cyclosporin-treated patients is a consequence of the cyclosporin-associated decrease of GFR, and that there is no evidence for impaired tubular handling of uric acid. Their conclusions are mainly supported by the fact that, in bone marrow transplant patients, the fractional clearance of uric acid remained unchanged over time, regardless of whether the patients were on or off cyclosporin A (CsA), and the absence of significant differences among the fractional clearance of uric acid in bone marrow transplant patients, renal transplant patients, and living related kidney donors. It is well established that with increasing severity of chronic renal failure, plasma uric acid increases progressively [2]. When hyperuricaemia is the result of reduced renal uric acid elimination, it may reflect abnormalities in the renal mechanisms for transport of urate in humans: glomerular filtration, presecretory reabsorption, secretion, and postsecretory reabsorption (four-components hypothesis). A reasonable assessment of the components of tubular urate transport is possible with the use of pharmacological tests such as probenecid (PB) and pyrazinamide (PZA) tests, even in patients with several degrees of renal failure [2]. In the paper by Zürcher et al. [1], only GFR measured by inulin clearance was performed, and as the other components were not investigated, a possible tubular dysfunction cannot be completely ruled out. Furthermore, in their work, they did not separate hyperuricaemic from normouricaemic patients, and differences in the renal handling of urate could have gone unnoticed.

When we studied a group of 133 renal transplant patients on CsA, with CCr between 40 and 120 ml/min [3], renal function measured by serum creatinine was poorer in hyperuricaemic than in normouricaemic patients (1.6±0.4 vs 1.2±0.3, p < 0.001), and fractional excretion of urate was lower (8.2±3.0% vs 9.3±3.2%, p < 0.05). The renal handling of urate was assessed in 35 patients (12 normouricaemic on AZA, nine normouricaemic on CsA and 12 hyperuricaemic on CsA) by a combined PZA and PB test [4]. The combined test showed a lower fractional excretion of urate during the maximal PB-induced uricosuria (p < 0.05), and a lower urate secretion (p < 0.05) in hyperuricaemic patients on CsA than in the other two groups of normouricaemic patients. There were no differences among groups either in the presecretory reabsorption or in the post-secretory reabsorption. In these patients, plasma uric acid was related to serum creatinine (r = 0.76, p < 0.001) and to secretion (r = 0.66, p < 0.001). Although interpretation of combined tests should be made with caution [5], our results suggest that decrease of urate secretion plays an important role in urate retention. Similar findings have been reported in patients with essential hypertension, in which serum uric acid related inversely to fractional excretion of uric acid and urate secretion was significantly reduced in hyperuricaemic patients [6]. Messerli et al. [7] think that a reduction in renal cortical blood flow reduces the delivery of urate to the site of tubular secretion and limits urate secretion. A similar vascular effect could be induced by CsA, which could result in an impairment of urate secretion. Nifedipine, which improves haemodynamic disturbances, increases tubular secretion, but as it increases reabsorption of secreted urate by the same amount, it does not normalize serum uric acid [8].

Reply by author

Sir,

We agree with Marcén et al. on the high prevalence of hyperuricaemia in CsA-treated patients, and on the validity of the four-components hypothesis in renal urate excretion. In our study we did not find any difference in fractional clearance of uric acid between CsA-treated patients and different groups of patients not treated with CsA at comparable renal function. Consequently we concluded that tubular dysfunction can be ruled out as a mechanism in the pathogenesis of hyperuricaemia. The fractional clearance of uric acid is the result of the 'overall' renal handling of uric acid, i.e. filtration, resorption, and secretion; in the absence of a difference in the fractional clearance of uric acid between CsA-treated patients and non-CsA-treated patients, we conclude that there is no evidence to point to impaired tubular handling of uric acid.

Based on their own study results, Marcén et al. suggest that a difference in renal handling of uric acid exists between hyper- and normouricaemic patients, which results from impaired tubular secretion of uric acid in CsA-treated patients. Their hyperuricaemic CsA-treated patients had higher serum creatinine levels, a higher prevalence of hypertension, and higher diuretic use than their normouricaemic patients [6]. As for the finding of diminished fractional excretion of uric acid, this again was found in their hyperuricaemic patients (i.e. with a higher prevalence of hypertension and diuretic use). Hypertension and diuretic use, however, are well-known factors favouring uric acid retention, thereby explaining small differences in the fractional clearance of uric acid.

As for the assessment of tubular handling of uric acid by the combined PZA and PB test, we can only underline the statement of the authors that results should be considered...
cautiously. Moreover, in this test, their hyperuricaemic patients had significantly lower urine output than their normouricaemic patients, making interpretation of results even more difficult.

In conclusion, the data by Marcén et al. confirm our finding that it is mainly renal function (i.e. GFR) that is responsible for the higher prevalence of hyperuricaemia in CsA-treated patients, and that diuretic use and hypertension are the most important confounding variables in this context.

R. M. Zürcher