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Effect of cyclosporin A on proteinuria in patients with Alport's syndrome

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Abstract. Eight patients with Alport's syndrome and massive proteinuria (129 ± 60.57 mg/m² per hour) were treated with cyclosporin A (CyA) for 8 months. The average dose of CyA administered to all patients was 4.21 ± 0.26 mg/kg per day and blood CyA levels of 63.4 ± 4.1 ng/ml were attained. In five patients, proteinuria abated during the 3rd week of treatment. In the remaining three, all of whom had low creatinine clearance (82.0, 46.0 and 43.2 ml/min per 1.73 m² respectively), proteinuria persisted but at levels lower than before treatment: 32.5 ± 15.9 mg/m² per hour versus 183.3 ± 29.7 mg/m² per hour. No permanent decrease in creatinine clearance was observed in any of these patients throughout treatment. In those patients in whom proteinuria abated, it reappeared 2 weeks after discontinuation of CyA treatment. We observed no significant increases in angiotensin II plasma levels in our patients during CyA administration. Although we have shown that CyA will reduce massive proteinuria in patients with Alport's syndrome, we cannot yet recommend its use as a therapeutic measure.

Key words: Alport's syndrome – Cyclosporin A – Proteinuria

Introduction

Our experience of Alport's syndrome is based on the study of 41 patients, in all of whom the presence of massive permanent proteinuria, unrelated to macroscopic haematuria, constituted an unequivocable sign of onset of and progression towards renal failure [1]. Our observations, and those of other authors [2–7], on the effect of CyA on proteinuria in nephrotic syndrome due to minimal lesions, led us to consider the possible beneficial effect of CyA on proteinuria in Alport's syndrome. The hypothetical haemodynamic effects of CyA [8–10] prompted us to study the possible changes in angiotensin II levels in our selected patients.

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Patients and methods

The diagnosis of Alport's syndrome was based on the presence of haematuric nephropathy, a family history of renal involvement, renal insufficiency in the propositus or in a sibling, neural hearing loss in the propositus or in a sibling, membrane thickening of the glomerular basement by electron microscopy with splitting and splintering of the lamina densa [1, 11–14].

Eight patients met these criteria and were selected because of the presence of massive persistent proteinuria which reached nephrotic range (>40 mg/h per m²) [15]. The disease was inherited through the mother in these eight selected patients, and family history of renal involvement and neural hearing loss was proved in three generations of each family.

Proteinuria was measured in a 24-h urine collection by sulphosalicylic acid precipitation and turbidimetry. Nephrotic range proteinuria was defined as greater than 40 mg/h per m²; hypoalbuminaemia as a serum protein at less than 2.5 g/dl [15]. Creatinine clearance was calculated from the serum creatinine concentration and rates of creatinine excretion over a 24-h period. The maximum urinary osmolarity was measured after a 10 h nocturnal hydropenic period, and urine was investigated for a cryoscopic decrease. Hearing loss was bilateral and neurogenic, affecting mainly high and middle frequencies. CyA treatment was initiated after informed parental consent had been obtained, and was maintained for 8 months. The patients initially received 5 mg/kg per day, in two oral doses. In each patient the daily dose of CyA was adapted in order to maintain blood levels between 50 and 100 ng/ml throughout treatment. CyA was measured in total blood by specific monoclonal radioimmunoassay (RIA). Regular evaluation of renal and liver function was performed. Angiotensin II was measured by RIA, prior to CyA administration and after 1 month of treatment.

Results

The clinical features of these eight patients (mean age 11.2 ± 4.27 years) at the beginning of the study are shown in Table 1. Arterial blood pressure was normal in all patients except one who required antihypertensive therapy; six patients had nerve deafness. Creatinine clearance was

Table 1. Clinical information at presentation and prior to the administration of cyclosporin A (CyA)

Patient no.	Presentation		Laboratory data prior to CyA administration			
	Sex/age (years)	Features[a]	Total serum protein g/100 ml	Serum albumin g/100 ml	Proteinuria mg/h per m^2	MxUOSM mosmol/kg
1	M 6	A	5.0	2.0	123	953
2	M 7	N	6.8	4.0	46	1010
3	M 7		6.5	4.5	76	1212
4	M11	N	6.9	3.9	70	1080
5	M12	N	7.1	4.4	150	980
6	M14	N, A	5.1	2.2	172	920
7	F16	N	7.2	3.7	193	600
8	M17	N, BP	6.3	4.1	207	400

