67</td>
<td>7.14</td>
<td>7.14</td>
</tr>
<tr>
<td>CVVHF (× 1 h)</td>
<td>2.74</td>
<td>4.58</td>
<td>2.42</td>
<td>6.60</td>
<td>16.67</td>
</tr>
<tr>
<td>CVVHD (× 1 h)</td>
<td>2.52</td>
<td>4.25</td>
<td>2.47</td>
<td>6.67</td>
<td>16.67</td>
</tr>
<tr>
<td>CVVHDF (1 h)</td>
<td>2.60</td>
<td>3.72</td>
<td>1.60</td>
<td>3.10</td>
<td>8.25</td>
</tr>
<tr>
<td>CVVHDF (× 3 h)</td>
<td>1.38</td>
<td>2.74</td>
<td>1.40</td>
<td>4.52</td>
<td>50.00</td>
</tr>
<tr>
<td>CVVHDF (× 7 h)</td>
<td>0.93</td>
<td>2.52</td>
<td>0.85</td>
<td>4.52</td>
<td>50.00</td>
</tr>
<tr>
<td>6 h after CVVT</td>
<td>1.49</td>
<td>2.74</td>
<td>1.40</td>
<td>5.95</td>
<td>50.00</td>
</tr>
<tr>
<td>10 h after CVVT</td>
<td>1.08</td>
<td>3.02</td>
<td>2.33</td>
<td>6.55</td>
<td>6.55</td>
</tr>
<tr>
<td>17 h after CVVT</td>
<td>1.00</td>
<td>3.24</td>
<td>2.55</td>
<td>7.94</td>
<td>7.94</td>
</tr>
<tr>
<td>Cumulative data</td>
<td>†6900</td>
<td>†34068</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*1000 ml/h ultrafiltrate and dialysate flow rates; †1000 ml/h ultrafiltrate and 2000 ml/h dialysate flow rates. Clearances are calculated as final effluent lithium concentration or final urine lithium concentration/serum lithium concentration obtained at the midpoint of the respective time period × achieved diuresis or effluent output over same time period.

Discussion. This case illustrates the efficacy and safety of CVVHDF in a grade 2 to 3 acute lithium overdose, as assessed by the classification of Hansen and Amdisen [4]. The indication for extrarenal support in our case was given by persistent myoclonic movements in the absence of encephalographic evidence of epileptic disorder, despite the observed decrease in serum lithium concentration after fluid loading [2,3]. Lithium is the highest of the alkali metals. It has a molecular weight of 6.94 Da, a volume of distribution of 0.8 to 1.2 l/kg and is not bound to plasma proteins [2]. Moreover, its 100% bioavailability and the absence of metabolism are theoretical indications for removal with dialysis or filtration [2,5]. In the present case, the performance of lithium elimination was directly correlated with the volume of ultrafiltrate exchanged and the dialysate flow rate. Lithium clearance was 14 ml/min during the first hour with 1000 ml/h ultrafiltration alone, 15 ml/min during the second hour with 1000 ml/h bicarbonate dialysis alone and 28 ml/min with 1000 ml/min ultrafiltrate plus 1000 ml/min dialysis (Table 1). Our data indicated that continuous dialysis with bicarbonate solution was as efficient and well tolerated as continuous filtration alone. The filtration associated with dialysis clearance was approximately equal to the totality of respective filtration and dialysis clearances (Table 1). The calculated pool of lithium removed was 2.42 mEq/h with CVVHF and 2.47 mEq/h with CVVHDF.

The clinical symptoms disappeared 4 h after initiation of CVVHDF. At this time the serum lithium concentration was 1.49 mEq/l (Table 1). There was no rebound phenomenon in our case, in contrast to intermittent HD [2,5]. The high permeability of the polycrylonitrile membrane and the low dialysis flow rate in CVVHF or CVVHD explained in our case why effluent lithium concentrations remained similar to serum concentrations throughout the entire procedure.

Decrease in serum pentosidine levels of ESRD patients during polysulfone haemodialysis

Sir, The advanced glycation end product (AGE) pentosidine, whose formation is closely related to oxidative processes and carbonyl stress [1], accumulates markedly in the albumin-
linked form (approximately 95%) and in the free form (approximately 5%) in the serum of patients with end-stage renal failure (ESRD) [2]. Albumin-linked pentosidine cannot be cleared during standard haemodialysis. By contrast, the free form of pentosidine is totally excreted via the glomerulus in patients with normal renal function. Therefore, free pentosidine levels increase as a result of decreased glomerular filtration rate. Although the albumin-linked pentosidine may not be removed through dialysis, the elimination of precursors causing its generation is possible using high-flux membranes for haemodialysis or haemofiltration.

