**Letters and Replies**

[The views expressed in Letters do not necessarily represent the views of the Editor]

**How to keep the dialysis patients normotensive?**

Sir,

Allow me to comment on the Personal Opinion of my old friend Guy Laurent on how to normalize blood pressure in dialysis patients [1]. Whilst applauding the magnificent results obtained in Tassin, I feel that one vital factor in the Tassin recipe was not mentioned by Dr Laurent. According to personal information I am assured that patients are placed on salt restricted diets which average 4 to 5 g of salt per day. I do not believe the results obtained in Tassin can be reproduced without salt restriction.

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**Reply**

Sir,

My dear friend Stanley Shaldon is quite right when he states that salt restriction is mandatory to achieve blood pressure control in hemodialysis. I could not possibly be complete and say everything in this 'personal opinion' within the strictly allotted limit of a few hundred words.

Indeed a recent survey of our patients population indicates a mean salt intake of 5 g per day, which correlates well with a mean interdialytic weight gain of 1.5 kg.

But may I ask a question: when every nephrologist knows the necessity of this low salt diet, how can we explain that over 50% of the patients on dialysis remain hypertensive and/or receive antihypertensive medications?

I suggest the same answers: (i) lack of ‘doctor dose’: it takes time to explain the necessity of this restriction and to control the evolution of the dry weight at each session; (ii) lack of time: what is the good of a salt restriction if on the other hand one must increase the dialysate sodium concentration or give saline to prevent or to treat the hypertensive episodes and cramps induced by the very high ultrafiltration rate needed by a too short dialysis session?

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**Left ventricular consequences of renal transplantation and calcium-channel blockers**

Sir,

In their very interesting article, Rockstroh and colleagues have shown that echocardiographically-derived left ventricular morphology of renal transplant patients given nitrendipine evolved in a different way compared to matched non-treated controls, where both groups had rigorous, effective and equal control of blood pressure [1]. There are several questions that arise.

First to be considered are the implications of the fact that control and nitrendipine groups, though well-matched in many ways, did not start this study with the same LV morphology (their Table 5)—specifically, the group to receive nitrendipine had larger hearts (LVM 163 ± 43 cf 139 ± 37, $P = 0.06$) by virtue of having thicker left ventricular walls (RWT 0.48 ± 0.08 cf 0.42 ± 0.08, $P = 0.039$). It is not clear why this should be, but issues such as regression to the mean may cloud the given interpretation of events. As no normal values are given for LV dimensions, it is difficult to decipher exactly how many patients had LVH (which can be defined as LVM > 110 g/m² for females, > 130 g/m² for males) at entry, and after the study period. While changes in LV geometry are of importance [2] one is struck by the fact that the largest difference of all was the condition of the two groups at the study outset, and subsequent changes were smaller and in opposite directions, meaning that at study end, both groups had similar LVM, though the change for the nitrendipine group was a reduction in LVM brought about by a reduction in wall thickness, tempered by an unexplained increase in LV internal diameter, while for the placebo group the change was an increase in LVM brought about by a thickening of both LV walls. As haematocrit, and the AV fistula, have powerful influences on LV diameter [3], I assume that there were no systematic differences in haemoglobin and patency of AV fistula in the two groups over the study period?

I am not clear that there is additional risk of adverse cardiac events if subjects alter their LVM but stay within ‘normal’ values e.g. go from normal to high/normal ranges, which is why we need to know the proportion of patients in each group at beginning and end that had LVH. I am not convinced that the nitrendipine group if it had been given placebo instead would necessarily have seen an alteration in LVM. I am not clear if the authors are arguing that nitrendipine reversed existing LVH, as their interpretation suggests, or, as they also state, is ‘cardioprotective’, that is to say, prevented more LVH. Semantics can matter. If the trial had included a reversal or switch of therapy, and had LV geometry then changed appropriately, this would have been highly persuasive evidence of cause and effect. Finally, echocardiography, though convenient and much practised, is a very blunt instrument when assessing LV mass before and after an intervention, as recent studies have shown [4]. Indeed, the standard error of LV mass estimations using M-mode echocardiography is > 30 g [5]; given the general problems with standardization, such as repeating the same views in a given patient at the end of a study as at the beginning, and inter-observer variations, it is questionable whether with the small numbers in this study the ‘differences’ in LV mass are real.

In fact, studies by Gerard London’s group in haemodialysis patients have shown that nitrendipine is capable of altering arterial wave reflections from peripheral sites, and, by so doing, reducing aortic pressure and increasing aortic compliance, which effects were shown to have highly favourable
cardiac consequences [6,7]. Brachial artery blood pressure is frankly of much lesser importance than aortic blood pressure with respect to the left ventricle. These changes in wave reflection intensity and timing are the likely explanation of nitrendipine’s action in the drug-treated group [8].

I do not understand the generalization in the discussion that ‘dihydropyridine calcium channel blockers have a rapid onset and a short duration of action’. The dihydropyridine amlodipine has a half-life of about 50–60 h. Lacidipine has a longer duration of action too. There is certainly an important issue as to abruptness of action, with stimulation of the sympathetic nervous system, but this could occur with a dihydropyridine or a non-dihydropyridine [9]. Another, separate issue is systematic pharmacological differences inducing different biological effects, as argued repeatedly by Bakris and co-workers in diabetic nephropathy studies [10].

This study is of merit, and may add to the expanding canon supporting the concept that reversal of LVH can occur in treated secondary hypertension, within the limitations of serial echocardiography. Ultimately, if drugs can be shown to be both ‘nephro-’ and ‘cardio-’ protective after renal transplantation, the arguments for their use are persuasive.

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Reply

Sir,

We are grateful for the important questions raised by Dr Goldsmith and although some cannot be answered by this study it might lead to further studies in this field which are urgently warranted. We agree that despite careful matching procedure and randomization both study groups varied with regard to left ventricular morphology at study begin which may be a result of the relatively small study number. Since left ventricular structure is assessed by continuous parameters such as left ventricular mass and relative wall thickness we feel that it only adds additional bias by further arbitrarily dividing the groups into two categories, those with and without left ventricular hypertrophy. With regard to hematoctrit and AV fistula no systemic difference in haemoglobin and patency of AV fistula was observed within the two groups over the study period.

We would agree that a trial including a switch or a reversal of therapy with nitrendipine would add further valuable information on the possible cardioprotective effects of calcium-channel blockers on left ventricular structure in renal transplant recipients. However, we would like to underline that our study is the first examination to look at potential reduction of left ventricular hypertrophy in secondary hypertension and therefore, cannot address all important issues in one study. We hope that our work stimulates and possibly induces further investigations in this rather new field.

We would also like to thank Dr Goldsmith for pointing out that nitrendipine is capable of altering arterial wave reflections from peripheral sites leading to overall reduction in aortic pressure and increased aortic compliance. Indeed this may be part of the explanation for the observed effect of nitrendipine on left ventricular hypertrophy in renal transplant recipients.

Regional incidence of rapidly progressive glomerulonephritis in Estonia

Sir,

Epidemiological studies reveal surprisingly low incidences of various autoimmune diseases, e.g., primary biliary cirrhosis (PBC), coeliac disease (CD) and insulin-dependent diabetes mellitus (IDDM) in Estonia compared with neighbouring countries [1–3]. The reasons for these differences are unknown. The incidence of glomerulonephritides with autoimmune pathogenesis in Estonia has not been studied previously. We therefore sought to establish the regional incidence of rapidly progressive glomerulonephritis (RPGN) in the part of South Estonia served by Clinics of the University of Tartu. Virtually all patients with newly diagnosed glomerulonephritis are referred for diagnosis and treatment to the Departments of Medicine of the University of Tartu. The catchment area of these departments is located in South Estonia for which regional census data for the total population were retrieved from the Population Register, Statistical Bureau, Tartu, Estonia. We selected patients with RPGN diagnosed between 1 January 1991 and 31 December 1994 and calculated the regional incidence of RPGN among a
population comprising approximately 486,000 inhabitants of Finno-Ugric and Slavic origin. Assessment of the clinical picture, tests for circulating autoantibodies, e.g. anti-nuclear (ANA), anti-glomerular basement membrane (anti-GBM) and anti-neutrophil cytoplasmic (ANCA) autoantibodies (AAB) and renal biopsy data allowed diagnoses to establish in most cases. Renal biopsy was prepared for light and immunohistochemistry by routine techniques. We adopted the traditional classification of RPGN: (i) patients with linear fluorescence along the GBM; (ii) patients with granular fluorescence; (iii) those with scanty or no immune deposits [4]. AAB tests were performed in all sera of patients with RPGN at the time of renal biopsy. ANA-s were determined by indirect immunofluorescent assay (IIF); ANCA-s by IIF on glass slides using ethanol-fixed granulocytes [5]. ANCA specificities were determined by ELISA using purified myeloperoxidase (MPO) and proteinase-3 (PR-3). Anti-GBM-AB were detected by commercially available ELISA kit (WiesLab).

