Letter and Reply

**Hyponatraemia and tonicity balance**

Sir.
M. J. Dickenmann and F. P. Brunner present an interesting case of hyponatraemia and polyuria following an allogeneic bone marrow transplant [1]. They stress that total parenteral nutrition induced a large amount of urea to excrete, resulting in large polyuria and then in hyponatraemia.

Their discussion however does not fit with the data provided and the conclusions should be drawn in a very different way.

For a hyponatraemia to be constituted, either a sodium gain, or a water deficit is required, or a combination of both. The former, excluded by the authors, was indeed present, while the latter remains to be proved.

The body weight was not reported. A loss of 5 kg is mentioned, a long time before the natriaemia variations are discussed.

From 27 October to 1 November the serum sodium concentration went from 145 mM up to 156 mM. Assuming the patient has a body weight of 70 kg the total body water is thus close to 42 l. For such an increase in the serum sodium concentration, the water loss should be at least 31 l. However for this period of time, the total cumulative water balance shows a gain of more than 1 l (1020 ml) (no values for the 28 October).

From the 28 October the patient received an infusion of isotonic saline and 5% glucose solution. Assuming the G5 infusate was infused each day at the maximum indicated (300 kcal/d), the amount administered would have been 1.5 l/d. Assuming also that no K was given, and since 1 l of saline contains 154 mmol Na, the minimum patient intakes can be summarized in Table 1.

These amounts given to a hyponatraemic patient could be considered as impressive. However, no urinary values for Na+K were given. Thus, the true gain of Na cannot be asserted.

Let us focus on the 1 November, the only day for which urinary Na+K values were provided: excretion for Na+K was (35 + 41) 6.61 l = 502 mmols. Still assuming a total body water of 42 l, the initial serum sodium concentration was 156 mM, electrolyte gain was + 176 mmols, water balance was − 0.75 l. If we calculate a tonicity balance, the predicted final serum sodium concentration is [(42 × 156) + 176]/42 − 0.75 = 163 mM. The observed serum sodium concentration the following day was 162 mM.

Therefore the conclusion is that this hyponatraemia was mainly due to sodium overloading and possibly to a slight water deficit.

Table 1.

<table>
<thead>
<tr>
<th>Dates</th>
<th>29 October</th>
<th>30 October</th>
<th>31 October</th>
<th>1 November</th>
</tr>
</thead>
<tbody>
<tr>
<td>G5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Saline</td>
<td>4.7</td>
<td>6.7</td>
<td>3.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Na mmols</td>
<td>724</td>
<td>1032</td>
<td>570</td>
<td>678</td>
</tr>
</tbody>
</table>

Was this development avoidable? Yes.

Two points need to be discussed: the polyuria, and the serum sodium concentration balance.

First, as noted by the authors, the protein parenteral feeding generates a large amount of urea osmoles to excrete which necessitates an increase of the urinary volume. Its mechanism is probably more complicated than a simple increase in urinary osmolality and involves the medullary function; this is, however, beyond the scope of this discussion. Such an increase in urinary volume would lead to an electrolyte-free water loss and then to a hyponatraemia. This is well known in ICU.

The patient’s water balance does not favour a water loss nor does the central venous pressure. I would suggest the urea-induced polyuria was overcorrected. In effect, compensating an electrolyte-free water loss with normal saline would result in an extra-cellular fluid expansion, leading to the excretion of this NaCl and water load. Since no urinary Na+K values were provided, it is difficult to distinguish between the urea-induced and the electrolyte-induced volumes in the polyuria.

However on 1 November there was a 6.6 l urinary volume with a [Na+K] of 76 mM while serum sodium concentration was 156 mM. Assuming a serum [K] of 4 mM, plasma cationic tonicity ([Na+K]) was 160 mM. Thus, the 6.6 l of urine contained 3.1 l isotonic to plasma and 3 l of electrolyte-free water. The patient received 4.4 l of isotonic saline and 1.5 l of electrolyte-free water as G5.

Second, since its introduction by Goldberg [2], the electrolyte-free water concept has become increasingly used. Earlier Edelman et al. [3] have reported a relationship between natriaemia and the [Na+K]/H2O ratio in the extra-cellular fluid. I suggested the term of tonicity balance to represent the [Na+K]/H2O equilibrium between intakes and losses [4]. Changes in this equilibrium imply changes in electrolyte-free water balance and result in serum sodium concentration variations [5]. Also, together with my friends and colleagues we have demonstrated that classical formulae (free-water clearance, osmole-free water, Na-free water, ...) are not helpful and misleading [4,5].

Finally, when faced with a polyuria, one should remember that the concentration [Na+K] infused should not exceed the urinary concentration [Na+K]. Also, at bedside, it is easy to determine whether the kidney excretes or retains electrolyte-free water (Table 2).

In conclusion this hyponatraemia was mainly due to a sodium gain caused by the large amount of normal saline infused. A good knowledge of the tonicity balance would

<table>
<thead>
<tr>
<th>Table 2.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider: P[Na+K] and U[Na+K]</td>
</tr>
<tr>
<td>(a) U[Na+K] &gt; P[Na+K] The kidney is defending against a rise in tonicity, or it is responsible for a dilution of body tonicity.</td>
</tr>
<tr>
<td>(b) U[Na+K] &lt; P[Na+K] The kidney is defending against a fall in tonicity, or it is responsible for a concentration of body tonicity.</td>
</tr>
</tbody>
</table>
probably have limited this perturbation, or might have avoided it entirely.

One important notion to emphasize, is that one should not be too confident in normal saline infusion. Especially in patients with mucositis, fever, pneumonia, and mechanical ventilation. We cannot be forgiven for not having reported the most important parameter of fluid balance, the body weight, which decreased from 96 kg (27 October) to 91.8 kg (2 November).