A, Hypoalbuminaemia; N, nerve deafness; BP, hypertension; MxUOSM, maximum urine osmolarity
[a] All presented with haematuria and proteinuria

Table 2. Creatinine clearance, proteinuria and angiotensin II levels during CyA treatment

Patient no.	Creatinine clearance (ml/min pr 1.73 m^2)			Proteinuria mg/h per m^2			Angiotensin II ng/ml per hour	
	Before CyA	After 3* weeks	After 8 months	Before CyA	After 1** week	After 8 months	Before CyA	After 1*** month
1	110.9	117.0	112.0	123	0.0	0.0	1.7	1.5
2	92.5	103.2	98.9	46	0.0	0.0	1.6	1.8
3	120.3	123.7	114.3	76	0.0	0.0	0.6	0.5
4	128.6	126.6	116.3	70	5.5	19.1	1.4	1.0
5	82.0	84.7	81.7	150	15.5	20.2	0.4	0.4
6	140.8	138.9	136.7	172	0.0	0.0	0.8	0.5
7	46.0	44.8	45.1	193	35	40	0.9	1.4
8	43.2	45.1	45.3	207	47	42	1.3	1.7

* P NS vs before CyA; ** P <0.001 vs before CyA; *** P NS vs before CyA
NS, Not significant

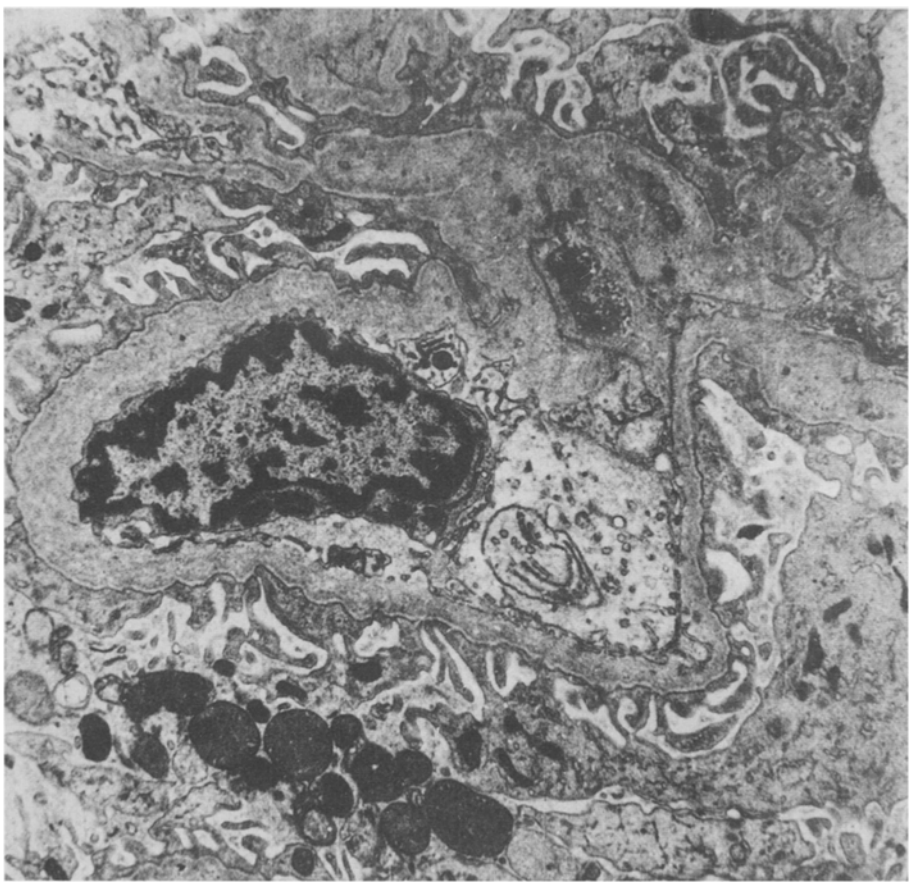

Fig. 1. Electron micrograph of patient no. 4: capillary loop showing irregular width and margins of the glomerular basement membrane, and apparent splitting and splintering of the lamina densa (uranyl acetate, ×7400)