Epidemiological and clinical data on patients with RPGN are listed in Table 1. In patients 6, 9, 10 and 12 renal biopsy data were not available. Pulmonary haemorrhage was present in patients 7 and 9. ANA was only found in two patients with biopsy-proven lupus nephritis. Anti-GBM was detected in three patients. ANCA-s were detected by IIF in sera from eight patients with RPGN who were positive for MPO or PR3 in all but one case (patient 11), in whom the antigen was unidentified. Both anti-PR-3 and anti-MPO antibodies were found in the serum of patient 3. Thus, for all patients that fulfilled the criteria of RPGN during the study period, the estimated annual incidence of RPGN was 0.55 per 100,000 in a region comprising approximately 486,000 inhabitants.

The incidence appears low when compared with other reports. However, few studies of the incidence of RPGN have been performed since ANCA tests became routine. Nevertheless, in three recent studies, the reported incidence of ANCA-associated renal diseases alone exceeds our total for RPGN: Garrett et al., [6] 0.6 per 100,000; Andrews et al. [7] 0.7 and Pettersson et al. [8] 0.9 per 100,000. Clearly these data would be expected to underestimate the total incidence of RPGN. Moreover, the incidence of RPGN in our study is lower when compared with a study from Heidelberg which found an incidence of RPGN of 0.7 per 100,000 [9].

This could imply a lower incidence of autoimmune glomerulonephritides in Estonia. It is also likely, however, that differences in diagnostic approaches and or demographics contribute to these discrepancies. Pettersson et al. found that the annual incidence of necrotizing crescentic GN in Stockholm doubled over 7 years, from 0.6 to 1.2/100,000 [8]. This was thought due, in part, to ageing of the population and also to changing patterns of diagnostic tests and procedures. Moreover, children were excluded from the study. In reviewing the diagnoses of patients whose sera were sent to our laboratory for AAB tests, we concluded that the lower incidence of RPGN in our study may reflect, in part, a low referral rate. Non-nephrologists may not appreciate renal involvement in cases of systemic disease, especially in the elderly. In keeping with this interpretation is the finding that the mean age of our patients with systemic vasculitis (48 years, age range 34–57 years) is lower than that in most published studies. Andrassy et al. [9] reported a mean age of 56 years (range 36–68); Pettersson et al. 67 years (range 20–84) [8]. The lower average life expectancy in Estonia (68 years; M = 62, F = 74 years) may also influence the incidence of RPGN in our region but this factor could not explain the lower incidences of diseases such as IDDM or CD which affect younger patients.

In Estonia, autoimmune diseases are relatively uncommon, as demonstrated by specific studies of PBC, CD and IDDM [1–3]. RPGN may also fall into this pattern but more data are needed before this can be determined with certainty.

We acknowledge Dr Allan Wiik (Statens Serum Institute, Denmark) for his kind help in donation of reference sera and introducing ANCA methods in Tartu; Drs Kaljo Poldvere, Aleksander Lohmus and Peeter Dmitriev for help—that fulfilled the criteria of RPGN during the study period, reviewing the diagnoses of patients whose sera were sent to our laboratory for AAB tests, we concluded that the lower incidence of RPGN in our study may reflect, in part, a low referral rate. Non-nephrologists may not appreciate renal involvement in cases of systemic disease, especially in the elderly. In keeping with this interpretation is the finding that the mean age of our patients with systemic vasculitis (48 years, age range 34–57 years) is lower than that in most published studies. Andrassy et al. [9] reported a mean age of 56 years (range 36–68); Pettersson et al. 67 years (range 20–84) [8]. The lower average life expectancy in Estonia (68 years; M = 62, F = 74 years) may also influence the incidence of RPGN in our region but this factor could not explain the lower incidences of diseases such as IDDM or CD which affect younger patients.

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Table 1. Clinical data of patients with RPGN

<table>
<thead>
<tr>
<th>Male/female age</th>
<th>Serum creatinine</th>
<th>U prot</th>
<th>Autoantibodies</th>
<th>Clinical diagnosis</th>
<th>Treatment, 1 year outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. M, 18</td>
<td>156</td>
<td>5.6</td>
<td>negative</td>
<td>Mesangiocapillary GN</td>
<td>Transplanted, alive</td>
</tr>
<tr>
<td>2. F, 16</td>
<td>147</td>
<td>6.8</td>
<td>anti-GBM, IIF-ANCA, anti-MPO</td>
<td>Anti-GBM GN</td>
<td>Transplanted, alive</td>
</tr>
<tr>
<td>3. F, 19</td>
<td>129</td>
<td>2.0</td>
<td>IIF-ANCA, anti-MPO, anti-PR-3</td>
<td>Pauci-immune GN</td>
<td>Im. suppress., alive</td>
</tr>
<tr>
<td>5. M, 27</td>
<td>1040</td>
<td>2.4</td>
<td>negative</td>
<td>Post-infectious GN</td>
<td>HD, deceased</td>
</tr>
<tr>
<td>6. M, 34</td>
<td>435</td>
<td>1.3</td>
<td>IIF-ANCA, anti-PR-3</td>
<td>Systemic vasculitis</td>
<td>Transplanted, alive</td>
</tr>
<tr>
<td>7. M, 16</td>
<td>1173</td>
<td>1.8</td>
<td>anti-GBM</td>
<td>Anti-GBM GN</td>
<td>Transplanted, alive</td>
</tr>
<tr>
<td>8. F, 27</td>
<td>800</td>
<td>3.0</td>
<td>IIF-ANCA, anti-MPO</td>
<td>Pauci-immune GN</td>
<td>Transplanted, deceased</td>
</tr>
<tr>
<td>9. M, 20</td>
<td>237</td>
<td>2.4</td>
<td>anti-GBM</td>
<td>Anti-GBM GN</td>
<td>HD, deceased</td>
</tr>
<tr>
<td>10. M, 51</td>
<td>320</td>
<td>1.2</td>
<td>IIF-ANCA, anti-PR-3</td>
<td>Systemic vasculitis</td>
<td>Im. suppress., alive</td>
</tr>
<tr>
<td>11. F, 32</td>
<td>540</td>
<td>2.2</td>
<td>ANA, IIF-ANCA</td>
<td>SLE</td>
<td>Transplanted, alive</td>
</tr>
<tr>
<td>12. F, 53</td>
<td>260</td>
<td>2.8</td>
<td>IIF-ANCA, anti-PR-3</td>
<td>Systemic vasculitis</td>
<td>Im. suppress., alive</td>
</tr>
<tr>
<td>13. M, 54</td>
<td>800</td>
<td>8.1</td>
<td>negative</td>
<td>Chronic GN</td>
<td>Transplanted, dead</td>
</tr>
<tr>
<td>14. M, 23</td>
<td>650</td>
<td>2.7</td>
<td>ANA</td>
<td>SLE</td>
<td>Transplanted, alive</td>
</tr>
</tbody>
</table>
8. Pettersson E, Sundelin B, Heigl Z. Incidence and outcome of follow-up proteinuria was 0.5 g/l of their treatment. We report a patient with HIV infection remission after 5 weeks of treatment. On the 14th week of follow-up proteinuria was 0.5 g/l, blood urea nitrogen 12.4 mmol/l, plasma creatinine 97.2 μmol/l, and creatinine clearance of 124 ml/min. The white-cell count was 4000/mm³, CD4+ T cell count: 30/mm³, CD8+ T cell count: 0.8–4.9 with normal values of IgG, IgM, C3, C4, ANA, anti-DNA, ANCA, HbsAg, and IgM. C3, C4, ANA, anti-DNA, ANCA, HbsAg, and IgM were seen at glomerular vascular poles. Immunofluorescence pattern demonstrated diffuse mesangial deposits of IgG (+++/+++/+++), IgA (++) in all glomeruli, with granular deposits in some small arterioles. Weak traces of C3, IgG and IgM were seen at glomerular vascular poles.

We started antiproteinuric treatment with captopril at a dose of 25 mg twice a day. It was well tolerated without hypotension or deterioration of renal function. Proteinuria decreased progressively and nephrotic syndrome was in remission after 5 weeks of treatment. On the 14th week of follow-up proteinuria was 0.5 g/l. Simultaneously total protein and serum albumin increased (Figure 1).

