

Letters and Replies

The clinical spectrum of shunt nephritis

Sir,

I read with considerable interest the article by Haffner *et al.* [1] on the clinical spectrum of shunt nephritis. I would like to make the following comments:

I agree with the authors that cases of shunt nephritis are often misdiagnosed, and because of this, effective treatment can be delayed for months or even years while treatment is directed towards the renal disease alone. The clinical diagnosis of longstanding ventriculoatrial (VA) shunt infections is not easy, and both blood and CSF cultures can be negative or misleading [1,2]. We have for over 20 years provided a diagnostic service for VA shunt infection based on a very reliable serological test [3,4], and we have shown that it can be used in screening patients undergoing VA shunt insertion. If the test is carried out on blood drawn 6 months post-operatively and compared with a preoperative sample, those with sub-clinical shunt infection due to any of the coagulase-negative staphylococci will show a rising titre. Prompt treatment at this time will prevent cases of shunt nephritis [3,4]. In those where screening is not carried out which progress to immune complex disease, the diagnosis can be quickly made or confirmed using the same test. For example, in a young adult the normal titre would be approximately 320, while titres of 2560–20480 are commonly seen in shunt nephritis.

I would respectfully disagree with Haffner *et al.* [1] on the point of aetiology. They state that for those infections occurring later than several months after operation, bacteria can be presumed to have gained access to the shunt from skin abrasions etc rather than at operation. Our clinical, microbiological and immunological data collected over many years [4,5] show that, in all cases studied by us, the causative bacteria gained access at operation, but in the longstanding cases leading to shunt nephritis they failed to give rise to overt signs and symptoms of infection, the first significant manifestation often being immune complex nephritis.

The final comment concerns recommendations for treatment. A National Working Party Report [6] recommends that, following shunt removal and placement of an external ventricular drain, vancomycin should be given intraventricularly, not intravenously as Haffner *et al.* recommend. We agree that this should be accompanied by rifampicin.

I found the article interesting and hope that it raises awareness of shunt nephritis among nephrologists.

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Reply

Sir,

We believe that the measurement of anti-*Staphylococcus epidermidis* titre according to Dr Bayston may indicate shunt infection. If this test is not available low serum complement (C₃) levels and circulating immune complexes are other indicators as found in all our patients with shunt-nephritis, and reported in more than 90% of patients in the literature. These diagnostic tools, therefore, may keep their practical interest.

Dr Bayston states that also those infections occurring several years after the last shunt operation are due to bacteria gaining access at operation. The sometime long time interval between shunt operation and first sign of shunt nephritis (up to 21 years) raises doubt that this mechanism is obligatory especially in cases where other bacteria than *S. epidermidis* (15% of all cases) are detected. Other causes of shunt infection have been documented in the literature, e.g. sepsis, injuries to the skin, perforation of bowel or other intraabdominal organs [1,2].

With respect to the recommendations for treatment of shunt-nephritis, we did not state that 'following shunt removal and placement of an external ventricular drain, vancomycin should be given intravenously *only*'. As most other units we prefer in addition to the removal of the infected shunt a *combined* intraventricular and intravenous antibiotic treatment with vancomycin or rifampicin. However, we would like to emphasise that despite the widespread clinical practice the intraventricular application of antibiotics might be questioned because of possible side effects, e.g. toxicity due to high local concentrations. In our unit we observed two cases of permanent hearing loss due to intraventricular aminoglycosid application. In addition, there is a lack of data regarding the optimum dosages and pharmacokinetics of intraventricularly applied antibiotics. The latter, is quite difficult to establish due to variable ventricle volume, presence of occlusive or communicating hydrocephalus, and antibiotic elimination by external drainage of cerebrospinal fluid.

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The *BSM-1* vitamin D receptor polymorphism and secondary hyperparathyroidism

Sir,

In their recent editorial, Torres and Salido [1] reviewed the role of polymorphisms in the vitamin D₃ receptor gene in renal osteodystrophy. In support of an association between the bb *BSM-1* genotype and the development of secondary hyperparathyroidism in dialysis patients, they cite reports by Tsukamoto and colleagues [2] and Fernandez and colleagues [3]. These authors report higher plasma PTH levels in patients with the bb genotype compared with those with BB genotype; an observation in keeping with one published association between the bb genotype and primary hyperparathyroidism [4]. However, Torres and Salido neglect a report in the preceding issue of *Nephrology, Dialysis and Transplantation* [5] by Schmidt and colleagues who found no difference in the *BSM-1* genotype distribution between haemodialysis patients who had, or had not, required parathyroidectomy; nor any significant difference in PTH levels by genotype. Moreover, in a previous report [6], Torres and colleagues found that pre-transplant PTH levels were markedly lower (albeit not statistically significant) in patients with the bb genotype. These apparently contradictory findings reflect the need for large population samples in genetic association studies to produce consistent results; failure to recognize this, together with the bias in favour of publication of positive results, has resulted in many contradictory associations of the vitamin D₃ receptor [6] and other [7] polymorphisms.