Letters

Abnormalities of kidney and urinary tract in epidermolysis bullosa

Sir,

I read with interest the recent report by Cuesta-Estelles et al. [1]. The authors may be correct in their speculation that IgA glomerulonephritis accounts for nephrotic range proteinuria in their patient with recessive dystrophic epidermolysis bullosa, but coinheritance of epidermolysis bullosa [2] with hereditary nephritis, as we reported previously [3], is an alternative explanation. Martinez-Hernandez and Amenta recently described multilamination of epidermal and dermal vascular basement membranes in Alport kindred similar to that found in their glomerular basement membranes [4]. However, clinical abnormalities of the skin, such as bullous disease, are rare in Alport patients [3], probably because Alport syndrome arises from mutations in the type IV collagen gene (COL4A3, COL4A4 or COL4A5) [5], whereas in epidermolysis bullosa (dystrophic epidermolysis bullosa) mutations are found in the type VII collagen gene (COL7A1) [6]. The possible clinical relationship between skin and glomerular basement membrane lesions in these two hereditary diseases remains to be determined.

A variety of kidney and urinary tract abnormalities associated with epidermolysis bullosa have been reported from 1937 [7]. Moreover, the association of IgA nephropathy with epidermolysis bullosa was previously reported in 1984 [8]. Finally, the list of renal involvement in epidermolysis bullosa include amyloidosis, IgA nephropathy, postinfectious glomerulonephritis, hereditary nephritis and upper and lower urinary tract obstruction [1,3,7–11].

Familial distal renal tubular acidosis

Sir.

Familial distal renal tubular acidosis (dRTA) is a rare disorder, with both autosomal dominant and recessive transmissions [1, 2]. About 30 families with 300 individuals affected with hypokalemic dRTA have been described in the literature, with as many as 55 coming from just two families [1, 3, 4]. We report a family in which three brothers presented in adulthood with dRTA, one of whom progressed to end-stage renal disease (ESRD). This is the first report of familial dRTA from South Asia.

The index case, a 55-year-old male, was well until the age of 35 years when he developed acute onset flaccid quadriaparesis. There was no preceding history of diarrhea. Investigations done at a local hospital revealed that his serum potassium was 2.4 mEq/l, sodium 130 mEq/l, creatinine 1.8 mg/dl, calcium 8.2 mg/dl, phosphate 4.5 mg/dl, alkaline phosphatase 13 KA units/dl, pH 7.23 and bicarbonate 18 mEq/l. Urinalysis showed pH of 6.7, 1+ albumin, 2–3 erythrocytes and plenty of calcium oxalate crystals/hpf. Abdominal X-ray revealed bilateral medullary nephrocalcinosis. Oral potassium chloride supplementation led to a prompt and complete recovery of muscle power. He was advised to take oral sodium bicarbonate and potassium chloride. However, his treatment compliance was very poor and he had seven episodes of flaccid quadriaparesis over the next 16 years. He developed acute anterior wall myocardial infarction at the age of 52 years at which time hypertension and renal insufficiency (serum creatinine 3.9 mg/dl) were also detected. He reached ESRD by the age of 55 years and was referred to our institute for further management. On examination, he was pale, had a pulse of 82 beats/min, blood pressure of 130/88 mmHg and bilateral direct inguinal hernias. Audiology revealed normal hearing in both ears. His haemoglobin was 7.6 gm/dl, serum sodium 132 mEq/l, potassium 3.8 mEq/l, chloride 106 mEq/l, bicarbonate 16.8 mEq/l, creatinine 3.9 mg/dl, calcium 7.6 mg/dl, phosphates 4.2 mg/dl, alkaline phosphatase 28 KA units/dl and glucose 88 mg/dl. Blood and urine pH were 7.3 and 6.8, respectively. The urinalysis revealed 1+ protein, 3–4 pus cells and 1–2 erythrocytes/hpf. The 24-h urinary protein excretion was 450 mg (7.5 mg/kg/day). Plain X-ray abdomen revealed a calculus in the lower calyx of the left kidney. He was started on oral dipotassium hydrogen citrate. At last follow-up, his serum bicarbonate of 70 and 67 years of natural causes and had no history of urological complications. J Urol 1998; 159: 2122–2125.

The dRTA genotype is expressed as impaired renal acidification, hypercalciuria, hypophosphaturia and nephrocalcinosis in varying combinations. In the autosomal dominant (AD) variety, four genotypes viz. ‘San Francisco’, ‘Philadelphia’, ‘Atlanta’ and ‘Oklahoma city’ have been described [5]. In the first two genotypes, the defective gene leads to impaired renal acidification and hypophosphaturia whereas in the latter two, the defect presents primarily with hypercalciuria and the resulting nephrocalcinosis later leads to renal tubular acidosis and renal failure. A mutation in the red cell HCO−3/Cl− exchanger band 3 (AE1, SLC4A) gene has been described in dominantly inherited dRTA [6]. Sensorineural deafness is present in a large number of cases with the autosomal recessive (AR) type of dRTA [7, 8]. In one series of 28 children with dRTA, deafness was noted in all familial cases, but was absent in all non-inherited patients. Recently, mutations in ATP6B1, the subunit of the apical H+/ATPase mediating distal nephron acid secretion have been implicated in the genesis of dRTA with sensorineural deafness [9].

The exact mode of inheritance was difficult to establish in the present report since the defect was seen in only one...
generation. However, since dRTA was not detected in any of the patients of Case 2, it is likely to have been inherited in an AR fashion.