Fig. 1. Course of proteinuria, serum total proteins and serum albumin in relation to captopril treatment.
IgA nephropathy has been described in 28 HIV-infected patients so far (MEDLINE June 1997, [6]), but most of them were in necropsy studies. Beaufils et al. [4] reported diffuse mesangial deposits of IgA in 9 (7.7%) of 116 necropsies from HIV-infected patients, most of them showing minimal proteinuria. Nochy et al. [2] in a series of 60 kidney-biopsied patients with HIV infection and urine abnormalities found IgA nephropathy in four (6.6%) of them. This incidence was higher than the one detected in the general population, and suggests a possible relation between HIV infection and the presence of IgA nephropathy.

The presence of polymeric IgA1 and the detection of immune complexes HIV p24 bound to anti-p24 IgA in blood and in renal tissue give support to the hypothesis that IgA nephropathy in HIV-infected patients is an immune-complex disease [3], with a different pathogenic mechanism from the HIV-associated nephropathy [1,3]. The histological findings in our patient were diagnostic of IgA nephropathy; serum IgA levels were elevated and the determination of circulating complexes were negative, results similar to those reported by others [6]. In HIV-infected patients, IgA nephropathy was usually asymptomatic, and nephrotic range proteinuria was detected in only four (14%) of the 28 cases published in the medical literature.

In HIV patients nephrotic syndrome induces a nitrogen negative balance, it aggravates the immunodeficiency state, and it exposes the patient to various secondary complications [5,7]. In our patient, progressive reduction of proteinuria and remission of nephrotic syndrome was observed after captopril administration. Burns et al. [8] obtained the same effect with the administration of lisinopril to a HIV-infected patient with focal and segmental glomerulosclerosis, but no one case has been reported previously with this effect in patients with IgA nephropathy associated with HIV infection. This reduction of proteinuria has been related to improvement of intrarenal haemodynamics, but Ouellette et al. [9] detected elevated levels of angiotensin-converting enzyme in HIV-infected patients, suggesting that this enzyme could play a more specific role in the pathogenesis of glomerulosclerosis through the modulation of the cellular growth and synthesis of mesangial matrix, or even affecting HIV proteinase activity [10].

Our case indicates that captopril should be considered in the treatment of proteinuria in HIV patients with IgA nephropathy, although more patients and longer follow-up are needed to settle its beneficial effect on the evolution of the renal disease and the course of HIV patient.

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Acute renal failure and alendronate

Sir,

Alendronate sodium, an aminobiphosphonate, is a selective inhibitor of osteoclast-mediated bone resorption; it is used for the treatment of postmenopausal osteoporosis [1] and of Paget’s disease [2,3].

The impressive results of the Fracture Intervention Trial [1] showed that alendronate reduces the frequency of morphometric and clinical vertebral fractures, as well as other clinical fractures in women with osteoporosis at high risk of fracture. However, there is no information on alendronate in patients with diminished renal function. In the Fracture Interventional Trial women with impaired renal function (serum creatinine > 144 µmol/l) were excluded [1]. According to the preliminary data alendronate is not recommended for patients with mild impairment of renal function.

There are no data on the use of alendronate in patients with multiple myeloma. We present a woman with IgG kappa myeloma who developed acute renal failure associated with alendronate treatment. A 57-year-old woman was well until 1994, when she developed skeletal pain localized in the thoracic and lumbar-sacral regions. Spondylodyplasia and osteoporosis were diagnosed, but orthopaedic therapy produced no improvement. Six weeks before admission the patient consulted an internist.

Our case indicates that captopril should be considered in the treatment of proteinuria in HIV patients with IgA nephropathy, although more patients and longer follow-up are needed to settle its beneficial effect on the evolution of the renal disease and the course of HIV patient. At this time erythrocyte, platelet, white blood cell, and differential counts were normal, the serum creatinine level was 62 µmol/l, erythrocyte sedimentation rate 17 mm/h, and urinalysis (2 ×) were normal.

Two weeks later therapy with alendronate (10 mg daily) was initiated. She continued to take the drug for a month despite nausea, but because of weight loss (5 kg) and vomiting she was admitted to the General Hospital in Linz on 15 October 1996. Laboratory findings on admission are shown in Table 1. Additional laboratory findings were as follows: serum protein 73 g/l; electrophoresis: albumin 51.0 g/l, globulins alpha-1 2.2 g/l, alpha-2 2.9 g/l, beta 7.6 g/l, gamma 6.3 g/l. Serum immunoglobulins: IgG 4.48 g/l, IgA 0.14 g/l, IgM 0.13 g/l. An IgG kappa band was found in the serum. Urinalysis revealed a large amount of protein (5.86 g/day), while on urine electrophoresis only a globulin fraction was seen, raising suspicion of the formation of ‘immune complexes’. Urinary electrolytes: sodium 84 mmol/l, potassium 20 mmol/l, chloride 84 mmol/l. A skeletal radiological survey showed lytic lesions in the skull, in the ilium,
ischemium, in the right distal femur, and in the left proximal humerus.

Examination of a bone-marrow biopsy specimen revealed a large population of abnormal plasma cells (56%), suggesting a diagnosis of plasma cell myeloma, which was confirmed by renal biopsy. Two weeks later serum and urinary analyses were repeated (Kurt Bauer, Donauklinik, Vienna). IgG kappa and free kappa light chains (1.22 g/l) were found in the serum and kappa Bence Jones protein and kappa light chains (269.4 mg/l) in the urine. The acute renal failure improved after alendronate was discontinued (BUN 13.6 mmol/l, serum creatinine 388 μmol/l) and normalized after three high-dose pulses of vincristine—doxorubicin—dexamethasone chemotherapy (in February, BUN 4.3 mmol/l, serum creatinine 97 μmol/l).

In this patient the predominant symptoms of multiple myeloma were skeletal pain and diffuse osteoporosis. A skeletal radiological survey showed many osseous lytic lesions. Multiple myeloma coexists frequently with renal dysfunction. However, before alendronate was given, renal function was normal (s-creatinine 62 μmol/l) and urinary analyses performed twice revealed no proteinuria.

Just 1 month after starting alendronate orally, an acute, non-oliguric renal failure (BUN 19.3 mmol/l, s-creatinine 451 μmol/l) developed. The urine output was normal but severe proteinuria (5.86 g/24 h) with light chain and Bence Jones proteins was noted.

Alendronate can cause chemical oesophagitis, including severe ulcerations in some patients [4–6]. Therefore nausea, vomiting, loss of 5 kg body-weight, dehydration, and hypovolaemia may have predisposed to the development of acute renal failure in our patient. Alendronate sodium (4-amino-1-hydroxybutylidene biphosphonic acid monosodium salt trihydrate) is not metabolized in animals or humans, and the same is true for all biphosphonates. Studies on rats indicated that 30–40% of systemically administered alendronate is excreted in the urine within 24 h with most of the drug being excreted in the first 3–4 h [7].

Preclinical studies in humans show that following a single i.v. dose of radiolabelled alendronate about 50% goes to bone, the rest being excreted in the urine within 72 h. Renal excretion is the only route of elimination. Renal clearance was estimated to average 71 ml/min. Since alendronate is eliminated predominantly by renal glomerular filtration with a presumed secretory component specific to biphosphonate, the renal excretion may be decreased by a significant compromise of renal function [8].

For the development of acute renal failure in our patient with IgG kappa myeloma some pathogenetic factors may be discussed. First, alendronate may have potentiated the nephrotoxicity of light-chain proteins, second, a synergistic nephrotoxic effect of both light-chain proteins and alendronate cumulation by impaired renal function, and third alendronate-induced chemical alterations on oesophagus, leading to vomitus, dehydration and hypovolaemia. We postulate that alendronate either exaggerated the basic disease or that both alendronate and kappa light-chain proteins had a synergistic toxic effect on renal tubular cells.

We conclude that control of renal function is necessary after starting alendronate treatment in patients with suspected light-chain disease.