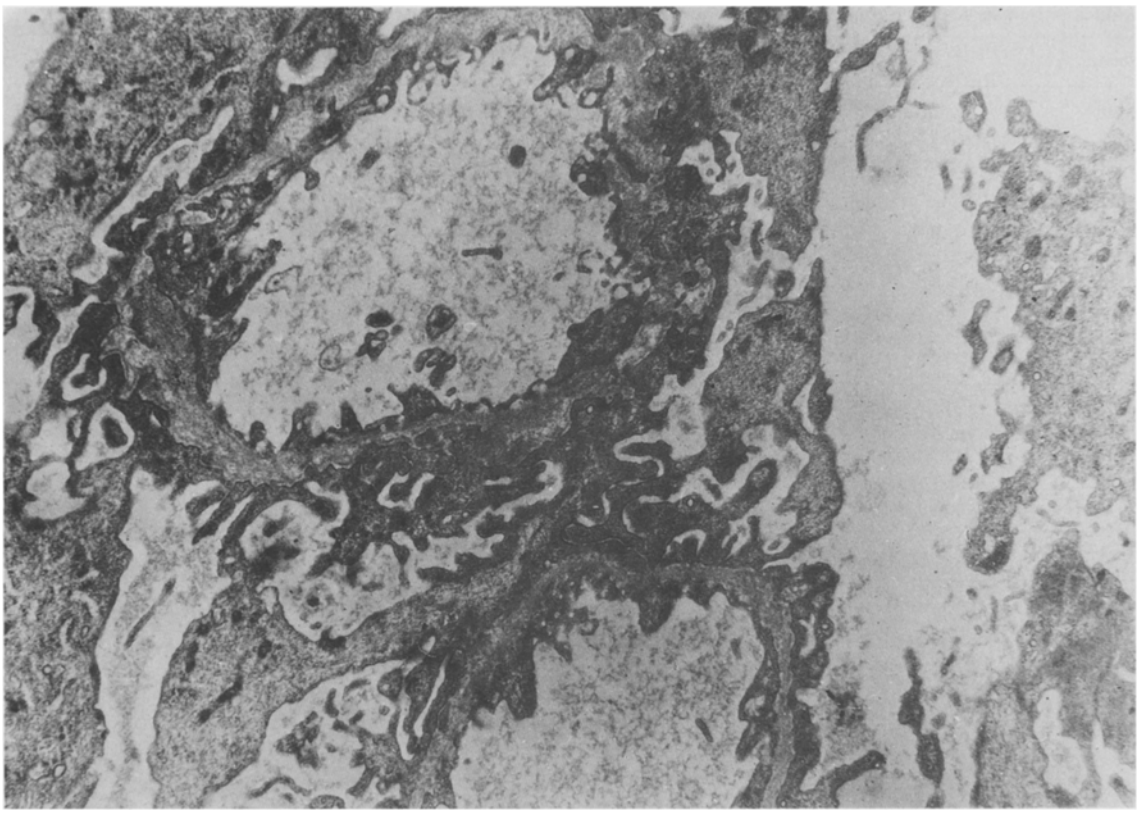

Fig. 2. Electron micrography of patient no. 7: capillary loop showing irregular thickening and thinning of the glomerular basement membrane, and splitting and splintering of the lamina densa (uranyl acetate, ×7400)