We have also examined the role of the *BSM-1* polymorphism in haemodialysis patients and concur with the findings of Schmidt and colleagues. We studied 176 caucasian patients on regular haemodialysis, 50 of whom had previously required parathyroidectomy. DNA was extracted from peripheral blood and the *BSM-1* polymorphism detected by digestion of a PCR product on agarose gel. Standard methods and primers were utilized [5]. Clinical data was extracted retrospectively from the computerized clinical and biochemical database at the Western Infirmary. Levels of parathyroid hormone, serum calcium (corrected for albumin), and alkaline phosphatase were recorded pre-dialysis (when serum creatinine reached 500 µmol/l), at the time of starting dialysis and 6 months after starting dialysis. Genotype frequencies were compared by the Chi square test; comparisons of continuous data between genotypes were made by the Kruskal-Wallis test. There was no significant difference (Chi square=4.9) between the genotype distribution in the study population (bb (32%), bB (38%), BB (30%)) and 176 healthy controls of similar age and sex distribution (bb (35%), bB (45%), BB (20%)). We were also unable to identify any significant differences between those who had required parathyroidectomy (bb (32%), bB (38%), BB (30%)) and those who had not ((bb (34%), bB (37%), BB (29%)). These results are in general agreement with those of Schmidt and colleagues [5] although the genotype distribution is clearly different reflecting the known racial and geographical variation in genotype distribution [6,8]. When the effects of genotype on biochemical indices was examined there were also no significant effects of genotype. These results are shown in Table 1.

These data support the findings of Schmidt and colleagues [5], in that there was no significant difference in genotype distribution or in biochemical parameters between patients who had, and had not, required parathyroidectomy. We did, however, observe a trend towards increased frequency of the bb genotype in patients compared with controls and for PTH

Table 1.

Genotype	bb	bB	BB
Gender (M/F)	(30/27)	(37/29)	(21/32)
PTH-1	21.8±6.1	27.1±7.6	16.8±3.3
PTH-2	28.5±8.6	24.3±3.8	21.6±3.8
PTH-3	27.3±9.1	24.7±6.1	17.5±2.8
cCa-1	2.23±0.04	2.17±0.05	2.28±0.04
cCa-2	2.21±0.04	2.18±0.03	2.26±0.02
cCa-3	2.37±0.03	2.29±0.06	2.39±0.02
AlkPhos-1	215±13	261±24	222±25
AlkPhos-2	202±18	217±22	219±21
AlkPhos-3	198±30	210±17	189±18

Parathyroid hormone (PTH, pmol/l), corrected serum calcium (cCa, mmol/l), serum alkaline phosphatase (AlkPhos i.u/l). Data are given as mean±SEM. 1,2,3 indicate the three time points described in the text:- pre-dialysis, at initiation of dialysis, and 6 months after the start of dialysis. There were no significant differences between groups.

levels to be higher in patients with the BB genotype in keeping with previous reports [2,3]. Although the absence of data on bone density, or histology, in the present study may be criticised, we have studied a reasonably large population and the results do not support a major clinical role for the *BSM-1* polymorphism in renal osteodystrophy. However, the findings do not exclude a more subtle role in the pathogenesis of renal osteodystrophy as has ultimately been suggested in osteoporosis [6]. Moreover, these results illustrate once again the pattern of reporting genetic association studies, with the publication of conflicting results from small scale studies reflecting the need for large scale collaboration to produce meaningful results [7].

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Reply

Sir,

In our recent Editorial Comment we attempted to summarize the published peer-reviewed papers about the association of the *Bsm-1* VDR polymorphism with the parathyroid function of dialysis patients [1]. At that time, the available evidence suggested that VDR variants may be a contributing factor to the development of parathyroid hyperplasia. We were not aware of a letter submitted to NDT that eventually appeared just one issue before the final version of our Editorial Comment. Thus, we did not mean to neglect any published evidence, either in favour or against such an association.

Hypocalcaemia, hyperphosphoraemia, and low calcitriol levels are the common pathogenetic factors of secondary hyperparathyroidism in renal failure. Other factors such as age of the patient, duration of renal failure, time on dialysis, the presence of diabetes mellitus, calcium content of the dialysis fluid, vitamin D therapy, and aluminium exposure are among the large list of factors known to modify the magnitude of secondary hyperparathyroidism. Thus, in order to demonstrate an association of the 'bb' genotype with higher PTH levels in dialysis patients, all these factors should be taken into account. As a matter of fact, the study by Fernández *et al.* [2] may illustrate the relevance of controlling for all these variables in association studies. In this paper, the relevance of the VDR polymorphism became conclusive only after excluding patients predominantly affected by strong environmental factors common in chronic renal failure. Of course, this may be interpreted as if the clinical relevance of the genetic component is negligible when compared to strong environmental factors. This is the view that McCarey *et al.* [3] seem to support. We also agree with them that large scale studies are needed. However, these studies should be not only large but also well designed and should use multivariate analysis in order to isolate and quantitate the effect of one gene on the magnitude of secondary hyperparathyroidism.