### Table 1. Laboratory findings on admission

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>75</td>
</tr>
<tr>
<td>Erythrocytes (T/1)</td>
<td>3.78</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.5</td>
</tr>
<tr>
<td>Haematocrit (%vol.)</td>
<td>34.4</td>
</tr>
<tr>
<td>Platelets (G/l)</td>
<td>295</td>
</tr>
<tr>
<td>White cell count (G/l)</td>
<td>11.4</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>75</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>18</td>
</tr>
<tr>
<td>Monocytes</td>
<td>4</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>2</td>
</tr>
<tr>
<td>Basophils</td>
<td>1</td>
</tr>
<tr>
<td>BUN (mmol/l)</td>
<td>19.3</td>
</tr>
<tr>
<td>S-creatinine (μmol/l)</td>
<td>451</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>12</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>138</td>
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<tr>
<td>Potassium (mmol/l)</td>
<td>6.5</td>
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<tr>
<td>Chloride (mmol/l)</td>
<td>107</td>
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<tr>
<td>Calcium (mmol/l)</td>
<td>2.46</td>
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<tr>
<td>Phosphate (mmol/l)</td>
<td>2.08</td>
</tr>
<tr>
<td>Magnesium (mmol/l)</td>
<td>0.85</td>
</tr>
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</table>


### Acute renal failure mimicking haemolytic uraemic syndrome in a patient with factor V Leiden mutation and essential thrombocytemia

Sir,

It is well known that thrombosis is the result of multiple genetic and non-genetic risk factors. It has recently been demonstrated that the inherited resistance to activated protein C (APC), which is caused by a single point mutation in the gene for coagulation factor V (predicting replacement of Arg506 with Gln) is strongly associated with a 5–10 (heterozygosity) to 50–100-fold (homozgyosity) increased risk of the thrombosis [1,2].

We will describe the case of a patient carrying factor V (FV) genetic mutation (Arg506→Gln) in heterozygous form, who used oral contraception and developed essential thrombocytemia and acute renal failure mimicking haemolytic uraemic syndrome present with tubular and focal cortical necrosis.

An obese 29-year-old woman with heterozygous β thalasse-
Haemolytic uraemic syndrome during cyclosporin therapy for Behcet’s disease

Sir,

Cyclosporin A is being used increasingly for the treatment of ocular inflammatory disease [1]. Haemolytic uraemic syndrome (HUS) is a rare but well-described complication of cyclosporin following renal and bone marrow transplantation [2,3]. HUS has also been described in a small number of cases in whom cyclosporin was administered for autoimmune diseases, the outcome being dialysis dependence or death [4,5]. Cyclosporin-induced HUS may, however, have a favourable outcome if diagnosis is made early as we demonstrated recently in a patient with Behcet’s disease.

A 26-year-old Caucasian woman presented with a ten-week history of ocular inflammation. She had also complained of intermittent arthralgia, but there was no history of orogenital ulceration or rashes. She could not perceive light in the left eye as a result of previous panuveitis giving rise to a cataract and rubeotic glaucoma, despite therapy with systemic steroids. At presentation the visual acuity in her right eye was 6/60 with a small hypopyon and marked vitritis, together with necrotising retinal vasculitis optic atrophy and cystoid macular oedema. Systemic examination was normal, the blood pressure being 100/70 mmHg. Immunology was negative, including ANF, ANCA and C3 and C4. A diagnosis of Behcet’s disease was made on the basis of the fundal findings, and she was commenced on prednisolone 2 mg/kg and cyclosporin A 10 mg/kg (250 mg twice daily). Apart from mild paraesthesiae, treatment was well-tolerated. A rise in blood pressure was treated by a gradual dose reduction of the cyclosporin to 5 mg/kg. Gomerular filtration rate (GFR) remained fairly stable throughout the period of treatment. Her retinal vasculitis settled and visual acuity improved to 6/9 over three months during which time the prednisolone was reduced to 15 mg daily and cyclosporin to 4 mg/kg. On this dose of steroids and cyclosporin (level 34 ng/ml), she relapsed and required further high dose prednisolone. Enalapril was added to control her blood pressure. Eleven months after starting cyclosporin, she complained of worsening epigastric pain and vomiting, despite having been on ranitidine.

The patient was discharged with a creatinine clearance of 30 ml/min. During the follow-up time of 3 years, alkyllating agents (hydroxyurea) were administered on an intermittent schedule together with diuretics, antihypertensive agents and warfarin. Renal function remained stable as well as platelet count.

This is, to our knowledge, the first case of haemolytic uraemic syndrome and ischaemic renal damage in a patient with FV genetic mutation. The role of the genetic background coupled with other risk factors (i.e. oral contraception) in determining essential thrombocytaemia, cerebral and renal ischaemic damage, haemolytic-uraemic syndrome is an interesting matter for speculation [4,5].
We recently treated a 54-year-old woman with a presumed diagnosis of capnocytophagia sepsis who exhibited a dramatic response to large volume fresh frozen plasma. She presented 4 days after a dog-bite to the hand with a 48-h history of backache, neckache, fever with rigors, confusion, and a purpuric rash notably limited to the face (including a subconjunctival haemorrhage), hands, buttocks and feet. Tests revealed thrombocytopenia (24 × 10^9/l), a neutrophil leukocytosis (23.2 × 10^9/l), mildly deranged clotting indices (PT 22.2 (NR 12–15.6), APTT 32.4 (NR 23.8–34.7) D-dimer 1000 (NR < 500) with normal fibrinogen 3.5 g/l (NR 1.5–4), and renal failure (urea 25 mmol/l, creat 520 μmol/l). LDH and AST were raised (2055 u/l (NR < 430) and 855 μl/l (NR < 43)) in the context of a normal γ-GT suggestive of haemolysis. There was occasional red-cell fragmentation on the peripheral blood film.

An initial working diagnosis of meningococcal septicaemia was made and treatment initiated with penicillin. Subsequently treatment included amoxycillin, metronidazole, and cefotaxime in view of the dog-bite. She received blood, platelets, and 8 units of fresh frozen plasma (FFP) over 2 days, renal replacement therapy being provided by continuous venovenous haemofiltration.

Despite an improvement in her clinical condition, she remained thrombocytopenic for 9 days. During this time red-cell fragmentation was seen on blood films and she was found to have hypocomplementaemia (C3 0.65 g/l). We would tend to agree with Finn et al. [1,2] that plasma exchange may have a role in treatment. Experience in this case is that plasma exchange was not helpful.

Within 48 h the platelet count started to rise and within 4 days had normalized (Figure 1), allowing renal biopsy on day 12. This, however, showed ischaemic changes only and no evidence of thrombotic microangiopathy. In the context of a normal γ-GT, there seemed to be no precipitating cause for the occurrence of HUS in this case after eleven months of cyclosporin therapy.

The mechanism of HUS, therefore, cannot be easily explained in this case as high cyclosporin and AST were raised (2055 u/l (NR < 430) and 855 μl/l (NR < 43)) in the context of a normal γ-GT suggestive of haemolysis. There was occasional red-cell fragmentation on the peripheral blood film.

**Acute renal failure with hypocomplementaemic microangiopathy secondary to presumed capnocytophagia sepsis; response to fresh frozen plasma**

Sir,

Two recently published letters have described the potentially devastating effects of capnocytophagia sepsis complicating a dog-bite, including acute renal failure and digital gangrene [1,2].
Use of i.v. iron saccharate in haemodialysis patients not responding to oral iron and erythropoietin

Sir,

It has been reported that a significant number of dialysis patients either do not respond to erythropoietin (Epo), or require high doses of the drug (Epo) [1,2]. Deficiency of iron has been found to be a major cause of Epo non-responsiveness, but the route of administration of iron, whether oral or i.v. for effective erythropoiesis is controversial [3,4]. This study evaluates the use of i.v. iron saccharate in patients who did not optimally respond to Epo in spite of oral iron administration.

Seventeen patients (12 females and 5 males) were included in this 4-month study. Average age was 42.2 years (range 20–76). All of the patients had been on regular haemodialysis for longer than 6 months and all had been on i.v. Epo (Eprex, Cilag) for at least 6 months. All the patients were chosen because of poor response to Epo as determined by high Epo dosages (up to 150 mg/kg/dialysis), and/or suboptimal haemoglobin and haematocrit levels (<8.5 g/dl and 24%, respectively). All patients were on oral iron supplementation (47 mg bioavailable iron and 5 mg folic acid) three times daily. All oral iron supplementation was stopped during the study period. All other causes of poor response to Epo were ruled out.

Patients were given a bolus of i.v. iron (III) hydroxide saccharate (Ferosac, Spimaco, Saudi Arabia, 100 mg/5 ml) according to the following formulae:

\[
\text{Dry weight} \times (\text{Desired Hb} - \text{Present Hb}) \times 0.24 + 500, \\
\text{or} (\text{Desired Hb} - \text{Present Hb}) \times 150.
\]

The target Hb was 10.0 g/dl in patients with arteriovenous (AV) grafts and 11.0 g/dl in patients with AV fistulae. The bolus dose ranged between 300 and 800 mg, after which no further iron was given for 1 month in order to monitor the effect of the bolus dose. After 1 month, 50 mg i.v. iron was given weekly. Hb, Hct, and red-cell parameters were measured prestudy and weekly thereafter. Serum ferritin was measured prestudy and then monthly over the course of the study.