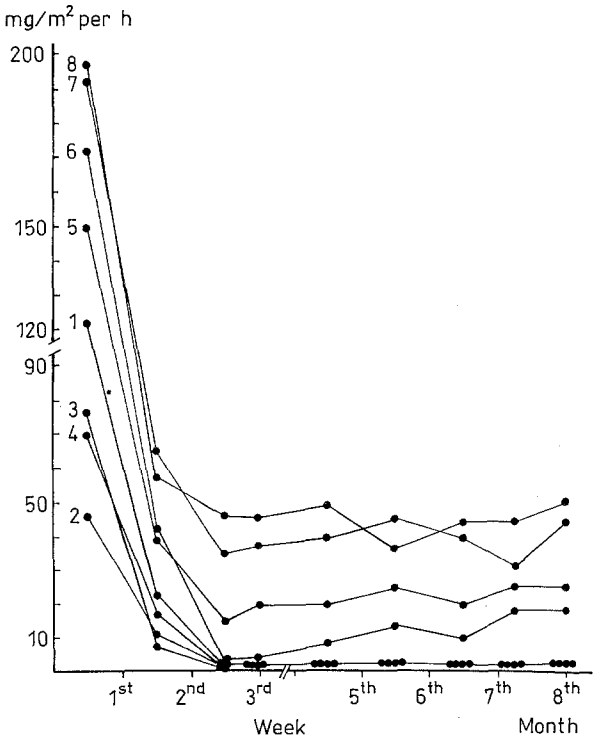

Fig. 3. Effect of cyclosporin A on proteinuria in all eight patients with Alport's syndrome

normal in five patients and moderately low in the other three. Maximum urinary osmolarity was normal in six patients (1025.8 ± 110.4 mosmol/kg) and decreased in two of the patients with low creatinine clearance (patients 7 and 8, Table 2).

Macroscopic haematuria was present in all patients. Proteinuria had been present for 2 years in four patients (nos. 1–4) and up to 6 years in the remaining four. All eight patients underwent renal biopsy prior to CyA administration. Moderate or light focal and segmental glomerular hypercellularity was observed by light microscopy in six patients; the remaining two (patients 7, 8) had focal and segmental lesions of the tuft, due to marked thickening of the glomerular basement membrane and mesangial matrix associated with hyaline deposits and collagen of capillary loops. Immunofluorescence was negative in all patients. Electron microscopy showed irregular thickening and discontinuity of the glomerular basement membrane, and splitting and splintering of the lamina densa of the glomerular basement membrane in all patients [1, 12–14 (Figs. 1, 2)].

During the 3rd week of CyA administration proteinuria abated in five patients (nos. 1–4 and 6, Fig. 3). In the remaining three patients (nos. 5, 7, 8) who presented with low creatinine clearance, proteinuria, although positive (32.5 ± 16.0 mg/h per m^2; 15.5, 35 and 47 mg/h per m^2, respectively), was markedly decreased when compared with previous values (183.2 ± 29.7 mg/h per m^2; 150, 192 and 207 mg/h per m^2; $t = 7.75$; $P < 0.001$). After 8 months

of CyA administration, proteinuria remained negative in patients 1, 2, 3 and 6, minimal (19.1 mg/h per m^2) in patient 4, and there were no significant changes in the other three. CyA therapy was withdrawn at this point and proteinuria returned to the levels observed prior to CyA therapy.

The nephrotic syndrome, present in only two patients (nos. 1, 6) disappeared after 3 weeks of CyA administration. Creatinine clearance remained unchanged in four patients (nos. 2, 3, 4, 6; 116.7 ± 22.9 ml/min per 1.73 m^2 vs 120.5 ± 20.5 ml/min per 1.73 m^2, NS). In the other four patients (nos. 1, 5, 7, 8), creatinine clearance decreased transiently (48.8 ± 19.5 ml/min per 1.73 m^2 vs 70.5 ± 32.2 ml/min per 1.73 m^2) this coincided with high initial blood CyA levels (176.7 ± 198.9 ng/ml). Once the CyA dosage was reduced, creatinine clearance returned to 72.9 ± 34.8 ml/min per 1.73 m^2 (initial value 70.5 ± 32.2 ml/min per 1.73 m^2) and remained unchanged after 8 months of treatment (Table 2). Angiotensin II levels prior to CyA administration were 0.6 ± 0.42 ng/ml per hour and 1.01 ± 0.62 ng/ml per hour after 1 month of treatment ($t = 22$; NS).

All patients have maintained a good clinical condition throughout treatment and lead a completely normal life. Hearing loss and maximum urinary osmolarity have remained unchanged. We have observed no abnormality in blood cell counts. Liver function tests (serum transaminases, alkaline phosphatase and bilirubin level) showed no changes.

We did not observe hypertrichosis and gingival hyperplasia in our patients (perhaps due to the short duration of treatment). Mean blood levels of CyA throughout treatment were 67.33 ± 7.4 ng/ml and the daily dose of CyA required to maintain these levels was 4.21 ± 0.26 mg/kg body weight.