After obtaining initial values from patients on dialysis with low-flux membranes (polycarbonate or cellulose), we investigated in a longitudinal study the influence of maintenance haemodialysis treatment on serum pentosidine levels using high-flux biocompatible polysulfone membranes (Superflux F800S and Highflux F60S, Fresenius Medical Care Germany; 6 months each). The membrane ultrafiltration coefficients were as follows: low-flux membranes: <5 ml/h*mmHg, F60S: 40 ml/h*mmHg, F800S: >60 ml/h*mmHg.

In eight diabetic patients (five females, three males, age: 61.5 ± 8.4 years) who had been on maintenance haemodialysis (4.8 ± 4.6 years), total pentosidine predialysis as well as free pentosidine pre- and post-dialysis serum levels were measured by high-performance liquid chromatographic assay [2]. Statistics was performed using the Wilcoxon test and Pearson correlation test. The total pentosidine levels are expressed as pmol/mg of total protein.

Total pentosidine serum levels of 20 healthy subjects (age: 58.2 ± 5.9 years) have been reported to be 1.57 ± 0.23 pmol/mg, whereas free pentosidine was not detectable [2]. In our patients on low-flux dialysis, the concentrations of total pentosidine (28.0 ± 13.4 pmol/mg) were found to be more than 15 times of those seen in healthy subjects.

Using the F800S dialyser, the pentosidine predialysis serum concentrations decreased significantly in the diabetic patient group as compared to values obtained with low-flux membranes (Figure 1). Four-month treatment with the F800S was associated with a 30% reduction in serum levels. Likewise, the predialysis serum levels of total pentosidine decreased with the F60S dialyser.

The total pentosidine serum levels, corrected for haemocencentration, remained constant during dialysis (e.g. F800S dialyser pre-and post-dialysis levels: 16.7 ± 4.5 pmol/mg vs 16.3 ± 3.3 pmol/mg).

Free pentosidine was cleared during dialysis by all three membranes used. Compared to low-flux dialysis (71.8%), the reduction rate was significantly higher when using F800S (80.5%) or F60S (78.8%). Predialysis total serum pentosidine correlated significantly with predialysis free serum pentosidine in our patient group (P < 0.001). Predialysis serum albumin levels remained constant over the study period.

Comment. Our results demonstrate that in dialysis patients serum pentosidine levels can be lowered by means of polysulfone high-flux membranes, with significant reductions obtained employing the Superflux F800S. Since more than 90% of circulating pentosidine is albumin linked, we assume that the formation of pentosidine-modified albumin is lower when using the F800S dialyser. On the one hand, the F800S is characterized by the highest reduction rate of free pentosidine as compared to the F60S and low-flux dialysers. On the other hand, free pentosidine levels correlate closely with the total amount of circulating pentosidine. These observations may indicate a possible link between the removal of free pentosidine and decreased total pentosidine levels resulting from dialysis using the F800S. The present study could provide evidence for reduced oxidative processes and decreased carbonyl stress associated with dialysis by means of the F800S, indicating that biocompatible polysulfone membranes may be superior to low-flux membranes, providing a lower risk for developing long-time complications, e.g. dialysis-related amyloidosis and atherosclerosis.

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**Fig. 1.** Total pentosidine predialysis serum levels in diabetic patients under haemodialysis treatment using low-flux (LF) and high-flux (F800S, F60S) membranes.
Neisseria subflava biovar perflava peritonitis in a continuous cyclic peritoneal dialysis patient

Sir,

Peritonitis is a major complication of chronic peritoneal dialysis. Although *Neisseria* species have been rarely implicated, they may cause peritonitis as demonstrated by the following case.

**Case.** A 45-year-old female with end-stage renal disease due to polycystic kidney disease had been treated with continuous ambulatory peritoneal dialysis (CAPD) since November 1997. The patient changed to continuous cyclic peritoneal dialysis (CCPD) in May 1998. There had been no previous episodes of peritonitis. In September 1998, the patient presented to the outpatient department with a 5-day history of abdominal pain and cloudy dialysis effluent. Physical examination revealed a temperature of 37.5°C, and abdominal tenderness with rebound tenderness. The peritoneal fluid white blood cell count (WBC) was elevated at 1.14 \times 10^9/l. A diagnosis of PD peritonitis was made, and after obtaining a peritoneal fluid culture, the patient was started on empiric antibiotic treatment with oral sulfamethoxazole/trimethoprim b.i.d. 400/80 mg.