Total i.v. iron administration averaged 1350 mg (range 1100–1800) per patient. Statistical analysis was performed using the students t-test. A P value of <0.05 was considered statistically significant. Throughout the study, none of the patients experienced any untoward side-effects.

At the end of the study all the patients experienced a significant increase in Hb, Hct, and ferritin. The patients parameters at baseline (prestudy), after the bolus dose, and post-study are shown in Table 1. Thirteen of the patients reached the target Hb without a significant increase in Epo dose (66.3 IU/kg/dialysis at baseline compared to 73.2 post-study). In a few patients it was necessary to increase Epo doses slightly and temporarily, which can be explained by the break of 4 weeks without iron between the bolus dose.
and the maintenance phase; yet during this time Hb levels rose higher than they were pretreatment. We feel that if the maintenance phase of treatment had been started immediately after the bolus phase, the response would have been much quicker and Epo doses may have been reduced further.

We conclude that i.v. ferrous saccharate is a safe, effective, cost-saving drug and more convenient than oral iron for patients on long-term haemodialysis treatment receiving Epo. In addition, we advocate small weekly doses of i.v. iron in HD patients for better monitoring of iron status and to avoid iron overload.

**Table 1. Comparison of Hb, Hct, ferritin and Epo doses (mean ± standard deviation) at baseline, post-bolus (1–2 weeks) and post-study (4 months) in chronic haemodialysis patients receiving i.v. iron saccharate**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-bolus</th>
<th>Post-study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>7.75 ± 1.41</td>
<td>8.32 ± 1.11</td>
<td>10.6 ± 1.48*</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>23 ± 4.2</td>
<td>26 ± 3.0</td>
<td>31 ± 4.0*</td>
</tr>
<tr>
<td>Ferritin (mg/l)</td>
<td>51.0 ± 42.6</td>
<td>123.5 ± 103.7</td>
<td>206.0 ± 130*</td>
</tr>
<tr>
<td>Epo dose (IU/kg/treatment)</td>
<td>66.17 ± 19.64</td>
<td>72 ± 21.43</td>
<td>75.32 ± 39.4*</td>
</tr>
</tbody>
</table>

Compared to baseline: *P = 0.0006; bP = 0.0006; cP = 0.0001; dP = 0.50.

Removal of morphine but not fentanyl during haemodialysis

Sir. The very sick patients in intensive care units frequently require high doses of sedatives/hypnotics, especially when they are maintained on mechanical ventilation. It is not uncommon for these patients to develop different degrees of renal insufficiency, from mild insufficiency to severe oliguric acute renal failure. It has long been known that morphine can cause prolong central nervous system/respiratory depression in patients with severe renal failure, which may last for days after the drug has been discontinued [1–3].

Most of the morphine is glucuronidated in the liver to morphine-3-glucuronide, morphine-6-glucuronide, and nor-morphine. In chronic renal failure there is a gradual accumulation of morphine and its metabolites in the central nervous system (CNS). Morphine is concentrated by the choroid plexus, by an active transport mechanism, with CNS effects and toxicity being related to the concentration of free morphine and/or its metabolites in the cerebral grey matter. Approximately 60–90% of the free and conjugated derivatives of morphine are excreted in the urine, about 10% are excreted in the faeces (mainly through bile, gastric juice, and saliva), and some are excreted in sweat [1]. Earlier studies using radioimmunoassay (RIA) suggested that morphine half-life is markedly increased in patients with severe renal failure, resulting in a very prolonged sedation in this patient population [4]. However, subsequent studies have indicated that RIA is non-specific for morphine, since the antisera to some extent also detect the glucuronide metabolites [5–7].

Although there is no evidence that morphine-3-glucuronide has any pharmacological activity, morphine-6-glucuronide has been shown to be pharmacologically active and indeed may be more potent than morphine itself [8,9]. More recent studies using specific high-performance liquid chromatography (HPLC) methods, which accurately measure morphine and its metabolites separately, have shown that the elimination half-life of morphine itself is not prolonged with morphine and then remained elevated for a prolonged period, with elimination half-life for morphine-3-glucuronide of 41 ± 4 h (renal failure vs normal kidney function respectively) [10]. A very prolonged elimination half-life of the metabolites, some of which are more potent than morphine itself, would explain the prolonged CNS/respiratory depression observed in patients with renal failure. It also explains the high morphine plasma concentration and half-life reported in earlier studies using tests (RIA) that detected both morphine and its metabolites.

In an interesting report, three patients with chronic renal failure were described as having classical signs of intoxication with morphine (CNS/respiratory depression) in the absence of measurable quantities of morphine in the plasma [12]. The observed clinical effect was attributed to the accumulation of the glucuronide metabolites, particularly the pharmacologically active morphine-6-glucuronide, which persisted at very high plasma levels for an average of 7 days after discontinuation of morphine, during which period the patients had remained in severe respiratory depression [12].

In an earlier report on patients treated with continuous arteriovenous haemofiltration (CAVH) using Amicon Diafilter 20 (Polysulphone membrane, hollow fibre, 0.25 m²) it was noticed that haemofiltration was associated with an increased sedative requirement [13]. In a subsequent study in which i.v. morphine infusion was given to 12 critically ill patients, four of whom had severe oliguric renal failure requiring haemofiltration (Amicon Diafilter 20) and haemodialysis, morphine could be detected in the ultrafiltrate with a mean extraction efficiency of 47% [14]. With dialysis sessions of 3–5 h using the same Amicon Diafilters the mean fall in the serum concentration of morphine during dialysis with ultrafiltration was 75% (range 47–100%), and the mean fall during dialysis without ultrafiltration was 48% (24–84%) [14]. Interestingly, they found that the fall in serum morphine concentration was much more than the fall in serum creatinine. This finding was as one would have expected with a water-soluble drug with relatively low plasma protein binding (20–30% plasma protein bound). However, in a widely used reference book on drug prescribing in renal failure it has been indicated that morphine is not haemodialysable and there is no need for supplemental doses at the end of haemodialysis [15].
In this report we present two cases with end-stage renal disease (ESRD) who required high doses of morphine for pain management, one of whom additionally required fentanyl i.v. drip. The patients were on maintenance haemodialysis and the one who was conscious always complained of worsening of the pain in her ischaemic cutaneous ulcers, while she was being dialysed. Morphine serum levels were assayed by gas chromatography/mass spectrometry (GC/MS) in a reference laboratory (ARRIP Laboratories, Salt Lake City, Utah). Blood clearance rate (ml/min) was calculated as: \( \frac{A}{V/A} \) \( Q^°A \), when \( A \) = concentration of the drug in the arterial line (predialyzer), \( V \) = concentration of the drug in the venous line (postdialyser), and \( Q^°A \) = blood flow rate (ml/min). Plasma clearance rate (ml/min) was calculated as: \( \frac{A}{V/A} \) \( Q^°A \) \( 1 \) \% HCT.

### Case 1

A 32-year-old white female, ESRD secondary to lupus nephritis, S/P renal transplant, developed severe renal allograft failure due to postpartum haemolytic uraemic syndrome (HUS). The hospital course became complicated with severe *Clostridium difficile* colitis requiring total colectomy. The patient weighed 46 kg. She required morphine infusion at the rate of 5 mg/h while receiving mechanical ventilation. She was on maintenance haemodialysis 3 times a week, with F8 membrane (Fresenius, Bad Homburg, Germany; polysulphone, hollow fibre, Kuf 8.1, surface area 1.8 m², Koa 800). Dialysis was via a Permcath through the left internal jugular vein with a blood flow rate of 400 ml/min. Haematocrit at the time of study was 30%. After 2 h on dialysis, in one of the routine dialysis sessions, the arterial (predialyzer) serum morphine level was 79 ng/ml while the venous (postdialyser) serum level had declined to 61 ng/ml (23% extraction rate). Calculated blood and plasma clearances of morphine were 91 and 64 ml/min respectively.