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Perirenal haematoma as the presenting feature of polyarteritis nodosa: one more case from Turkey

Sir,

In a recent issue of *NDT*, Öksüzöğlü *et al.* described a case of perirenal haematoma as the presenting feature of polyarteritis nodosa (PAN) in a 20-year-old male [1]. They pointed out that perirenal haematoma may be a more common complication of PAN in Turkey, speculating that higher hepatitis B carrier rate or higher prevalence of some other viral infections e.g. viruses of the Parvoviridae family [1], may be a potential explanation.

We want to report a case of massive spontaneous retroperitoneal haematoma in a 38-year-old, previously healthy man. He was admitted to our hospital after a two-week history of abdominal pain started in epigastrium and paraumbilical region and then radiating to his back and flanks. Pain was constant in quality, intensity and duration. In addition, he complained of fatigue, weight loss (5 kg) and fever. His previous history was unremarkable except for upper respiratory infection a month prior to the beginning of abdominal pain. He did not smoke and did not report alcohol use. Upper esophagogastroduodenoscopy was performed that revealed nonspecific gastritis; there was no sign of *Helicobacter pylori* infection. Urinary dipstick examination was ++++ for occult blood and +++ for proteinuria, while urinary sediment revealed plenty of RBCs and RBC casts, hyaline and granular casts. He was referred to our hospital with the diagnosis of acute glomerulonephritis.

On admission the patient appeared severely ill. Temperature was 38.5°C, pulse was 120/min, and respirations were 14/min. Blood pressure was 160/100 mm Hg and postural hypotension was not present. On physical examination the patient was pale. No rash or lymphadenopathy was found. The head, neck, lungs, and heart were normal. Abdominal examination revealed a mass that comprised almost the entire right side of the abdomen; bowel sounds were present. Neurologic examination was negative. Erythrocyte sedimentation rate was >145/h, C-reactive protein (CRP) 22.5 mg/dl (normal <0.6 mg/dl), haemoglobin (Hb) 72 g/l, WBC $14 \times 10^9/l$, platelets 271 000/ μ l. Peripheral blood smear showed hypochromic microcytic anaemia and shift to left. Blood urea nitrogen (BUN) was 12.8 mmol/l, creatinine 176.8 μ mol/l, serum albumin 23 g/l, globulin 44 g/l, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at the upper limit of normal. Viral markers for hepatitis B and C were negative. C3, C4 and ANA were normal; p-ANCA was weakly positive. Creatinine clearance was 60 ml/min and urinary protein excretion was 0.5 g/day. Repeated microscopic examination of the urinary sediment revealed >20 RBCs per high powered field, plenty of RBC casts and occasional hyaline and granular casts. Abdominal ultrasonographic examination performed immediately upon admission revealed a large heteroechoic perirenal mass, inferior and lateral to the right kidney (35 × 129 × 61 mm) that was evaluated as a perirenal haematoma. Contrast-enhanced computer tomography of the abdomen showed a large haematoma surrounding the right kidney and descending to the psoas muscle, and occupying almost the entire right retroperitoneum. Small areas of intrarenal and subcapsular bleeding in the right kidney were evident. Renal angiogram revealed multiple aneurismatic dilatations (2–3 mm in diameter) of the interlobular arteries of both kidneys. Arteriogram of the mesenteric artery was normal. A diagnosis of polyarteritis nodosa was established and intravenous pulse corticosteroid (1 g/day) and pulse cyclophosphamide (1 g/day) therapy followed by maintenance oral corticosteroids at a dose of 2 mg/kg was instituted. Immediately following therapy there was a dramatic decrease in patients symptoms, including complete dissolution of pain, stabilization, and subsequently a rise in serum haemoglobin as well as a significant decrease in the size of abdominal mass as revealed both with palpation and control abdominal ultrasound. He was discharged 1 week after institution of therapy with a recommendation of 60 mg oral prednisolone and 20 mg lisinopril for his hypertension. Serum Hb concentration on discharge was 96 g/l without any transfusion, and the previously palpated mass in the right abdomen had almost completely disappeared on physical examination.

Öksüzöğlü *et al.* directed attention to the fact that 9/60 (15%) of reported cases of perirenal haematoma caused by polyarteritis nodosa came from Turkey [1]. The authors speculated that apart from the high prevalence of hepatitis B virus infection, other factors may be involved, since not all cases had documented infection with hepatitis B or C [1]. We want to direct attention to another important association: the concurrent presence of familial Mediterranean fever (FMF) in Turkey. A total of 23 cases of FMF with polyarteritis nodosa have been reported: 11 from Turkey [2–6], 5 from Israel [7,8] and 7 from other European countries [9–14]. Almost 30.5% of these cases ($n=7$) developed a perirenal haematoma [4,7,8,10–12]. When one analyses data on patients with PAN and perirenal haemorrhage, 11.6% have concomitant FMF. This significant proportion of FMF especially among children may indicate that it could be the postulated predisposing mechanism in the Turkish population.