Five days after the initial presentation the patient still had abdominal pain, fever was absent, but the peritoneal WBC count had increased to 2.48 \times 10^9/l. A Gram stain of the peritoneal fluid was negative. The initial antibiotic treatment was continued. One week after presentation, the patient was admitted to the hospital because of increasing abdominal pain. On admission the patient was moderately ill, blood pressure was 128/81 mmHg, pulse 84/min and temperature 37.9°C. Physical examination of the abdomen showed a normal catheter exit-site. There was marked abdominal tenderness and rebound tenderness. The peripheral WBC was 9.3 \times 10^9/l, with 87% polymorphonuclear neutrophils. Investigation of the urinary sediment was unremarkable, with a negative culture. The peritoneal fluid WBC count was 1.90 \times 10^9/l, the Gram stain showed no bacteria or yeasts. Abdominal ultrasound showed no evidence of peritoneal catheter tunnel abscess, or abscess elsewhere in the abdomen. It was concluded that the patient still had PD peritonitis. Consultation with the microbiology laboratory revealed that the peritoneal fluid cultures of the day the patient visited the outpatient department, as well as those taken 5 days later showed growth of a Gram-negative coccal organism.

It was identified as a *Neisseria* species, most probably *Neisseria steara*, *Neisseria mucosa* or *Neisseria subflava*. The strain was sent to the National Institute of Public Health and the Environment, Bilthoven, The Netherlands, which is the national reference centre. It was determined as a *Neisseria subflava biovar perflava* due to its colony morphology and yellow colour, two rapid test kids, API NH (BioMérieux S.A., Marcy, France) and Neisseria 4H, (Diagnostics Pasteur, Sanofi, Marnes-La Coquette, France), fatty chain analysis and sequencing of the first 600 base pairs of the 16S Ribosome DNA. The disk diffusion test zone for penicillin was zero and the Minimal Inhibitory Concentration (MIC) determined by Etest (AB BIODISK, Solna, Sweden) was 4 μg/ml, indicating resistance of this *Neisseria* for penicillin. The zone of the disk diffusion test indicated that the microorganism would be susceptible for ceftazidime. Therefore, the patient was treated during 14 days with a four times daily CAPD schedule with intraperitoneal administration of ceftazidime 50 mg/l in each 2-litre bag of PD fluid, after one intravenous dose of 1000 mg. One day after admission the abdominal pain was greatly diminished, the peritoneal fluid WBC count became normal (0.1 \times 10^9/l) at the fifth day of treatment. At the present 3-month follow-up the patient is doing well.

Comment. *Neisseria subflava* is generally considered to be a non-pathogenic micro-organism, present in the nasopharynx. *Neisseria subflava* includes vibians subflava, flava and perflava. In the present case we assume that *N. subflava biovar perflava* was the cause of this first episode of CCPD associated peritonitis, because the organism grew in the routine culture on two occasions, while no other organisms were cultured. Furthermore, clinical symptoms and evidence of peritonitis were only resolved after institution of appropriate antibiotic treatment. The source of the infection with this microorganism was not identified.

In the literature, we found no previous reports of peritonitis caused by *N. subflava biovar perflava*. One case of asymptomatic bacteriuria with this microorganism in a child with obstructive uropathy was found [1]. Another case reported peritonitis by *N. sicca* in a 3-year-old child, who was immunocompromised because of previous treatment with anti-thymocyte globulin and OKT-3 after renal transplantation [2]. In one adult patient who was immunocompromised because of chronic steroid use and hypocoomplementaemia, two episodes of *Neisseria cinerea* peritonitis have been described [3,4]. The patient we describe in this case report had no present or previous use of immunosuppressant drugs, nor were abnormalities in the complement profile or immunoglobulin levels found.

In summary, *N. subflava biovar perflava* should be considered as a possible causative micro-organism in peritonitis associated with peritoneal dialysis.

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Conversion between cyclosporin and tacrolimus—
30-fold dose prediction

Sir,

Both cyclosporin and tacrolimus-based immunosuppressive drug regimens can be used in renal transplantation. It may sometimes be desirable to convert patients from one drug to the other, either because of immunosuppressive failure or adverse effects. It is normally recommended that cyclosporin or tacrolimus are started at a dose according to body weight and then doses are adjusted according to blood levels. We wished to see if this practice might be improved. Previous clinical studies examining outcomes after conversion or comparing the efficacies of these two drugs have not reported relative dosing in individual patients [1–6].

We examined 38 conversion episodes. Twenty patients were converted from cyclosporin to tacrolimus for steroid or OKT3 resistant rejection between October 1994 and May 1997. These patients were between 1 and 48 months after transplantation. The protocol was to stop cyclosporin and start tacrolimus at a dose of 0.15 mg/kg/day in two divided doses. Eighteen patients were converted from tacrolimus to cyclosporin between January 1996 and May 1997. Tacrolimus was induction therapy for 3–6 months in 15 patients, and conversion was performed as a routine protocol. Tacrolimus had been used as rescue therapy in three cases, but was stopped because of adverse effects. The protocol for transfer was to stop tacrolimus and start cyclosporin at a dose of 5 mg/kg/day in two divided doses. Elective conversion was part of a protocol approved by the Research Ethics Committee.