### Case 2

A 22-year-old white female, ESRD secondary to primary hyperoxaluria type I awaiting combined kidney/liver transplantation, was suffering from severe pain in the lower extremities secondary to multiple cutaneous ischaemic ulcerations. Pain management included morphine sulphate contin 60 mg p.o. b.i.d., fentanyl patches 300 µg/h, and fentanyl PCA (patient-controlled analgesia) at 60 µg/h with an additional bolus of 50 µg at the start of haemodialysis. During routine dialysis sessions the patient always complained of marked worsening of the pain in the cutaneous ischaemic ulcers in the lower extremities. She weighed 42 kg and had a haematocrit of 31.7%. She was dialysed with a CA-210 membrane (Baxter Health Care Corp., McGaw Park, IL, USA; cellulose acetate, hollow fibre, Kuf 10.1, surface area 2.1 m², Koa 930) via a Permcath in the left internal jugular vein, with a blood flow rate of 350 ml/min. During one of the routine sessions, after 2 h of haemodialysis, serum morphine level in the arterial line was 16 ng/ml, and in the venous line (postdialyser) was 7.8 ng/ml, with dialyser extraction rate of 51%. The blood and plasma clearance rates were calculated at 179.5 and 122 ml/min respectively. Moreover, predialysis morphine level was 26 ng/ml, which after 2 h of dialysis had declined to 16 ng/ml (38.5% decline over 2 h). Simultaneously, fentanyl concentration in the arterial line was 5.4 ng/ml, while in the venous line was 5.3 ng/ml, indicating no significant removal of fentanyl with dialysis. Predialysis fentanyl level had been 6.1 ng/ml with non-significant decline over 2 h of dialysis to 5.4 ng/ml; however, the patient had received a bolus dose of 50 µg at the start of haemodialysis.

Our results support the previous report that morphine is significantly removed during dialysis [14]. In our two patients there was 23–51% extraction rate (average 37%) with F8 and CA-210 dialysis membranes. We have also shown a blood morphine clearance of 91–179.5 ml/min (average 135 ml/min) and plasma clearance of 64–122 ml/min (average 93 ml/min) with these two dialysers. The better clearance with the CA-210 membrane may be due to its higher Koa, Kuf, and larger surface area.

In regard to the clearance of fentanyl with haemodialysis, there is currently no information in the literature [15]. Our results indicate that fentanyl is not removed to any significant extent by CA-210 dialyser.

---

**Table 1. Percentage extraction rate and plasma clearance of morphine with different dialysis membranes**

<table>
<thead>
<tr>
<th>Ref</th>
<th>Dialyser</th>
<th>Membrane</th>
<th>Surface area (m²)</th>
<th>Kuf</th>
<th>KoA</th>
<th>Extraction rate (%)</th>
<th>Plasma clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Amicon Dialfilter 20 (haemofiltration)</td>
<td>Polysulphone (hollow fibre)</td>
<td>0.25</td>
<td>47</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Amicon Dialfilter 20 (haemodialysis)</td>
<td>Polysulphone (hollow fibre)</td>
<td>0.25</td>
<td>48 (24–84)¹</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>F8 (haemodialysis)</td>
<td>Polysulphone (hollow fibre)</td>
<td>1.8</td>
<td>75 (47–100)²</td>
<td>23</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>CA210 (haemodialysis)</td>
<td>Cellulose acetate (hollow fibre)</td>
<td>2.1</td>
<td>51</td>
<td>51</td>
<td>122</td>
<td></td>
</tr>
</tbody>
</table>

¹Without ultrafiltration; ²with ultrafiltration.


The effect of dialysis membrane on serum \( \beta_2 \)-microglobulin in chronic haemodialysis patients

Sir,

One major area of current controversy relates to the question, as to whether membrane biocompatibility modifies the risk of \( \beta_2 \)-microglobulin amyloidosis. Drs Farrell and Bastani, in a retrospective study on five chronic hemodialysis patients [1], claim that high-flux ‘biocompatible’ membranes (cellu-
lose triacetate and polysulphone) are more effective in redu-
cing serum \( \beta_2 \)-microglobulin than ‘less biocompatible’ high-
efficiency membranes (cellulose acetate). However, we would like to stress the fact that it is very difficult to demonstrate the specific role of biocompatibility because high-flux mem-
bolanes are associated with the significant dialytic removal of \( \beta_2 \)-microglobulin. Furthermore, the authors found very high plasma levels of \( \beta_2 \)-microglobulin during less ‘biocompatible’ high-efficiency dialysis (we imagine \( 75 \) mg/l instead of the 75 mg/dl reported in the Figure and text).

Because there is no \( \beta_2 \)-microglobulin clearance when using cellulose acetate, and assuming steady-state plasma levels, for a whole-body clearance of 3.5 ml/min [2], the \( \beta_2 \)-micro-
globulin generation in the patients of Farrell and Bastani can be calculated as: generation = removal = 75/1000 × 3.5 = 0.26 mg/min (that is 15.6 mg/h) and, for a body weight of 70 kg, \( G = 0.22 \) mg/h/kg. This is a very high value because turnover studies with \(^{15} \)I-labelled \( \beta_2 \)-microglobulin in humans have shown that normal adults generation is 0.11–0.18 mg/h/kg, with a mean value of 0.13 mg/h/kg [3]. On the other hand, the authors found a decrease in plasma \( \beta_2 \)-microglobulin levels to 43 mg/l (–42.7%) during ‘biocom-
patible’ high-flux dialysis. On the basis of the results of previous kinetic studies [4,5], \( \beta_2 \)-microglobulin appears to be distributed in two compartments with volumes approxi-
mating those of plasma and interstitial fluid, and the capillary mass transfer coefficient is estimated to be \( 40–43.5 \) ml/min.

From a variable volume two-pool model, it can be estimated that a dialytic clearance of about 70 ml/min is necessary to obtain the reduction in plasma \( \beta_2 \)-microglobulin levels found in the patients of Farrel and Bastani. Unfortunately, the authors do not give any information concerning dialysis efficiency and treatment time, and so the effect of the generation and dialytic removal of plasma \( \beta_2 \)-microglobulin cannot be evaluated.

In a prospective trial involving 380 patients, we have also compared biocompatible and bioincompatible membranes [6]. The primary aim of the study was to evaluate whether, with bicarbonate dialysis, the polysulphone membrane offers any advantages in terms of pretreatment \( \beta_2 \)-microglobulin level over the cuprophane. A secondary aim was to assess whether the use of more sophisticated methods, consisting of biocompatible synthetic membranes with different hydraulic permeability (high-flux haemodialysis and haemo-
dialfiltration), offers any further advantages. After a follow-
up of 24 months, there was a significant decrease in pre-
dialysis plasma \( \beta_2 \)-microglobulin levels in patients treated with high-flux polysulphone membrane (both in high-flux dialysis and HDF) in comparison with the levels observed in the patients treated with cuprophane and low-flux polysul-
phone membranes, with no difference being found between the cuprophane and low-flux polysulphone membranes. During the 24-month follow-up, there was actually no change in the \( \beta_2 \)-microglobulin levels of the patients dialysed with cuprophane or low-flux polysulphone membranes. The results of our trial favour the effect of the removal of \( \beta_2 \)-microglobulin over the possibility of a lower rate of genera-
tion due to biocompatibility. Our data are therefore not in agree-
ment with the results of Hakim et al. [7], quoted by Farrel and Bastani as supporting the effect of bio-
compatibility.

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Dialysis technique modulates alpha interferon pharmacokinetics in a patient with chronic hepatitis C

Sir,

Alpha interferon (IFN), a glycoprotein of 165 amino acids, is effective in the treatment of hepatitis C virus infection. In blood, IFN does not bind to albumin and its breakdown...
occurs mainly in the kidney. After glomerular filtration, the molecule is reabsorbed by the proximal tubule where it undergoes lysosomal proteolysis. The liver plays a lesser role in the breakdown of the molecule [1].

After subcutaneous injection of 3 million IU of IFN in patients with normal renal function, serum IFN peaks at 4.6 ± 2.5 h and its half-life is between 6 and 8 h. Little is known concerning IFN pharmacokinetics in uraemic patients undergoing dialysis [2]. We had the opportunity to study IFN plasma kinetics in a patient who was first treated by continuous ambulatory peritoneal dialysis, then shifted to haemodialysis.

A 30-year-old man with uropathy due to congenital malformation, and end-stage renal failure was started on peritoneal dialysis (CAPD) in 1981. He was found to be hepatitis C virus positive soon after the PCR technique detecting the virus became available. While anuric, he was included in a protocol testing the effects of IFN on the course of chronic hepatitis. With an estimated dry weight of 56 kg, he received a dose of 3 MIU, thrice weekly, administered subcutaneously. Blood samples were drawn before drug administration and then after 4, 8, 12, 24 and 48 h. Similar kinetic studies were performed at days 1 and 150 after inclusion in the protocol. Because of recurrent peritonitis, the patient was shifted to haemodialysis on day 300. Haemodialysis was performed thrice weekly using a high-flux polyacrylonitrile membrane (AN69). IFN was administered at the end of each 4-h dialysis session. A third kinetic study was performed at day 335, 1 month after initiation of haemodialysis. IFN was assessed by radioimmunoassay [3] and its serum levels and clearance kinetics are indicated in Figure 1.