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Microscopic polyarteritis with antineutrophil cytoplasmic antibodies in polyglandular autoimmunity

Sir,

One of the basic caveats in endocrinology is that glandular abnormalities tend to occur together. Polyglandular autoimmunity (PGA) is a term used to define a complex spectrum of endocrine autoimmune diseases [1–3]. Patients with PGA may suffer from a variety of nonendocrine, immunologic or autoimmune diseases [1–3]. We report the occurrence of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis involving the kidneys and the peripheral nerves in a patient who was diagnosed as having PGA.

A 56-year-old woman was admitted because of malaise, nausea, weight loss, arthralgias and weakness. Since initial investigations revealed the presence of renal failure, she was referred to the Division of Nephrology. Two years earlier, because of the presence of goiter, the patient underwent thyroid assessment. She was disclosed to have elevated levels of anti-microsomes and anti-thyroglobulin antibodies together with an increase in serum TSH and histologic evidence of lymphocyte infiltration in the gland. Hashimoto's thyroiditis was diagnosed and treatment with levothyroxine (50 µg/day) was started. Since then, the patient has had persistently elevated anti-microsomes and anti-thyroglobulin antibodies and no sign of hypothyroidism. Six months prior to admission routine investigations showed normal renal function and a mild proteinuria.

The patient reported paresthesias in the lower extremities and pain in the right upper extremity followed by weakness of the hand in the last few months. Neurologic examination at admission showed marked atrophy and weakness of intrinsic muscles of right hand and weakness of tibio-peroneal muscles bilaterally. Ankle jerks were absent and tactile and pain sensation was decreased with a stocking distribution in the lower limbs and a glove distribution in the right hand. Physical examination was otherwise unremarkable.

Investigations showed serum creatinine 4 mg/dl, BUN 70 mg/dl, haemoglobin 10.8 g/dl, white cell count $6.1 \times 10^9/l$ (64% neutrophils and 20% lymphocytes), platelets $359 \times 10^9/l$, erythrocyte sedimentation rate 65 mm/h. Blood sugar, liver function tests, coagulation studies, gammaglobulins and complement were normal. There was no clinical or laboratory sign of hypothyroidism. Urinalysis revealed microhaematuria and proteinuria (1.2 g/24 h) of mild selectivity. Hepatitis B antigen, antibodies against hepatitis B and C viruses and a large number of autoantibodies including antinuclear and anti-glomerular basement membrane antibodies were negative. Search by indirect immunofluorescence (IF) for ANCA demonstrated a cytoplasmic fluorescence pattern (C-ANCA), confirmed several times. Other positive autoantibodies included rheumatoid factor, anti-microsomes, anti-thyroglobulin and anti-parietal cells antibodies. Gastric biopsies showed histological evidence of type A fundal atrophic gastritis, which is commonly associated with anti-parietal cells antibodies.

Both kidneys were found normal in size by ultrasonography. Percutaneous renal biopsy was performed and demonstrated predominant changes in the glomeruli. Glomerular lesions were of mixed types and stages: necrosis (segmental or global) or circumferential crescents were observed in many glomeruli, whereas other glomeruli showed global sclerosis and some were normal. There was an interstitial inflammatory infiltrate and focal atrophy of tubules. Extraglomerular vessels showed intimal thickening. IF studies were negative but for fibrinogen. The electrophysiological

findings were indicative of an asymmetric axonal sensory-motor neuropathy. Sural nerve biopsy showed a small vessel vasculitis characterized by inflammatory infiltration of epineural vessels, intimal proliferation and fibrinoid necrosis. There was a severe depletion of myelinated fibers indicative of an axonopathy. Direct IF showed deposits of IgG, IgM, complement and fibrinogen within the wall of vessels.

The patient received prednisone and cyclophosphamide, but the latter was discontinued because the patient was intolerant of it. After 7 months, there was a partial recovery of renal function (serum creatinine 2.1 mg/dl); neurological examination was substantially unchanged except for distal hypoesthesia which had progressed up to the knee level bilaterally. Since PGA often has a familial distribution, family members of the patients were subsequently investigated, and one out of two sisters (a 51-year-old woman with normal body weight) was disclosed to be affected by non-insulin-dependent diabetes mellitus.

Polyglandular autoimmunity has been subdivided into three main groups: type I, type II and, more recently, type III [1–3]. The reported case is consistent with a type III PGA, also called 'thyrogastric syndrome' since Graves' disease or Hashimoto's thyroiditis and type A fundal atrophic gastritis or pernicious anemia are the main associated clinical features [2]. The constellation of clinical, laboratory and pathologic features of the reported case is indicative of microscopic polyarteritis, a systemic vasculitis involving small vessels which may be associated with asymptomatic proteinuria for long periods and insidious loss of renal function. Different patterns of neuropathy may be observed in systemic necrotizing vasculitis [4] including the features displayed in our patient.