The presentation depends upon the genotype, severity of RTA, presence and degree of hypercalciuria and hypocitraturia and time of institution of therapy [1]. Hypocitraturia is particularly severe in the inherited forms of dRTA and may be seen in the absence of acidosis [2,10]. Nephrocalcinosis develops in the first few years of life in the AR form with sensorineural deafness [1,2,5]. In one report, nephrocalcinosis was detected as early as 5 weeks [11]. Once present, nephrocalcinosis amplifies the acidification defect, setting up a vicious cycle. Hypocitraturia or hypercalciuria can be the primary expression of dRTA, and the acidification abnormality becomes apparent only after nephrocalcinosis has developed. All three brothers described here became symptomatic in adulthood and showed the full spectrum of clinical abnormalities including hypercalciuria. Urinary citrate levels, however, could not be measured in any of our patients. Nephrocalcinosis as the cause of dRTA was excluded by the demonstration of acidification defect in the absence of the former in Case 3.

Curiously, the first symptom in all our patients was a rapidly occurring skeletal muscle weakness consequent to hypokalaemia. Seen commonly in the autoimmune variety, this presentation is rare in genetically transmitted dRTA [1,5]. The reason for this difference in presentation is not known.

Management consists of lifelong alkali therapy. Potassium supplementation is required during episodes of hypokalaemia. Prevention of secondary hyperparathyroidism by use of anion exchange resins is important in children; failure to do so can cause nephrocalcinosis. Urinary citrate levels were in the normal range. Plasma homocyst(e)ine since 1992. On admission she complained of abdominal muscle weakness [1]. Hypocitraturia persists despite correction of acidemia and therefore alkali should preferably be given as sodium or potassium citrate [10]. Once apparent, nephrocalcinosis and nephrolithiasis persist despite therapy but stones are passed less frequently [1]. The prognosis is good in families where the trait is not expressed primarily as hypercalciuria. Renal function can deteriorate in patients with hypercalciuric forms, or in whom therapy is not instituted in time because of unabated progression of nephrocalcinosis and nephrolithiasis [1,2,5,10,11].

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Inferior vena cava thrombosis in a patient with chlorpromazin-induced anticardiolipin antibodies

Sir,

A pathogenic role in venous thrombosis has been postulating for anticardiolipin antibodies (aCLA) [1]. aCLA may be induced by drugs but some studies suggested that drug-induced aCLA were not associated with thrombosis [2]. We report the case of a woman who exhibited thrombosis of the inferior vena cava in the setting of chlorpromazin-induced aCLA.

A 25-year-old woman was admitted in October 1995 in our unit because of acute renal failure. Schizophrenia had been diagnosed 6 years before and she received chlorpromazine since 1992. On admission she complained of abdominal and bilateral loin pain. Physical examination was normal. Significant laboratory data were the following: serum creatinine concentration, 203 μmol/l; white blood cell, 12 500/mm³; haemoglobin concentration, 140 g/l; platelet count, 100 000/mm³. Blood and urine cultures were negative. Urinary analysis revealed microscopic haematuria (25 700/mm³) and mild proteinuria (0.9 g/d). Chest radiography was normal. Renal ultrasound showed enlarged kidneys. The day after admission, she complained of right thoracic pain and dyspnea. Arterial-blood gases were the following while breathing oxygen at 6 l/min: partial pressure of oxygen, 9 kPa; partial pressure of dioxide 3.2 kPa; pH 7.51.

Significant laboratory data were the following: serum creatinine concentration was 10·5 μmol/l (normal range: 10–12 μmol/l). Plasma homocyst(e)ine concentration was 10·5 μmol/l (normal range: 10–12 μmol/l). Assay for resistance to activated protein C was negative and factor V Leiden was not present. IgG aCLA were strongly positive (45 GPL units; normal <23 GPL units). Chlorpromazin was withdrawn. Six months after chlorpromazin withdrawal, aCLA were negative (12 GPL units). Serum creatinine concentration was 104 μmol/l.

There is some evidence that aCLA detected in our patient were related to chlorpromazin. First, large studies have reported that aCLA may be associated with certain drugs, particularly those known to produce a lupus-like syndrome such as chlorpromazine. Secondly, aCLA disappeared 6 months after chlorpromazin withdrawal. In most series, drug-related aCLA were not linked to a history of thrombosis. In patients with psychiatric disorders and chlorpromazine-induced aCLA, the frequency of thrombosis is extremely low, even though in many cases aCLA are present for several
years [2]. It has been suggested that the poor association between drug-related aCLA and thrombosis may be attributable to the fact that these antibodies are predominantly IgM rather than IgG class. The anatomic site of thrombosis reported in our observation is rare and suggested the presence of a predisposition towards thrombosis. Nevertheless, our patient had no other cause of thrombophilia than positive aCLA. Moreover, our patient exhibited thrombocytopenia which is a hallmark of the antiphospholipid syndrome.

In conclusion, chlorpromazin-induced aCLA, especially when IgG class, may be the cause of severe thromboembolic disease. This observation suggests that patients receiving chlorpromazin should be regularly tested for the presence of aCLA. When IgG aCLA are present in the course of chlorpromazin therapy, physicians should consider either to withdraw this drug or to care with thrombotic complications.

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**Endothelial cell dysfunction in diabetes**

**SIR.**

The article by Stehouwer et al. [1] highlights this important problem, which Nitenberg and Antony [2] have suggested could be due to the effects of 0 radicals, and that is in line with current thinking.

In view of the associated lipid abnormalities in diabetics [3], may I suggest attention to the use of soyprotein antioxidant diets [4,5], both to lower cholesterol and reduce plasma lipid hydroperoxides, and hopefully stop the microvascular leakage of albumin. Radio-iodinated albumin was used for a long time to quantify this key feature [6], and recently assays for soluble selectins in plasma have been used to advantage.