We recorded the last dose and drug level before changeover, and then the dose and blood level of the new drug as soon as the treating clinician judged stable dosing had been achieved. Target trough whole blood levels for tacrolimus were 10–15 ng/ml immediately after changeover, and for cyclosporin 150–250 ng/ml. Assays were performed using standard assays (Abbott Laboratories, Maidenhead, UK for both drugs).

There was a correlation between the cyclosporin and tacrolimus doses required to achieve stable target drug levels ($r=0.67$, $P<0.001$). The mean cyclosporin dose was 31 times the mean tacrolimus dose (Figure 1).

Initial dosing by body weight resulted in a first blood level outside the therapeutic range in 22/38 (58%) of conversions. In particular, 9/38 (24%) of conversions resulted in an initial blood level of the new drug below our therapeutic range, which could be unsafe immunologically. Two patients had an initial cyclosporin trough levels of $>1000$ ng/ml, and three had tacrolimus levels of $>25$ ng/ml, clearly likely to be associated with toxicity.

For cyclosporin to tacrolimus conversion, a tacrolimus dose calculated by the cyclosporin dose divided by 30 was a better predictor than body weight dosing in 28/38 (75%) of cases.

It is perhaps not surprising that there is an association between the dosage requirements for these drugs, as their uptake in the bowel and elimination by the liver are dependent upon the cytochrome P450 pathway [7,8]. However, there are significant differences in the behaviour of the drugs, notably that cyclosporin is water insoluble and is delivered in an emulsion formulation, whereas tacrolimus is water soluble. An association between the dosage requirements of these drugs could not have been assumed without measurement in clinical practise, as we have done.

In conclusion, we have shown that the dosage requirements for cyclosporin and tacrolimus are strongly associated, and that more accurate and safer dosing for these drugs may be achieved on conversion by factoring the previous drug dosage by 30.

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Fig. 1. Individual patients’ tacrolimus and cyclosporin dose require-
ments before and after conversion. $r=0.67$, $P<0.001$. 
Spontaneous iliac artery dissection in a kidney transplantation treated with an endovascular stent

Sir.

External iliac artery dissection is a very rare vascular kidney transplantation complication. Mercus et al. [1] described two cases where this adverse event was related to prior traumatic handling (an arteriography and a vascular clamp). We report an unusual spontaneous external iliac artery dissection with acute graft dysfunction, corrected by an endovascular prosthesis.

A 58-year-old renal transplant male from a cadaver donor was admitted to the centre due to acute renal damage.

He had been transplanted 2 years before and had normal renal function, on prednisone and CyA therapy. There was no rejection episode. The primary renal pathology was unknown, though he suffered from atherosclerotic disease, high blood pressure on a single hypotensive drug (nifedipine) and hypercholesterolaemia on HMG-CoA reductase inhibitor treatment.

On a regular check-up, a bruit around the allograft was discovered. Blood pressure was 140/80 mmHg, total cholesterol was 270 mg%, and serum creatinine (SCr) and clearance creatinine (CCr) were 2.3 mg% and 39 ml/min, respectively. The CyA level was 200 μg/ml, while urinary sodium and sodium excretion fraction 14 mmol/l and 0.30%, respectively. A diagnostic angiography was carried out and showed a double channel in the right external iliac artery, 2 cm proximal to the allograft artery anastomosis. One of the lumens was blind at the distal end, suggestive of intimal dissection (Figure 1). Following systemic heparinization, a Strecker stent (8 × 40 mm) was advanced to the area of interest and expanded (Figure 2). Five days later, Scr and CCr were 1.1 mg% and 82 ml/min, respectively.

External iliac artery dissection after kidney transplantation should be suspected when hypertension becomes difficult to control, when renal function deteriorates, or when a graft bruit is detected [2]. Although allograft artery stenosis is the most common vascular complication, with a reported incidence between 1–25% [3], allograft intimal dissection is possibly presenting with greater frequency since percutaneous transluminal angioplasty (PTA) is becoming the first choice to treat allograft artery stenosis [4]. In our case, a graft bruit and renal ischaemia with increased SCr were discovered 2 years after the transplant surgery. There was no traumatic antecedent. Perhaps atherosclerotic disease and high blood pressure were decisive pathogenic factors. We decided on a vascular stent instead of surgery because of the localization of the lesion.

This is the first observation, among the 413 transplantations performed in our centre since 1983, of successful deployment of a stent in the treatment of an acute graft failure due to external iliac artery dissection.

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