Since it is unknown what induces the production of ANCA, it is not possible to establish whether there is a casual link to PGA. We may only speculate that the altered immunologic competence in PGA [3] may have promoted the production of those autoantibodies. Nevertheless the present report illustrates the potential relationships between autoimmune disorders and ANCA-associated diseases. We describe a case of ANCA-associated vasculitis occurring in polyglandular autoimmunity. It will be necessary to establish whether this is a new syndrome or a mere coincidence, and we would like to alert clinicians about this possible association.

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Non-oliguric acute renal failure in non-fulminant acute viral hepatitis

A 40-year-old Nigerian female patient was admitted to the Lagos University Teaching Hospital because of jaundice preceded for 5 days by severe malaise, anorexia, vomiting (once daily), and right upper abdominal pain. There was no history of renal or hepatic diseases and no intramuscular or intravenous injections in the preceding 2–3 months. She resided in a densely populated area with poor water supply, and had been in contact with a friend with acute viral hepatitis.

Clinical findings included mild jaundice, moderate tenderness in the right hypochondrium, 2 cm tender hepar, no splenomegaly, no ascites, no signs of dehydration, no peripheral oedema, blood pressure 110/50 mmHg, pulse of 82 beats per minute, regular, and of good volume.

The mean biochemical data in the first 5 days and on the 12th day are as shown in Table 1. Histology of the renal biopsy on the 3rd day of admission showed interstitial oedema, infiltration by inflammatory cells, tubular dilatation, tubular casts, and patchy tubular necrosis. The patient responded well to conservative therapy; biochemical data had improved by the 12th day and she was discharged by the 2nd week of admission.

Biochemical data of our case and some of the reported cases [1–4] are shown in Table 2. Our patient presented in non-oliguric acute renal failure. From the absence of Hbs serology, low social status, and history of contact we inferred she had acute viral hepatitis A. To date, from the literature, 26 cases have been reported, and the first Chinese case [4] was by Lin *et al.* Our case is probably the first reported from Nigeria.

The mechanism of renal failure in acute viral hepatitis is uncertain. Wilkinson *et al.* [5] proposed the contributory role of endotoxaemia for the acute renal failure.

The recovery of our patient was in keeping with the good prognosis associated with most reported cases.

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Table 1. Mean values of renal and hepatic indices during the first days of admission and values on the 12th day of admission

	24-h urine volume (ml)	Plasma creatinine (mg/d)	Urine creatinine (mg/dl)	Creatinine clearance (ml min ⁻¹)	Urine Na+ (mmol/l)	Urine protein g/day	SGOT (IU/l)	SGPT (IU/l)	Total bilirubin (mg/dl)
1st to									
5th day	1662	5.8	59	12	44	0.52	90	60	3.1
12th day	1996	2.1	71	46.9	28	0.5	50	40	1.5

NA+, sodium; SGOT, aspartate aminotransferase; SGPT, alanine transferase.

OUP – Nephrology Dialysis Trans.

Table 2. Clinical and laboratory data of our case and some of the reported cases with acute renal failure and hepatitis A infection

Case	Age (years)	Sex	Aspartate aminotransferase (IU/l)	Alanine transferase (IU/l)	Total bilirubin (mg/dl)	Plasma creatinine (mg/dl)	Proteinuria	Urine sodium (mmol/l)	Renal biopsy
Our case	40	F	160	95	3.1	5.8	520 mg per day	44	Interstitial oedema; infiltration by inflammatory cells; tubular casts; patchy tubular necrosis
Ref. [1]	43	M	2160	6914	7.8	9.7	NA	24	Acute tubular necrosis
Ref. [2]	30	M	6957	5134	7.5	13.2	560 mg per day	Fractional excreted Na ⁺ (FeNa ⁺) > 3	Mild interstitial nephritis and mild tubular necrosis
Ref. [3]	42	M	9980	3228	3	NA	+	55	Acute tubular necrosis; interglomerular deposition of fibrin
Ref. [4] Chinese case	30	M	3461	2348	9.8	15.4	Trace	65	Acute tubular necrosis

NA, not available; Na⁺, sodium.

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Renal tolerance of combined treatment with foscarnet and indinavir

Sir,

Drug-associated nephrotoxicity has been recently associated with protease inhibitors. Other drugs such as foscarnet are known to potentially induce nephrotoxicity [1–3]. However, little is known about their concomitant administration.