Oxford UK

E. N. Wardle


The vitamin D receptor gene polymorphism and parathyroid function

**SIR.**

The role of vitamin D receptor gene polymorphism on parathyroid function is controversial. Among patients with primary hyperparathyroidism, Carling et al. find a high prevalence of genotype bb [1], whereas Menarguez does not observe any differences in the distribution of genotypes in a similar group of patients [2].

In secondary hyperparathyroidism of chronic renal failure patients, the results are also controversial. So, in haemodialysis, Tsuchimoto et al. [3] and Fernández et al. [4] show high serum PTH levels in those patients with bb genotype. In a group of 34 patients with serum PTH levels lower than the normal range, the latter authors find a higher prevalence of BB genotype. Because of the known effect on parathyroid function, patients with diabetes mellitus or long term treatment on dialysis were excluded from the study [4]. Acute suppression of PTH secretion related with calcitriol therapy in haemodialysis [5] or in predialysis patients [6] is more prevalent in those patients with BB genotype. Other authors, in larger but non-selected group of patients, as McCarey et al. [7] in 176 patients or Schmit et al. [8], do not find significant differences in PTH levels among the three genotype groups.

We have studied the vitamin D receptor in a group of 217 patients on haemodialysis. Seventy-six of them had been parathyroidectomized, 42 patients had serum PTH levels >500 pg/ml, 59 showed PTH levels 100–500 pg/ml and 40 persistently had PTH levels <100 pg/ml in absence of hypercalcemia, aluminum intoxication or calcitriol therapy. Twenty-five percent of the latest group were diabetics and 30% had been diagnosed with amyloidosis or chronic inflammatory diseases. Genotype distribution (Table 1) is the same found in a control group of 113 healthy subjects. There were no significant differences in the distribution of VDR genotypes (Table 1) between the patients with severe hyperparathyroidism and those with low PTH levels. Excluding those patients with diseases associated to relative hypoparathyroidism, although the number of patients in this group was low, there were still no significant differences.

Our data suggest that the influence of factors such as calcium and phosphate levels, aetiology of chronic renal failure and the time on dialysis decrease the possible role of VDR gene polymorphism. To confirm the possible effect of VDR genotype on the evolution of hyperparathyroidism, new studies in very selected patients are necessary, as Torres and Salido have suggested in a recent comment [9].

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J. M. Chalopin J. Mena

2. Menarguez J. Lack of relationship between Bsm1 receptor and primary hyperparathyroidism in a Spanish female population. Calcification Tissue Int; in press

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Neuropsychiatric complications following quinolone overdose in renal failure

Sir,

We read with keen interest the report by Tattevin et al. of a case of quinolone overdose complicated by neuropsychiatric manifestations in a patient suffering from end-stage renal disease [1]. We encountered a very similar clinical problem in the setting of a somewhat different prescription error.

It happened in a 81-year-old female suffering from advanced renal insufficiency secondary to chronic interstitial nephritis of unknown origin. In May 1995 she was hospitalized for treatment of bladder retention. Her serum creatinine and creatinine clearance were 3.5 mg/dl and 8 ml/min, respectively. Her medical treatment consisted of erythropoietin, intravenous iron, digoxin and calcium carbonate. She was taking neither theophylline nor NSAIDs. To treat a urinary infection, ofloxacin 200 mg/day orally was prescribed, on June 6th. On June 9th, pefloxacin 400 mg IV daily was prescribed for her degree of renal insufficiency secondary to chronic interstitial nephritis of unknown origin. In May 1995 she was hospitalized for treatment of bladder retention. Her serum creatinine and creatinine clearance were 3.5 mg/dl and 8 ml/min, respectively. Her medical treatment consisted of erythropoietin, intravenous iron, digoxin and calcium carbonate. She was taking neither theophylline nor NSAIDs. To treat a urinary infection, ofloxacin 200 mg/day orally was prescribed on June 6th. On June 9th, pefloxacin 400 mg IV daily was inadvertently added. Thus each quinolone formulation was incompletely prescribed for her degree of renal insufficiency while the total dosage achieved more or less double the recommended dose [2–4].

The next day she was confused. On June 13th her confusion worsened and we observed diffuse muscle rigidity, myoclonic movements and the absence of response to stimuli. That day the error in prescription was discovered and all quinolone stopped. The next day the clinical picture was unchanged with massive muscle spasticity while on June 15th on there was a progressive recovery which was complete on the 17th.

Electroencephalographic examination demonstrated a slow background rhythm with diffuse non-focalized dysrhythm.

The patient had no past neurological history. The follow-up until now has been free of recurrence of similar neuropsychiatric problems, although relapsing urinary infections justified prescribing again ofloxacin 200 mg daily on a long-term basis from October 1995 till March 1997, at which time she began haemodialysis treatment.

This case history confirms the neurotoxicity of quinolone overdose in renal insufficiency. This side effect seems to be a rare occurrence since the company that manufactures one of the incriminated quinolones was contacted at the time and did not have such an occurrence on its files. Since then, however, these possible side effects are mentioned in the vignette accompanying these drug packages. It also suggests that the neurotoxicity is not linked to a particular formulation of the quinolone but is rather inherent to the basic molecular structure of that antibiotic family. Reduction of dosage in renal insufficiency is necessary, as now recommended by most experts, although it is more important for ofloxacin than for pefloxacin because of the predominantly renal excretion of the former.

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Clinique St-Jean
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Table 1.