Because of paucity of blood samples we could not measure exact kinetic parameters. However, we can point out that during the CAPD period area under the curve, calculated by the trapezoidal method, increased from 2004 to 9300 h IU/ml. During the haemodialysis period, the patient being still on the same protocol, IFN kinetics, showed a decrease of the area under the curve to 5236 h IU/ml. In parallel, IFN trough levels (at 48 h) were 150 and 50 IU/ml for the CAPD and the haemodialysis periods respectively. Half-life estimated from the late part of the curve was between 20 to 24 h, similar to the values calculated from Hirsch et al. [4].

The data collected in the present study suggest that the dialysis technique modulates the steady-state kinetics of IFN in the uraemic patient undergoing dialysis. IFN bioavailability, as assessed by area under the curve, is decreased by more than one-third when using haemodialysis as compared to CAPD, whereas apparent half-life remains unchanged. The simplest explanation for this phenomenon may be related to the higher permeability of IFN to the synthetic dialysis membrane than to the peritoneum. We did not measure membrane sieving coefficient for the drug, but one may speculate that it was in the same range as for proteins of similar molecular weight such as β₂-microglobulin [5]. Despite a decrease of drug accumulation during the haemodialysis period, side-effects such as the influenza-like syndrome that follows IFN administration remained unchanged.

IFN is one of the few drugs which decrease hepatitis C virus replication in man. However, studies designed to demonstrate a long-term beneficial effect in uraemic patients are still in progress. IFN accumulates in renal failure and this could explain the sustained clearance of the virus which has been documented in haemodialysis patients treated with the drug [6]. Since IFN retention appears greater when renal failure is treated by peritoneal dialysis than haemodialysis (at least with a highly permeable synthetic membrane), it is suggested that the averaged serum concentration should be considered in evaluating protocols for antiviral therapy in dialysed patients with chronic hepatitis.
in those haemodialysis units where the dialysers are repro-
cessed manually, a procedure often used in underdeveloped
countries. In Chile there are approximately 4500 haemodia-
lysis patients, most treated with dialysers reused by manual 
methods. The prevalence of HCV-positive cases is 8.8%, but 
unfortunately some outbreaks of HCV have occurred, one 
centre reporting an increase in the percentage of seropositivity 
up to 69% in the patients and 20% in the nurses on the 
affected unit [1]. To investigate the incidence of seroconver-
sion, we present the results obtained after a 3-year follow-
up of 200 patients treated for more than a month in a single 
unit, using manual techniques to reuse dialysers, after having 
applied hygienic precautions that did not include complete 
isolation of the HCV-positive patients. Anti-HCV-positive 
patients were assigned to two dialysis machines without 
isoiation; the HCV(+) filters and lines were rinsed and 
treated for reuse at a separate location; new patients with 
unknown HCV status were dialysed in segregated machines 
until the status was known. Active disinfection of equipment, 
patients. similar to those reported in the literature [6]: anti-HCV-
positive patients received more blood transfusions, showed 
once a year an HCV antibody was determined by first-
(1993–94) or second- (1995–96) generation ELISA (Abbott). In 1996 the anti-HCV-positive cases were also 
submitted to serum RNA determination by the nested RT-
PCR technique using primers from the S untranslated region. 
The genotyping was determined by restriction fragment 
length polymorphism based on a modification of Simmond’s 
method that is able to recognize the most frequent types of 
HCV: 1a, 1b, 2, 3a, 4/5. The HCV risk factors were also 
studied in this population. A method of logistic regression 
analysis was applied to discriminate the relative preponder-
ance of each risk factor. 

Sixty-six patients completed a 3-year observation period 
and had four HCV antibody determinations. HCV antibodies 
were positive in 17 patients (8.5%). The prevalence of 
seroconversion for each year is shown in Table 1. In the 66 
patients followed for 3 consecutive years it was found that 
60 patients were HCV(−) and six HCV(+) in the four 
determinations. 

No seroconversion and no cases of hepatitis were registered 
in this group or in any other of the studied patients. The 
No seroconversion and no cases of hepatitis were registered 
in this group or in any other of the studied patients. The 

\begin{table}
\centering
\begin{tabular}{lcccc}
\hline
 \multicolumn{2}{c}{Patient characteristics and risk factors: HCV(−) vs HCV(+)} \\
 \hline
 HCV(−) & HCV(+) & \(P^*\) \\
 \hline
 n (%) & 183 (91%) & 17 (9%) & =0.0116 \\
 Sex, M/F & 104/79 & 15/2 & \\
 Age 11–30 & 18 & 1 & \\
 31–60 & 73 & 13 & =0.01 \\
 61–93 & 92 & 3 & \\
 Glomerulonephritis & 30 (16%) & 5 (29%) & NS \\
 Diabetic nephropathy & 41 (22%) & 0 & NS \\
 Nephroesclerosis & 27 (15%) & 1 (6%) & NS \\
 Polymyositis & 12 (7%) & 3 (18%) & NS \\
 Polyathyelonephritis & 6 (3%) & 0 & NS \\
 Obstructive nephropathy & 3 (2%) & 1 (6%) & NS \\
 Other & 64 (35%) & 7 (41%) & NS \\
 No transfusion & 49 (27%) & 0 & NS \\
 >20 transfusions & 90 (49%) & 12 (71%) & =0.09 \\
 Previous transplant & 13 (7%) & 7 (41%) & =0.0003 \\
 Time on dialysis & 56.9 & 105.1 & <0.0003** \\
 Previous dialysis in another unit & 79 (43%) & 14 (82%) & =0.0019 \\
 Dialysis in another unit & 82 (45%) & 9 (53%) & NS \\
 Surgery & 76 (42%) & 7 (41%) & NS \\
 Erythropoietin & 37 (20%) & 9 (53%) & =0.0043 \\
 Mortality & 32 (17%) & 1 (6%) & NS \\
 \hline
\end{tabular}
\caption{Characteristics of patients and risk factors: HCV(−) vs HCV(+)}
\end{table}

\*All chi-square except **logistic regression.

PCR test was also positive. The most frequent HCV genotype 
was 1b (67%), which is also predominant in Europe and has 
been associated with more serious liver disease and poorer 
treatment response [2]. We found only two cases of genotype 
3a in our dialysed patients, even though it is predominant 
(65%) in our blood donor population. 
The prevalence of seropositivity in this group of patients 
treated in a single unit was 8.5%, the same as in the national 
haemodialysis population. 
We can speculate that the hygienic measures that were 
adopted at the beginning of the study contributed to the 
absence of transmission of the HCV antibodies that affected 
17 patients at some time during the observation. The Center 
for Disease Control states that dialysers from patients 
infected with HCV and HIV can be reprocessed safely, 
provided there is strict adherence to proper aseptic technique. 
We would like to emphasize that the measures adopted in 
the dialysis unit did not include the isolation of the HCV-
positive patients, a subject that has been controversial and 
debated [3]. Similar absence of seroconversion has been 
described in a unit with no dialyser reuse [4], and also in 
Europe countries that have a policy of severe restriction 
of blood transfusions [5]. 

The study also looked at the risk factors associated with 
HCV seropositivity. After applying the Chi-square method 
to compare HCV(+) vs HCV(−) the results obtained were 
similar to those reported in the literature [6]: anti-HCV-
positive patients received more blood transfusions, showed 
a higher incidence of previous transplants, were younger, 
and probably had an increased tendency to anaemia, given 
the fact that they were more frequently treated with erythro-
poietin and had a higher percentage of multitransfusions 
(Table 2). When all the data were analysed by logistic 
regression, the duration of haemodialysis was the most 
significant independent risk factor for anti-HCV positivity 
\(P=0.003\) probably because it concentrates all the other 
implicated factors. 