We have retrospectively analysed the evolution of renal function after 18 courses of foscarnet associated with indinavir (mean duration 13.8 weeks, range 2–39) in patients with acquired immunodeficiency syndrome and CMV infection related to HIV infection. There were 17 men and one woman with a mean age of 39 ± 2 years. The CMV localization included retinitis (13), encephalitis (two), gastritis (two) and colitis (one). Foscarnet was given by continuous infusion (daily cumulative dose 3–12 g) in 500–2000 cm³ isotonic saline/day. All patients were receiving concomitantly indinavir (2400 mg/day).

The mean creatinine clearance (assessed with Cockcroft and Gault formula) prior to onset of foscarnet therapy and at the end of the association were 98 ± 5 ml/min (range 63–145) and 88 ± 6 ml/min (range 40–142), respectively. A decrease in creatinine clearance >25% from baseline level leading to stop foscarnet therapy while protease inhibitor was pursued occurred in only three patients (Table 1). Proteinuria was less than 1 g/24 h and no abnormality was evident in the urinary sediment. Renal echography showed no dilatation of intrarenal excretory cavities. The patients had no hypertension, diabetes mellitus or other nephrotoxic drugs. However, risk factors such as dehydration, sepsis or a pre-existing renal insufficiency were found in these three patients (Table 1).

Renal function returned to normal in one patient within 2 weeks. A mild persistent decrease in creatinine clearance (52 and 47 ml/min 3 months later) was noted in the two

Table 1.

	Creatinine clearance (ml/mn)			Risk factors
	At baseline	During both treatments	2 weeks after stopping Foscarnet	
Patient 1	102	71	101	Diuretic
Patient 2	66	42	52	Renal insufficiency
Patient 3	63	40	47	Renal insufficiency, sepsis, diarrhoea

other patients with a pretreatment moderate renal failure and while indinavir treatment was continued.

We have shown that the renal tolerance of a combined treatment with foscarnet and indinavir is good in HIV patients. It should be outlined that the solubility of foscarnet and indinavir are strictly similar, both drugs being more soluble in acid aqueous solution. Foscarnet and indinavir tolerance are highly dependent on hydration status and a strict compliance to hydration procedure needs to be observed when those drugs are prescribed together.

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Paraoxonase activity stimulation by salts is higher in chronic renal failure patients than in controls

Sir,

Human paraoxonase (PON) is an A-esterase that is closely associated to circulating high density lipoproteins. First known for its ability to hydrolyse organophosphorus compounds such as paraoxon (diethyl-4-nitrophenylphosphate), the active metabolite of the insecticide parathion, PON has recently been shown to have an antioxidant effect on the peroxidation of low density lipoproteins *in vitro*. Thus, it has been suggested that PON may play a protective role against atherosclerosis [1].

Caucasian healthy populations showed a bimodal distribution of individual levels of serum paraoxonase activity (distributed in 'low' and 'high' activities). A method for identifying the PON polymorphism has been developed, based upon the effect of NaCl upon the hydrolysis of paraoxon [2]: the 'high activity' group (called B group) showed higher stimulation by 1 M NaCl than the 'low activity' (A) group. This difference has been related to the Gln/Arg polymorphism at position 191 in the amino acid sequence of the protein.

Considering the high prevalence of cardiovascular disease in uraemia, we have recently studied serum paraoxonase activity in chronic renal failure patients [3]. As the assay

method used NaCl to obtain higher activities and to discriminate different phenotypes, and as recently a higher salt stimulation has been found in haemodialysis patients compared to healthy subjects [4], we evaluated the effect of NaCl on serum paraoxonase in several groups of uraemic patients.

Blood was sampled after a 12 h fast. PON was measured by UV spectrophotometry in 11 non end-stage chronic renal failure patients (NESRF), in 17 haemodialysis patients (HD), in 9 renal transplant patients (RT) and in 10 healthy subjects (HS) using paraoxon as substrate. Basal paraoxonase activity was measured without adding NaCl, and salt-stimulated activity was measured with 1 M NaCl. The degree of salt stimulation was expressed as $(\text{PON with NaCl} - \text{basal PON}) / (\text{basal PON}) \times 100\%$. Results were analysed by Mann-Whitney test.

As shown in Table 1 when compared to HS, salt stimulation was higher (but not significantly) in NESRF (+26%), was the highest in HD (+200%), and seemed to decrease but was still significantly higher in RT (+143%).

This preliminary study shows the importance of taking into account the effect of NaCl when PON is explored in different renal failure stages, and suggests that the serum environment of PON may modify its structure and thus its interactions with NaCl. Recently, a reduction of the specific activity of PON has been shown in renal failure patients [5] and has been interpreted as a post-translational modification of the enzyme. Salt sensitivity variations seem to confirm such modifications and make us hypothesize that other structural alterations in various sites of the enzyme may modify the antioxidant activity of paraoxonase and may participate in the accelerated atherosclerosis in chronic renal failure.