Discussion

Haematuria may be detected from birth in patients with Alport's syndrome, independently of whether or not the patient progresses to renal insufficiency [1, 12, 13]. The mechanisms determining whether some patients with Alport's syndrome progress towards renal failure, while others do not, remain unknown. However, in our experience and that of others [1, 11–13], persistent progressive proteinuria exceeding 40 mg/h per m^2 indicates very poor prognosis, especially if it is associated with extrarenal signs such as neural hearing loss. This was observed in these eight selected patients. Haematuria remained unchanged throughout the 8 months of CyA treatment. In contrast, during the 3rd week of treatment, proteinuria either became negative or decreased significantly, and remained stable throughout the 8 months of treatment (Table 2). The nephrotic syndrome present in two patients disappeared with CyA treatment (Table 2). Tolerance to CyA was good in all patients, and creatinine clearance remained stable throughout the 8 months of CyA treatment.

Male sex, neural hearing loss, ocular abnormalities and massive-persistent proteinuria suggest a poor prognosis and progression towards renal failure. In three patients with low creatinine clearances proteinuria decreased after CyA administration; two of these patients were found to have evident focal and segmental glomerular hyalinosis. In contrast, in the remaining five patients (Table 2) with normal creatinine clearance, moderate mesangial cell proliferation and no evident glomerular hyalinosis, proteinuria abated throughout CyA treatment but recurred after discontinuation of therapy. Mechanisms by which CyA decreases proteinuria are not clearly defined, although two basic types may be accepted: those related to proven renal haemodynamic changes [11, 12] and those related to the immunological effects of CyA [7, 16–18].

The positive effect of CyA on massive proteinuria in patients with Alport's syndrome is undeniable, but whether or not this has a significant prognostic value in the progression of these patients towards renal failure remains in doubt. The apparently good tolerance of these patients to CyA might permit continuation of this treatment, but the risk of nephrotoxicity continues to cause concern [5, 19, 20]; repeated renal biopsies should be performed in these patients before CyA treatment can be recommended. However, only a placebo-controlled trial of long-term CyA treatment can demonstrate whether this effect of CyA on massive proteinuria in patients with Alport's syndrome signifies control of progression to renal failure. In conclusion, although the effects of CyA on reducing massive proteinuria in patients with Alport's syndrome have been shown, at this stage we cannot recommend its routine use as a therapeutic measure.

References

1. Callis L (1983) Alport's syndrome. Proceedings of the 17th International Congress of Pediatrics, Manila, vol 2. pp 21–22
2. Abarca A, Alarcon A, Alsina J (1988) The use of ciclosporin in glomerulonephritis. Data of 61 patients in the Cooperative study of the Spanish Society of Nephrology. Nefrologia 1 [Suppl 1]: 15–23
3 Brandis M, Burghard R, Leititis J, Zimerhackl B, Hilbrandt F, Helmchen U (1987) Cyclosporin A for treatment in nephrotic syndrome. Pediatr Nephrol 1: C42
4. Hoyer PF, Krull F, Brodhel J (1986) Cyclosporin in frequently relapsing minimal change nephrotic syndrome (letter). Lancet II: 335
5. Niaudet P, Habib R, Tete MJ, Hinglais N,, Broyer M (1987) Cyclosporin in the treatment of idiopathic nephrotic syndrome in children. Pediatr Nephrol 1: 566–573
6. Tejani A, Butt K, Khawar R, Sthabthuran M, Rosenthal CJ, Tachtman H, Fusi M (1985) Cyclosporin(CY) induced remission of relapsing nephrotic syndrome (RNC) in children. Kidney Int 29: 206
7. Vela M, Egido J, Lozano L (1988) Treatment of glomerular disease with cyclosporin A. Nefrologia 8 [Suppl 1]: 9–14
8. Mimram A, Mourad J, Ribstein J (1990) The renin-angiotensin system and renal function in kidney transplantation. Kidney Int 38: [Suppl 30]: S114–S117
9. Murray BM, Paller MS, Ferris TF (1985) Effect of cyclosporine administration on renal hemodynamics in conscious rats. Kidney Int 28: 767–774
10. Perico N, Benigni A, Bosco E, Rossini M, Orisio S, Ghilardi F, Piccinelli A, Remussi G (1986) Acute cyclosporine A nephrotoxicity in rats. Which role for renin-angiotensin system and glomerular prostaglandins? Clin Nephrol 25: 583–588
11. Antonovych TT, Deasy PF, Tina LU, Albora JB d', Holerman CE, Cacagno PL (1969) Hereditary nephritis: early clinical, functional and morphological studies. Pediatr Res 3: 545–550