We speculate that if universal precautions are adopted in 

\begin{table}
\centering
\begin{tabular}{lcccc}
\hline
 \multicolumn{2}{c}{Patient characteristics and risk factors: HCV(−) vs HCV(+)} \\
 \hline
 HCV(−) & HCV(+) & \(P^*\) \\
 \hline
 n (%) & 183 (91%) & 17 (9%) & =0.0116 \\
 Sex, M/F & 104/79 & 15/2 & \\
 Age 11–30 & 18 & 1 & \\
 31–60 & 73 & 13 & =0.01 \\
 61–93 & 92 & 3 & \\
 Glomerulonephritis & 30 (16%) & 5 (29%) & NS \\
 Diabetic nephropathy & 41 (22%) & 0 & NS \\
 Nephroesclerosis & 27 (15%) & 1 (6%) & NS \\
 Polymyositis & 12 (7%) & 3 (18%) & NS \\
 Polyathyelonephritis & 6 (3%) & 0 & NS \\
 Obstructive nephropathy & 3 (2%) & 1 (6%) & NS \\
 Other & 64 (35%) & 7 (41%) & NS \\
 No transfusion & 49 (27%) & 0 & NS \\
 >20 transfusions & 90 (49%) & 12 (71%) & =0.09 \\
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\end{tabular}
\caption{Characteristics of patients and risk factors: HCV(−) vs HCV(+)}
\end{table}

\*All chi-square except **logistic regression.
haemodialysis units working in similar conditions to ours, they will escape the spectre of HCV nosocomial transmission.

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3. Jadoul M. Transmission routes of HCV infection in dialysis. New Viral Dial clearly documented [4]. However, other than blood, in the literature we could not find any report with regard to examination of body fluids for the presence of HGBV-C RNA. A small group of our patients who have been undergoing haemodialysis and positive for HGBV-C and HCV genomes in the blood were studied for the presence of HGBV-C and HCV genomes in the saliva to get some clues for the possible common routes of non-parenteral transmission of these hepatotropic viruses in haemodialysis units. We studied 10 patients, three men seven women with end-stage renal failure who were undergoing haemodialysis in our centre. The mean age of the patients was 43 ± 16 years (range, 18–71), the mean haemodialysis duration was 72 ± 41 months (range, 7–132) and the mean ALT was 48 ± 17 U per litre (15–68). All, except three had a history of previous blood transfusions with a mean number of 10 ± 6 units (range, 4–20).

To detect the HCV and HGBV-C genomes, first the nucleic acids were isolated from a sample of the patient’s serum by the acid guanidinium thiocyanate–phenol–chloroform extraction method [5]. Then determination of HCV and HGBV-C RNAs as by RT-PCR assay was performed with multiple nested primer sets from the non-structural (NS3) region of HGBV-C (1) and from the 5′ non-coding region (NCR) of HCV (5). Ten patients were all positive for HCV and HGBV-C viral nucleic acids in their blood. The collected saliva samples were also tested for HGBV-C and HCV genomes with RT-PCR assay with the same nested primer sets after the extraction method noted above. The results showed that two of the saliva samples were positive for both HGBV-C and HCV RNA, one sample was positive for only HGBV-C RNA, and the other one for only HCV RNA.

This study demonstrates the secretion of HGBV-C RNA into the saliva which is a previously unreported finding and, identifies the potential risks of contamination by this virus through saliva. Percutaneous infection through saliva may serve as a possible common non-parenteral route of transmission for both HGBV-C and HCV in haemodialysis patients.

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Intraosteoiblastic iron assimilation in two dialysis cases with iron overload

Sir,
The risk of iron-induced osteomalacia has been reported as a long-term complication of dialysis therapy [1]. Although an in vivo study indicated that iron might have some toxic effect on osteoblasts [2], the main mechanism of bone metabolic disorder associated with iron overload was believed to be mineralization disturbance because iron deposition was found along the calcified front in their biopsied bone specimens [3]. This distribution pattern of iron in bone is similar to that of aluminium. In fact, iron and aluminium often coexist along a calcified front in dialysis patients [4].

Recently we experienced two dialysis cases with iron overload. The first case was a 39-year-old male who had been undergoing maintenance haemodialysis thrice weekly for 10 years for chronic glomerulonephritis. He had received frequent transfusion therapy. His serum biochemical analysis showed extremely elevated levels of alkaline phosphatase (917 IU/l). C-terminal PTH was 42.7 ng/ml, ferritin 4125 ng/ml, and aluminium < 10 μg/l. Iliac bone biopsy demonstrated markedly developed fibrous tissue formation and bone resorption with a high degree of osteoclast infiltration. Mononuclear cells without tartrate-resistant acid phosphatase activity were seen around the bone surface, with heavy metal deposits in the cytoplasm. The deposit presented Berlin-blue iron reaction while the calcified front did not.

The second case was a 28-year-old female who had been on maintenance haemodialysis thrice weekly for 7 years for chronic glomerulonephritis. She had received frequent transfusions and iron supplements. Her serum biochemical analysis demonstrated elevated levels of alkaline phospha-
Reactivation of systemic lupus erythematosus after transfer to peritoneal dialysis

Sir,

No preference seems to exist for dialysis modality in patients with systemic lupus erythematosus (SLE), who have progressed to end-stage renal failure (ESRF). We recently have seen a patient, in whom this choice clearly was important. An Afro-Caribbean woman, born in 1952, was diagnosed with SLE in 1972 (polyarthritis, malar rash, oral ulcers, pleuritis, psychosis, proteinuria, skin vasculitis and antinuclear antibodies). She developed ESRF in 1982 due to lupus nephritis. Chronic hemodialysis (HD) was initiated and SLE remission ensued. In September 1992 she was switched to peritoneal dialysis (Baxter, Twin-bag) (CAPD) on her own request and after an uneventful 5 months, she consequently developed several episodes of lupus peritonitis (fever, abdominal pain with normal leukocyte-counts in sterile CAPD fluid, normal levels of C-reactive protein), bilateral keratoconjunctivitis, intermittent cytopenias, arthritis, increasing levels of anti-dsDNA (from 472 to 643 IU/ml by Farr-assay) and low C3 levels (21 mg/l). In November 1994 HD was reintroduced and while the chronic conjunctivitis disappeared rapidly, after 3 months she developed severe crico-arytenoiditis (necessitating tracheotomy) and lupus pneumonitis with anti-dsDNA peaking at 920 IU/ml. High-dose steroid therapy (80 mg Prednison) largely reversed this situation and she is now again in a stable phase, despite persistently increased anti-dsDNA levels (1340 IU/l). The literature offers some arguments in favour of HD as the preferred dialysis modality in SLE patients. Rodby et al. describe persistent disease activity after CAPD initiation and considered less effective T-cell suppression, possibly by ways of the increased middle-molecule clearance the likely cause [1]. In a later report, comparing HD and CAPD in lupus patients, CAPD patients had poorer survival, while experiencing more serositis, cytopenias and serological activity [2]. Both reports support our belief, that the transfer to CAPD triggered this patients disease exacerbation, adding to doubts about the appropriateness of CAPD treatment in lupus patients.


Fig. 1. (a) Osteoblasts assimilated heavy metal particles (*). Confocal laser scanning microscopy. Bar = 5 μm. (b) Mineral distribution detected by electron-probe microanalysis method. Aluminium was deposited along the edge of calcified bone (large arrowheads), namely the calcified front, whereas granular iron accumulation was noted at the surface of osteoid tissue (small arrows). Iron was not detected along the calcified front or in the bone-marrow tissue. CB, calcified bone; BM, bone-marrow tissue. Bar = 50 μm.

tase (806 IU/l). C-terminal PTH was 9.2 ng/ml, ferritin 14000 ng/ml, and aluminium 42 μg/l. Iliac bone biopsy showed discontinuities of trabecular bone, scattered tunnel-like absorptive lacunas, and extreme development of osteoid volume. Mononuclear cells along the osteoid surface assimilated heavy metal particles in the cytoplasm. Electron-probe microanalysis identified the heavy metal as iron. Linear aluminium deposition was detected along the calcified front.

In both cases, iron was concentrated in bone tissue; however, it was assimilated in the mononuclear cells surrounding bone surface, most probably osteoblasts, but not deposited along the calcified front. In the first case, mineralization disturbance was not evident. It seems likely that aluminium deposition alone disturbed bone mineralization in the second case.

Sato and his colleagues [5] found that iron suppressed bone formation without disturbing bone mineralization in cultured mouse calvaria. Iron was detected in the cytoplasm of mononuclear cells that surrounded bone surface but not along osteoid tissue. The suppression of osteoblast function is likely to have caused disturbance of bone formation. We assumed from this experiment that iron may disturb bone formation when assimilated in osteoblasts, whereas it disturbs bone mineralization when deposited along calcified front.

The present cases demonstrated intraosteoblastic iron assimilation in dialysis patients. In both cases, bone resorption promoted by secondary hyperparathyroidism was also evident. If this *in vitro* observation occurs *in vivo*, iron assimilation in osteoblasts will accelerate the progression of osteopenia through suppression of bone formation.

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