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Table 1. Paraoxonase activity (PON) sensitivity to NaCl is expressed as percentage of stimulation in non end-stage renal failure patients (NESRF), haemodialysis patients (HD), renal transplant patients (RT) compared to healthy subjects (HS)

Patients	Number	NaCl stimulation (%) of PON			Mann-Whitney test
		Minimum	Maximim	Mean \pm SD	
HS	10	12.44	174.48	104.86 \pm 60.9	
NESRF	11	1.29	306.82	126.26 \pm 92.8	NS
HD	17	154.15	492.03	308.25 \pm 108.6	$P < 0.01$
RT	9	54.37	414.44	243.46 \pm 120.7	$P < 0.05$

Subcutaneous erythropoietin alpha (Eprex) is more painful than erythropoietin beta (Recormon)

Sir,

In 1994 we demonstrated that recombinant human erythropoietin alpha (Eprex, EPO α) produced significantly more pain than erythropoietin beta (Recormon, EPO β), and that the improvement produced by local anaesthetic cream reduced this difference only slightly [1]. The results of our study in forty-eight haemodialysed adult patients did not surprise us in view of the dramatic clinical difference we had seen when using these two products in children. Since then we have continued to use only EPO β until recently.

Since our study, Janssen-Cilag have produced a new formulation of EPO α , containing a phosphate rather than a citrate buffer. In a study proposed and monitored by Janssen-Cilag, the discomfort of the new EPO α was compared to EPO β in twenty healthy adult volunteers [2]. This study failed to demonstrate any difference between the two products. We therefore changed ten children in our care, aged 4.8–14.8 years, from EPO β to EPO α because of the obvious advantage that this product is available as a solution in a pre-filled syringe, rather than as a lyophilized powder.

The result of this changeover was dramatic. The five children aged up to 10 years were quite unable to tolerate the EPO α because they were very distressed by the intense, persistent pain of the injection. Two boys aged 11 and 15 years complained that it was very much worse, but did not refuse to have the injection, and the other three teenagers did not consider it a problem.

Children with renal failure inevitably have discomfort and disruption to their lives which are far greater than healthy children suffer. Every effort should be made to minimize their discomfort. We admit that these observations are open label and uncontrolled and should be followed by a randomised controlled study.

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Bilateral spontaneous avulsion of quadriceps tendons

Sir,

We read with interest the case report by Kalantar-Zadeh *et al.* in a recent issue of *NDT* [1]. The authors reported a diabetic patient with severe hyperparathyroidism on maintenance haemodialysis presenting with non-traumatic, simultaneous, bilateral rupture of the patellar tendons in relation with her parathyroid disease. They correctly pointed out that three cases, including their patient, of simultaneous bilateral patellar tendon ruptures in dialysis patients had been reported. Therefore, we will briefly report the fourth case which has recently been seen in our department. A 30-year-old white man with end-stage renal disease due to Berger's

disease on chronic haemodialysis since March 1988 was admitted to our department on 5 September 1997 for bilateral rupture of quadriceps tendons which occurred during jogging and was confirmed by RMI. The patient was known to have severe secondary hyperparathyroidism (iPTH = 2541 pg/ml) with high calcium phosphate product because he was non-compliant with the vitamino-calcic therapy and recalcitrant in the matter of the surgical parathyroidectomy. He also had anaemia resistant to high doses of rHuEPO and never took glucocorticoids, aluminium compounds, or fluoroquinolones. As stated in their report, there was severe anaemia (haemoglobin 7.5 g/dl), high serum phosphate (3.4 mmol/l), high normal serum calcium (2.45 mmol/l), and elevated serum alkaline phosphatase (670 U/l).

Tendon ruptures in dialysis patients were reported to be associated with B2-amyloidosis [2], but a biopsy of synovia was negative for amyloid in our patient, excluding this pathology as a cause of the tendinous ruptures. Likewise, gout, systemic lupus erythematosus, steroids, fluoroquinolones, and arteriosclerosis were reported to be risk factors predisposing to tendon ruptures [3]. However, these factors were also ruled out in our patient.

Ultimately, in our case, secondary hyperparathyroidism remained the main factor, explaining the avulsion of both quadriceps tendons as reported by Kalantar-Zadeh *et al.* [1] and firstly proposed by Preston [4].

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Significant removal of phenytoin during high flux dialysis with cellulose triacetate dialyzer

Sir,

End-stage renal failure (ESRF) patients who are maintained on chronic haemodialysis may require phenytoin (dilatant) therapy for control of seizure disorders. The pharmacokinetics for phenytoin differ markedly between patients with normal renal function and uraemics. Phenytoin is highly protein-bound (~90%) in normal serum. However, the protein binding is significantly reduced (70–80%) in uraemic serum, due to the accumulation of dialysable uraemic toxins that displace phenytoin from albumin [1]. This decrease in the protein binding is accompanied by an increase in the volume of distribution (0.5–1.0 l/kg) for the bound drug, while the volume of distribution of the unbound drug (free phenytoin) is not changed. Thus, the accepted therapeutic range for total drug concentration of 10–20 mg/l for normal renal function is reduced to 5–10 mg/l in ESRF [2]. Moreover, phenytoin has a bioavailability of 85–95% after oral administration. Its plasma half-life is ≥ 24 h (in a dose-dependent fashion), and is unchanged in patients with ESRF [2]. Elimination is largely by hepatic metabolism, primarily to inactive hydroxylated metabolites; and solely the free drug

is available for hepatic elimination. In patients with normal renal function only 2% of the drug is excreted unchanged in urine.