<table>
<thead>
<tr>
<th>Parathyroid hormone (pg/ml)</th>
<th>&gt; 500 + PTX</th>
<th>100–500</th>
<th>&lt;100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.6 ± 5.8</td>
<td>62.5 ± 13.1b</td>
<td>63.8 ± 11.3b</td>
</tr>
<tr>
<td>Calcium (mg/dl)a</td>
<td>10.5 ± 1.0</td>
<td>10.2 ± 0.8</td>
<td>9.9 ± 0.6b</td>
</tr>
<tr>
<td>Phosphate (mg/dl)a</td>
<td>6.2 ± 1.4</td>
<td>4.9 ± 1.6b</td>
<td>5.4 ± 1.2b</td>
</tr>
<tr>
<td>Alkaline phosphatase (i.u.)/l</td>
<td>700.8 ± 68.7</td>
<td>244 ± 96.9b</td>
<td>206 ± 83a</td>
</tr>
<tr>
<td>Genotype BB (%)</td>
<td>19.5</td>
<td>16.9</td>
<td>15.0 NS</td>
</tr>
<tr>
<td>Genotype bb (%)</td>
<td>35.6</td>
<td>37.3</td>
<td>27.5 NS</td>
</tr>
<tr>
<td>Genotype Bb (%)</td>
<td>44.9</td>
<td>45.8</td>
<td>57.5 NS</td>
</tr>
</tbody>
</table>

*Data are mean ± SEM for the last two years. *P < 0.01.


Isolation of HCV patient is efficient in reducing the annual incidence of HCV infection, but is it really necessary?

Sir,

The isolation of hepatitis B virus infected patients is a measure generally applied in haemodialysis (HD) units, but the creation of independent sections for the hepatitis C virus (HCV) infected patients is in discussion. We have done research, through a prospective study, on the repercussion that the isolation of HCV antibodies (HCV-Ab) positive patients has on the incidence and prevalence of this infection during 5 years of follow-up.

From July 1, 1991 to December 31, 1997, a total of 131 patients were dialysed in the HD unit. During this period 114 sick persons were examined who had normal amino-

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transferrases at their admission in the unit (without any evidence of a previous increase of these), and who had negative HCV-Ab. During 1991 and 1992 all the patients were dialysed in one room. Starting from January 1st 1993, the HCV-positive patients were isolated in a zone separated, with different machines and medical staff, and from 1993 to 1997 a follow-up was carried out with the patients who were dialysed in the HCV-negative room. The aminotransferases and HCV-Ab were measured every month (ELISA of second generation (Abbot) and the additional test for synthetic peptides (INNO-LIA)).

An increase of aminotransferases with simultaneous or posterior seroconversion of the HCV-Ab was observed in 15 patients. In 1991–1992 11 hepatitis C cases appeared in the unit. Starting from the beginning of the isolation measures, on January 1 1993 and up to December 31 1997, only four new cases of seroconversion were detected. Three of those cases appeared until May 1993, all of them had shared a HD machine and room with the HCV-Ab positive patients previously isolated and might be considered to be unit cases prior to January 1993, since they were within the incubation period. The fourth patient who showed seroconversion appeared in January 1996 and had received blood transfusions for 6 months before. Of the patients showing seroconversion to HCV during the study: one of them had never received transfusions, six had received the last transfusion more than 12 months ago, and four had no transfusions for more than 2 years.

The prevalence of hepatitis C in our unit was similar to that observed by other Spanish groups [1] (about 30%) which just like the rest of the Mediterranean countries, is placed among the highest in Europe [2]. This showed a rising tendency from the beginning of the study up to, and including, 1993. This increase did not only depend on the appearance of new cases in our unit, but also on the admission of HCV-Ab positive patients coming from other units. During the post-isolation years the prevalence went down progressively, although without reaching statistic significance ($P=NS$) (Figure 1) and this was due to the decease or transplantation of the patients carrying HCV-Ab, and to the absence of new cases since isolation. There would have to be accomplished a longer term follow-up in order to see the behaviour of the prevalence of hepatopathy C in the unit, which would predictably follow the same falling tendency.

The annual incidence of seroconversion to HCV decreased significantly during the years of isolation in relation to earlier years ($P=0.002$), until reaching 0%, (Figure 2) and the isolation measures proved to be efficient in order to decreasing the risk of acquiring hepatitis C in the unit ($P=0.003$).

This confirmed the hypothesis of hospital transmission of hepatitis C unrelated to blood transfusions. Whether transmission occurs through the HD machines, or through direct contact with the staff or indirectly through contaminated surfaces transported by the medical staff, is a subject for discussion and our study does not allow us to discriminate whether it is due to separating the machines or separating the staff. In any case it seems evident that isolating infectious patients in independent units blocks all these possible ways and makes hospital infection nonexistent, by which the appearance of new cases is drastically reduced, as is shown in our unit.

Is it necessary to adopt this measure in an obligatory form or would it be enough to separate machines only, or to apply the universal precaution measures? Perhaps in particular circumstances it may be necessary to adopt this measure (units with very high prevalence, control of outbreak of hepatitis ...), however this involves economical as well as logistic problems and at the present time it is difficult to identify in advance the patients capable of contaminating. (Some patients in HD do not increase the aminotransferases because of the state of immunosuppression [3,4], there are patients with negative antibodies and positive PCR [5]; and others in which the PCR becomes negative after treatment with interferon, one can not exclude the possibility that they will not be positive again after some time without treatment.) The other problem is, if one decides to choose isolation, on what basis should the patients be separated.

There are authors who consider that it might be justified to separate the patients on basis of HCV-Ab [6]. Others consider however, that the enzyme-immuno-test cannot be a good predictor of HCV viraemia in HD [7], and suggest separating the patients in terms of the viral RNA detection, although the HCV-Ab are negative [8].

The attempts to isolate HCV in ultrafiltrate were unsuccessful in most of the studies [9]. All the same, some authors find tracking of viral particles with ultrafiltrate, works with very high transmembrane pressures [10]. There will have to be a future investigation on whether the passage of the virus might be favoured by the use of highly efficient techniques with high convective power like haemodialfiltration.