12. Gubier M, Levy M, Broyer M, Naizot C, Gonzalez G, Perrin D, Habib R (1981) Alport's syndrome, a report of 58 cases and a review of the literature. Am J Med 70: 493–505
13. Bernstein J, Kissane JM (1978) Hereditary nephritis. In: Edelmann CM Jr (ed) Pediatric kidney disease. Little Brown, Boston, pp 571–580
14. Spear GS, Slusser RJ (1972) Alport's syndrome. Am J Med 69: 213–223
15. A report of the International Study of Kidney Disease in Children (1978) Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. Kidney Int 13: 159–165
16. Al-Muzairai IA, Innes A, Hillis A, Stewart KN, Bone JM, Catto GRD, MacLead A (1989) Renal transplantation: cyclosporin A and antibody development after donor-specific transfusion. Kidney Int 35: 1057–1063
17. Salomon DR, Pickard LL (1987) Cyclosporine permits suppressor T cell induction but inhibits an amplification circuit dependent on IL2 and a suppressor-inducer lymphokine (SIL) (abstract). Kidney Int 31: 468
18. Jackson NM, Convery ME, Humes HD (1987) Cyclosporine-induced cell proliferation is unique to the kidney (abstract). Kidney Int 31: 468
19. Ter Borg EJ, Tegzess AM, Kallenberg OG (1988) Unexpected severe reversible cyclosporine A induced nephrotoxicity in a patient with systemic lupus erythematosus and tubulointerstitial renal disease. Clin Nephrol 29: 93–95
20. Mihatsch MJ, Steiner K, Abeywickrama KH, Landmann J, Thiel G (1988) Risk factors for the development of chronic cyclosporine-nephrotoxicity. Clin Nephrol 29: 165–175

Ask the expert*

Why does renal tubular acidosis cause hypercalciuria?

Key words: Hypercalciuria – Renal tubular acidosis

Hypercalciuria is an outstanding feature of untreated distal renal tubular acidosis. In our experience, urinary calcium excretion is inversely related to the plasma concentration of bicarbonate, and normal or almost normal levels are only achieved after adequate and sustained correction of the acidosis [1]. Studies of chronic acid loading in normal individuals indicate that hypercalciuria mainly results from release of skeletal calcium [2], an effect observed in metabolic, but not in respiratory, acidosis [3]. An associated factor in the induction of hypercalciuria is a reduction in the distal tubular reabsorption of calcium related to decreased delivery of bicarbonate, an effect that is independent of vitamin D or parathyroid hormone [4]. Parathyroid hormone, however, may exert a direct calciuric effect during metabolic acidosis and thus contribute to the increased urinary calcium excretion if hyperparathyroidism is present [5].

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References

1. Rodríguez-Soriano J, Vallo A, Castillo G, Oliveros R (1982) Natural history of primary distal renal tubular acidosis treated since infancy. J Pediatr 101: 669–676
2. Lemann J Jr, Litzow JR, Lennon EJ (1966) The effects of chronic acid loads in normal man: further evidence for the participation of bone mineral in the defense against chronic metabolic acidosis. J Clin Invest 45: 1608–1614
3. Chabala JM, Levi-Setti R, Bushinsky DA (1991) Alteration in surface ion composition of cultured bone during metabolic, but not respiratory, acidosis. Am J Physiol 261: F76–F84
4. Sutton RAL, Wong NLM, Dirks JH (1979) Effects of metabolic acidosis and alkalosis on sodium and calcium transport in the dog kidney. Kidney Int 15: 520–533
5. Batlle DC, Itsarayoungyen K, Hays S, Arruda JAL, Kurtzman NA (1982) Parathyroid hormone is not anticalciuric during chronic metabolic acidosis. Kidney Int 22: 264–271

* The editors invite questions for this section