Recently, we have observed that some of our ESRF patients receiving phenytoin experience a grand mal seizure at the end of dialysis or in the early post-dialysis period. This raised the possibility that a significant amount of phenytoin was removed during dialysis. However, this was in opposition to the two major references on drug prescribing in renal failure which indicate that phenytoin is not dialysable and that no supplemental dose would be required post-haemodialysis [2,3]. These conclusions were based on a few studies reported in the 1970s using a Cuprophane membrane (surface area $\sim 1 \text{ m}^2$) in which only 2–4% of the intravenous dose was recovered in the dialysate, with a dialysis phenytoin clearance rate of 7–14 ml/min [4,5].

We recently measured pre- and post-haemodialysis serum phenytoin levels on 10 different occasions in four ESRF patients requiring maintenance haemodialysis. Patients were dialysed for 3.5–4 h each session using a CT-190G dialysis membrane (cellulose triacetate, hollow fibre, surface area 1.9 m^2 , Kuf 36, KoA 920; Baxter HealthCare Corp., McGaw Park, IL, USA). All patients (one African-American, three Caucasian) were males with a mean age of 52 years (range, 39–64 years old), and a mean duration of 36 months (range, 3–84 months) on maintenance haemodialysis. The mean (\pm SD) pre-dialysis serum total phenytoin levels were $19.2 \pm 8.6 \text{ mg/l}$ (range, 9.8–38.1 mg/l), and the corresponding mean post-dialysis values were 11.7 ± 6.6 (range, 3.9–26.4 mg/l). The percentage reduction in serum total phenytoin level was $41.3 \pm 12.8\%$ (range, 25.4–64.0%). Moreover, for one patient (weight 59 kg) two separate measurements for arterial, venous, and dialysate total phenytoin levels were obtained; each different dialysis occasion yielded values of 6.9, 4.7, and 1.5, and 4.0, 2.2, and 0.7 mg/l, respectively. Dialysis plasma clearance [calculated as $(A - V/A) \text{ QB} \times (1 - \text{Hct})$, where A = arterial (pre-dialyser) and V = venous (post-dialyser) total phenytoin concentrations, QB = blood flow rate (ml/min), and Hct = hematocrit] was 94.5 and 130 ml/min, respectively (average, 112 ml/min). Dialysate clearance of total phenytoin, based on direct measurement of total phenytoin in the dialysate fluid extrapolated to a 4 h dialysis period for each different dialysis, was 216 and 104 mg/4 h of dialysis. Considering a volume of distribution of 1 l/kg and arterial (pre-dialyser) total phenytoin concentration representing the peripheral blood level, the amount of total phenytoin removed during 4 h of dialysis was $\sim 48.5\%$ of the total body phenytoin store.

It is the free fraction of serum phenytoin that exerts both its beneficial and toxic effects. Phenytoin elimination is largely by hepatic metabolism, primarily to inactive hydroxylated metabolites, and only the free fraction of the drug is available for elimination. A unique feature of phenytoin metabolism is its saturability where therapeutic levels

are very close to its maximal rate of enzymatic metabolism, leading to a non-linear relation between phenytoin doses and serum levels. Thus, very small changes in phenytoin doses can lead to unexpectedly large changes in serum levels; and, as hepatic metabolism is saturated, elimination moves from a logarithmic function to a linear one. In ESRF patients there is a marked reduction in the percentage of protein bound phenytoin [6] leading to higher serum free phenytoin concentration, despite a lower total level due to a higher volume of distribution in patients with ESRF. This effect will be compounded by a low serum albumin which would further reduce phenytoin binding and increase free serum phenytoin level. Phenytoin toxicity which is usually manifested as central nervous system dysfunction correlates with its free serum level. The earlier reports, using very low flux Cuprophane membrane, indicate that phenytoin is not dialysable [4,5]. This has been widely reflected in the major reference literature [2,3]. However, our results indicate that a very significant quantity of phenytoin is removed with the CT-190G high flux dialyser; which together with the removal of uraemic toxins resulting in enhanced protein binding [1], can lead to a significant reduction in the serum free phenytoin level at the end of a dialysis session. Potentially this could precipitate seizure activity near the end of dialysis or in the early post-dialysis period.

This is the first report indicating significant dialysability of phenytoin with a high flux membrane. We suggest that patients receiving phenytoin who are being dialysed with the new high flux membranes may require an extra dose of phenytoin to be administered immediately pre-dialysis period to maintain the post-dialysis free serum phenytoin level within the therapeutic range.

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