It is necessary to emphasize the importance of adequate handling (on the part of the medical staff) of the material being contaminated with blood from the patients carrying HCV, in order to avoid spreading of the virus in the units. This way of contagion is perhaps the most important, and at the same time the most difficult to prove and control. Although the use of gloves and hand-washing before and after handling the tubes and potentially infected material...
must be accomplished in an obligatory manner, these activities are not always carried out by the medical staff [11].

Isolation has shown to be effective in controlling the infection [12], but also, large reductions of HCV transmission in HD have been observed after strict enforcement of standard precautions [13,14].

The question still remains: should we invest our resources patients isolation who are infected by the HCV? Or should we perhaps use our economic resources in the permanent updating of the personnel about the importance to systematically applying preventive measures to reduce the incidence of the infection of the HCV with limited expenses?

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The effect of alpha interferon therapy and short-interval intradermal administration on response to hepatitis B vaccine in haemodialysis patients

Sir,

Infection with hepatitis B virus (HBV) is one of the major threats for patients on long-term haemodialysis (HD). The risk to develop chronic disease following HBV infection varies between 3% and 10% among HD patients [1]. Although the efficacy of hepatitis B vaccine measured as antibody response shown to be effective in controlling the infection [12], but also, large reductions of HCV transmission in HD have been observed after strict enforcement of standard precautions [13,14].

The question still remains: should we invest our resources in isolating the patients who are infected by the HCV? Or should we perhaps use our economic resources in the permanent updating of the personnel about the importance to systematically applying preventive measures to reduce the incidence of the infection of the HCV with limited expenses?

Servicio de Nefrología del Sanatorio Perpetuo Socorro (Alicante) y Hospital general de Elche
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The effect of alpha interferon therapy and short-interval intradermal administration on response to hepatitis B vaccine in haemodialysis patients

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The defect in immune response to hepatitis B vaccine among HD patients is considered to be of multifactorial origin and is already present before initiation of chronic haemodialysis therapy [1-11]. Several impaired immune functions mainly of the cellular immune system, including impaired monocyte function, reduced T-cell proliferation and decreased IL-2 production have been described [7,12,13].

Limited data exist regarding the effect of interferon-α on healthy individual hepatitis B vaccine non-responders [14,15]. Groß et al. reported in their pilot study the success of adjuvant interferon-α therapy only in the group of low-responders. In the controlled, randomized trials performed among healthy adult non-responders by Goldwater et al. interferon-α was shown to increase the likelihood of seroconversion to a fifth HBV vaccine dose in non-responders but when compared with placebo, its effect did not reach statistical significance [14].

Our study is the first one that evaluates the effect of adjuvant interferon-α therapy on the antibody response among the non-responding haemodialysis patients. The results of this study support the value of additional fourth dose of vaccine. One possible beneficial effect of interferon was an accelerated anti-HBs antibody response. Significantly higher antibody response was achieved as early as at the 4th week in the group of patients receiving interferon-α. Antibody titers tended to be higher among the patients receiving interferon-α at the other study points although this difference did not reach statistical significance. These results are in agreement with the report of Goldwater et al. who reported higher antibody titers and earlier seroconversion among healthy adult non-responders receiving one additional doses of interferon-α [14].

In conclusion, intradermal vaccination with HBV vaccine at short intervals is an effective method of increasing the response to vaccine in chronic haemodialysis patients. This study does not support the value of concomitant interferon-α therapy in the augmentation of the antibody response rate among this group of patients. In order to further evaluate the response to concomitant interferon-α administration larger controlled studies with different doses and dosing frequency are required.

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A. S. Fük
E. Aysan
S. Çınar
R. Lawrence
E. Akgöl


Target haematoctrit during erythropoietin treatment in dialysis patients. Which value is ‘true-functional haematoctrit’?

Sirs,

Correction of anaemia in dialysis patients by recombinant erythropoietin is an established treatment. This results in better life quality, brain function, working capacity, physical activity, remission of cardiac hypertrophy and better cardiac function [1–8,10]. However, upper target haematocrit (Ht) is still controversial as the above mentioned improvement appears in their pilot study the success of interferon-α therapy only in the group of low-responders in which the interferon-α was added only to all three initial hepatitis B vaccines but not in the group of non-responders in which the interferon-α was added only to the fifth vaccine injection [15]. In the controlled, randomized trials performed among healthy adult non-responders by Goldwater et al. interferon-α was shown to increase the likelihood of seroconversion to a fifth HBV vaccine dose in non-responders but when compared with placebo, its effect did not reach statistical significance [14].

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Table 1. Variations of the parameters measured

<table>
<thead>
<tr>
<th></th>
<th>D0</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ht (%)</td>
<td>33.2 ± 3.7</td>
<td>36.2 ± 4.1</td>
<td>35.0 ± 3.4</td>
<td>32.8 ± 3.1</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>10.3 ± 1.2</td>
<td>11.4 ± 1.4</td>
<td>10.9 ± 1.1</td>
<td>10.3 ± 1.0</td>
</tr>
<tr>
<td>Proteins (g/dl)</td>
<td>7.2 ± 0.5</td>
<td>7.9 ± 0.6</td>
<td>7.7 ± 0.6</td>
<td>7.2 ± 0.5</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.5 ± 0.4</td>
<td>4.9 ± 0.5</td>
<td>4.7 ± 0.4</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>68.0 ± 9.3</td>
<td>66.4 ± 9.3</td>
<td>67.2 ± 9.4</td>
<td>68.0 ± 9.3</td>
</tr>
</tbody>
</table>


**Tuberculosis after renal transplantation**

Sir,

We were interested to read the clinical report by Yildiz et al. [1] and their experiences with tuberculosis following renal transplantation. Twenty-two cases of tuberculosis were identified from 520 transplant recipients. The majority of diagnoses were made either on the grounds of clinical features with subsequent response to anti-tuberculosis therapy or on typical histology. *Mycobacterium tuberculosis* was isolated/cultured only in five cases. Most of their patients were successfully treated without positive confirmation of *M. tuberculosis* and the knowledge of drug sensitivities. However, 27% of patients succumbed. Problems of drug-related side-effects associated with anti-tuberculosis treatment, in particular hepatotoxicity, were also encountered in 18% of patients.

This series highlights the diagnostic difficulties associated with *M. tuberculosis* and the risks of therapeutic trials of medication. These problems stem from a number of factors. Tuberculosis may present atypically, particularly in the setting of immunosuppression, making a clinical diagnosis difficult. Patients may be infected with an atypical mycobacterium rather than *M. tuberculosis* or have isolates which may be resistant to the drugs that have been prescribed. *Mycobacterium tuberculosis* can also be fastidiously slow growing, or indeed may never grow at all, thus definitive diagnosis and drug sensitivities may be delayed or never achieved.

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A number of newer diagnostic techniques may be of benefit. The use of the polymerase chain reaction (PCR) to amplify specific M. tuberculosis DNA sequences allows rapid diagnostic confirmation and an estimation of rifampicin sensitivity [2]. This technique has been used on both clinical samples, such as sputa and biopsy specimens [3,4], and culture material [5] to provide a specific and sensitive result.

Diagnoses based on acid fast bacilli identification on smear examination can be confirmed by PCR as either tuberculosis or atypical mycobacteria. This has particular clinical relevance as the latter are more common in the immunosuppressed and require different treatment strategies. A rapid estimation of rifampicin sensitivity may also be obtained using this technique [2] thus allowing appropriate therapy and public health measures to be taken. Additionally, PCR does not need to be performed on culture material so a result can be produced in a matter of days as opposed to weeks.

The reliance on clinical acumen or therapeutic trials of therapy may not be eliminated by the use of PCR, however, this technique will substantially improve the number of cases with a confirmed diagnosis of tuberculosis. We therefore suggest the increased use of these molecular techniques in this patient subset.

Kaposi’s sarcoma after renal transplantation: treatment with liposomal doxorubicin

Sir,

Post-transplant Kaposi’s sarcoma might result from reactivation or transmission through infected organs of the human herpesvirus 8 (HHV-8) [1]. If Kaposi’s sarcoma is a malignancy, we must treat it with cytotoxic drugs, if it is an infection one should focus more on antiviral strategies [2]. In his recent Clinical Update on Kaposi’s sarcoma after renal transplantation, Camille France’s discussed the dilemma to treat Kaposi’s sarcoma while preserving renal function [3]. In a most recent NDT letter, Gómez mentioned that reappearance of Kaposi’s sarcoma after mycophenolate could be stopped with antiviral treatment by ganciclovir [4]. We should like to add a report on cytotoxic therapy with doxorubicin, and conversion to tacrolimus without adverse events.

The 41-year-old patient of Greek origin had a congenital single kidney with nephrolithiasis. After a nephrolitholapaxy in 1988, an embolus occluded the renal artery. Maintenance haemodialysis was required. In November 1989 the patient underwent kidney transplantation. Because of bioptically proven rejections, the patient needed anti-rejection treatment with steroid pulses. Triple immunosuppression was given with steroids, azathioprine and cyclosporin (trough levels 100–150 ng/ml). Multiple skin angiomatoid tumours occurred mainly on the left leg after deep vein thrombosis. Kaposi’s sarcoma was diagnosed histologically by skin biopsy.


Fig. 1. Kaposi’s sarcoma in a 41-year-old kidney transplant patient. The cutaneous manifestations of the sarcoma were most prominent on the left instep (left, before doxorubicin). Kaposi’s sarcoma significantly faded after liposomal doxorubicin (right, 12 months later).
in 1991. An intestinal manifestation could be excluded by gastric and colonic endoscopy. The HIV test was negative, but HIV-8 was positive. Lymphocyte subtyping revealed 1020 μl CD4+ cells and 661 μl CD8+ cells, with a normal CD4+/CD8+ ratio.

Doxorubicin can arrest HIV-associated Kaposi’s sarcoma [5]. To stop the progression of skin tumours, we began a doxorubicin trial in the kidney transplant patient. In May 1996 we started with 38 mg intravenously (=0.5 mg/kg) every 4 weeks for 6 months (Doxil®). After 4 months, lymphocytes revealed a slight decrease in CD4+ cells and a greater increase in CD8+ cells. This formulation incorporates doxorubicin into polyethylene glycol-coated liposomes (pegylated), leading to a longer half-life of 55 h and less toxicity [5].

Since creatinine increased again and Kaposi’s angiomas disappeared. At present, 4 years after diagnosis, there are no signs of tumour recurrence. The patient’s renal function is unchanged on maintenance prednisone and cyclosporin. In this case, the tumour regression after local irradiation prevented the need to withdraw cyclosporin with its risk for graft rejection and/or irreversible loss of renal function.

Kaposi’s sarcoma after renal transplantation—withdrawal of immunosuppression or local irradiation?

Sir,

We have read with interest the review by Francés on Kaposi’s sarcoma after renal transplantation [1]. As mentioned, this tumour, frequently reported today after transplantation, affects as many as 5% of graft recipients of Mediterranean, Arabic, Jewish or black origin, especially those receiving cyclosporin [2–3]. The main therapeutic approach to Kaposi’s sarcoma requires reduction or cessation of immunosuppressive therapy, especially azathioprine and/or cyclosporin. This approach, however, may be associated with irreversible graft rejection and function loss. We want to report on successful treatment of cutaneous Kaposi’s sarcoma in a renal transplant patient by local irradiation, with maintenance of normal graft function. The patient, a 23-year-old male of Arab origin, received a renal graft from his mother. The patient’s renal function was normal with a plasma creatinine of 1.4 mg% (115 μmol/l) and a creatinine clearance of 80 ml/min. His maintenance immunosuppressive treatment included prednisone 10 mg/day, azothioprine 100 mg/day and cyclosporin 250 mg/day. Fourteen months after renal transplantation, diffuse lesions of cutaneous Kaposi’s sarcoma were noted on his right shoulder and upper part of the back. Repeated testing for the human immunodeficiency virus was negative. Azothioprine was discontinued but cyclosporin was maintained with no dose modification. The patient also received local irradiation at a total dose of 2000 cGy, 10 fractions of 200 cGy/fraction using electrons, energy 6 MEV. In a short time, the Kaposi’s sarcoma regressed and disappeared. At present, 4 years after diagnosis, there are no signs of tumour recurrence. The patient’s renal function is unchanged on maintenance prednisone and cyclosporin. In this case, the tumour regression after local irradiation prevented the need to withdraw cyclosporin with its risk for graft rejection and/or irreversible loss of renal function.

It will be of interest to hear whether the clinical course of Kaposi’s sarcoma in transplant patients receiving newer agents as mycophenolate mofetil or rapamycin, follows a similar pattern.

We thank Prof. Dr Thomas Mertens, Department of Virology for determination of the HHV-8, and Prof. Dr Peter Kern, Division of Infectiology for clinical advice.

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Immunosuppressive treatment for sclerosing peritonitis

Sir,

The paper by Rigby et al. [1] focuses the attention on a rare but serious complication of peritoneal dialysis (CAPD), sclerosing peritonitis [2]. We have read with great interest the immunosuppressive therapy schedule proposed by the Australian group, and the patient’s outcome. The association of prednisone and azathioprine seems to be effective although two points need to be clarified: the first problem is the low clinical results. The second, the most relevant problem, is how long the treatment must be performed.

We report our experience with one case of sclerosing peritonitis. Differences with the Australian observations are based on the induction therapy (colchicine + steroid) and the duration of immunosuppressive therapy (azathioprine + steroid) withdrawn only after 12 months with excellent clinical results.

The patient, S.R., female, 78-years-old, 60 kg bw, began CAPD on September 1990. In August 1994, and May and July 1995 she developed three episodes of peritonitis: the first caused by Klebsiella pneumoniae, the second by Pseudomonas aeruginosa, which was accompanied by sepsis, and the last by Staphylococcus epidermidis. All the episodes were treated successfully with specific intraperitoneal antibiotics. In August 1995 the peritoneal function decreased,
with a reduction of clearances and an increase of glucose absorption. For this reason the patient was switched to haemodialysis. In January 1996 S.R. was symptomatic with nausea, vomiting, epigastric pain after meal, and stipsis.

The patient was starving, with a decrease of haemoglobin and serum proteins. The clinical examination revealed a tenderness and dilatated abdomen: investigations were performed with abdomen echography and then with CT scan, which was diagnostic for sclerosing peritonitis showing numerous enlarged small bowel loops with an increase of the visceral peritoneum thickness, causing an encapsulating mass (Figures 1–2).

In March 1996, because of the impossibility to ingest a normal diet, the patient was put on total parenteral nutrition (TPN). At the same time we started immunosuppressive therapy: prednisone 25 mg dye for 1 month and then 12.5 mg alternate day, plus colchicine 1 mg dye for 2 months. At the end of the second month we began azathioprine 100 mg dye, reduced to 50 mg dye after 2 months. After 6 months, due to the dramatic improvement of the patient, we performed a CT scan showing a reduction of visceral peritoneum thickness and a decrease of small bowel loop diameter (Figure 3). The patient began to take food by mouth and for this reason we stopped TPN and azathioprine and continued only with prednisone 12.5 mg on alternate days for 4 months. The patient had no more symptoms and signs of malabsorption. In October 1997, 6 months after withdrawing prednisone, a CT scan (Figure 4) confirmed complete resolution with absence of visceral peritoneum thickening and small bowel loops dilatation. Currently the patient is on regular HD, on normal food and without any evidence of malabsorption or malnutrition (last values of serum proteins and albumin 7.6 and 3.9 gr%).

Sclerosing peritonitis is a very rare but usually fatal complication of CAPD, with unknown pathogenesis, possibly secondary to an immunologic mechanism [3–5].

The presented clinical case is interesting for two reasons: firstly because we administered colchicine, secondly because we stopped immunosuppressive therapy after 1 year. The rationale for using colchicine was based on the evidence that this drug is able to inhibit collagen production by fibroblasts.

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Previous studies had shown that colchicine is effective in decreasing hepatic fibrosis [6] and idiopathic pulmonary fibrosis [7,8]. The mechanism appears to be linked to the inhibition of fibroblast proliferation and total collagen synthesis, the latter accompanied by an inhibition of collagen secretion from this cellular line. Moreover, recent studies focus on the action of colchicine on T lymphocytes: this drug is able to down-regulate L-selectin, leukocyte function-associated antigen-1 and the expression of interleukin-2 receptor [9]. As to the association of azathioprine with prednisone used with this patient, based on several reports in literature, this combination appears to be more effective than other immunosuppressive schedules in treating sclerosing peritonitis.

In conclusion, our observation confirms that sclerosing peritonitis must no longer be considered as a fatal and irreversible complication of CAPD. This pathology is probably linked to an immunological derangement which can be controlled and reversed by immunosuppressive therapy.

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