Renal impairment induced by isotretinoin

Sir,

A 34-year-old man developed renal impairment after having been given isotretinoin (40 mg/day) for severe acne conglobata over a period of 2 months. His medical history consisted in a car accident 6 months previously, which had resulted in a left ischium fracture, and a haematuria that resolved spontaneously (the intravenous pyelogram was normal at this time, and creatinine was 81 μmol/l). He presented with severe bilateral lumbar pains suggesting renal colic. A renal ultrasound scan showed kidneys of normal size. An intravenous pyelogram found normal nephrogram, symmetrical kidneys without structural defect, lack of urinary concentration, and a normal bladder. Blood pressure was 140/80 mmHg. He was apyrexial, had a normal diuresis, and abdominal pain that was attributed to chronic constipation. There was a moderate inflammatory syndrome (erythrocyte sedimentation rate at 500/000/mm) and proteinuria (0.8 g/l). The patient was then hospitalized. APTT and prothrombin index were normal. There was no eosinophilia. There was no indication of infection, immunological results were normal (autoantibodies, complement, immunoglobulin). An abdominal CAT scan found no renal infarction and investigations of abdominal pain only showed an elongated colon. After stopping isotretinoin, and with intravenous hydration, the creatinine returned to normal in 7 days, and the proteinuria, haematuria and inflammatory syndrome disappeared after 3 days.

A literature review found only two cases of renal impairment due to retinoids. Horber et al. [1] described a renal impairment with hypercalcaemia and proteinuria in a 56-year-old patient treated with 25 mg of etretinate per day for a superficial bladder tumour. One year later, a renal biopsy showed a Burkitt lymphoma. More recently, Crieber et al. [2] reported the case of a 83-year-old man treated by etretinate. Blood pressure was 140/80 mmHg, he was apyrexial, had a normal diuresis, and abdominal pain that was attributed to chronic constipation. There was a moderate inflammatory syndrome (erythrocyte sedimentation rate at 30 mm, C reactive protein at 77 mg/ml), the creatinine was stable (259 μmol/l). Urinary analysis did not reveal any inversion of the Na/K ratio suggesting renal dysfunction. There was no eosinophilia. There was no indication of infection, immunological results were normal (autoantibodies, complement, immunoglobulin). An abdominal CAT scan found no renal infarction and investigations of abdominal pain only showed an elongated colon.

Renal impairment is not a classical complication of retinoid treatment. Fontau’s study [3] showed that after 3 months of treatment with retinoid (etretinate), the renal function of 59 patients was normal. There is no reported case of renal impairment due to isotretinoin. In rats, retinoids provoke enzyme changes in the proximal convoluted tubule [4]. Further studies are needed to link these findings to man. In our case, the acute renal dysfunction, then the complete return to normal of biological results in 7 days (duration necessary for isotretinoin to be completely eliminated) suggest drug toxicity. Unfortunately renal biopsy was not performed due to the patient’s satisfactory recovery. These events seem sufficient to implicate retinoids as being responsible. For ethical reasons, the treatment has not been recommenced, although this would have constituted formal proof of the drug toxicity of isotretinoin.

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Intracardiac thrombi in nephrotic syndrome

Sir,

In a recent issue of Nephrology Dialysis Transplantation, Mak et al. described a case of intracardiac thrombus formation in a woman with the nephrotic syndrome (NS) [1]. It was the second (not first) report of an adult patient with this complication in the literature [2]. However, we wish to draw attention to the fact that more than six paediatric cases have been reported.

Recently we presented eight children with thromboembolic complications of NS, amongst whom a 7-year-old boy had left ventricular thrombosis and a 2-year-old girl had right atrial thrombosis [3]. Three of our patients had arterial thrombosis, but the true incidence is presumably lower. Andrew and Brooker reviewed 79 nephrotic children with thrombotic complications. Only 27% had arterial thrombosis [4]. Mak et al. pointed to the role of abnormalities in the coagulation system in NS, but no investigations were performed in the described patient on admission! Platelet count, fibrinogen and AT III level together with more advanced D-dimer and TAT complex may help in identifying patients at high risk of thrombosis. APTT and prothrombin index are less helpful.

The question of whether it is reasonable to give anticoagulants to these patients is still unanswered. In Poland acetylsalicylic acid, dipyridamole, and coumarin derivatives are used, and heparin is once again under clinical investigation. In a case of very low AT III level and thrombosis we also recommend AT III concentrate together with heparin. The experience of Mak et al. with heparin does not prove that it is generally useful in NS, because it was used in a situation when considerable endothelial damage had occurred following embolectomy.

As an alternative to the surgical approach Mak et al. adopted, thrombolysis with natural or recombinant fibrinolytic agents should also be mentioned; this has the potential to dissolve the thrombus without causing mechan-
L-carnitine normalizes the reduced carnitine palmitoyl transferase activity in red cells from haemodialysis patients

Sir,

Peroxidation in the membrane lipid structure of the red blood cell (RBC) results in haemolysis and anaemia in patients with chronic renal failure [1]. It has been shown that peroxidation of polyunsaturated fatty acids esterified in membrane phospholipid (PL) is followed by increased PL fatty acid turnover [1]. The reversible transfer of long-chain fatty acids from CoA to free carnitine (FC), catalysed by erythrocyte carnitine palmitoyl transferase (CPT), modulates the acyl CoA/free CoA ratio, which is critical for the regulation of the membrane PL fatty acid turnover [2]. Long-chain acyl carnitines (LCAC) serve as a reservoir of acyl moieties for the reacylation of membrane PL, which is catalysed by lysophospholipid acyl-CoA transferase [3]. We have reported reduced carnitine palmitoyl transferase activity and altered acyl trafficking in red blood cells from haemodialysis patients [4]. Now we have studied the effect of intravenous administration of L-carnitine in those patients.

We studied 30 patients undergoing chronic haemodialysis treatment (CHD). Of them, 15 were receiving 3–5 mg/kg L-carnitine intravenously at the end of each dialysis session (group A) for 6 months. Blood samples were drawn before and after 1 month of discontinuation of L-carnitine therapy. In the remaining 15 patients (group B), not receiving L-carnitine treatment, basal blood samples were taken. The latter group was then treated with 3–5 mg/kg L-carnitine intravenously at the end of each haemodialysis session for 1 month; at that time point, blood samples were drawn again. All blood samples were obtained before dialysis and collected into heparinized or EDTA-treated tubes. Blood samples were also taken from age-matched healthy controls. RBC and ghosts were isolated as described [5]. CPT activity was measured in ghosts as reported [5]. RBC FC and LCAC levels were determined by a radiochemical procedure [6].

In group B, CPT basal values were significantly lower than in controls, whereas the basal LCAC/FC ratio was significantly greater than in controls. In both groups, L-carnitine treatment restored the LCAC/FC ratio to normal levels, and caused a marked increase in RBC CPT activity. Patients receiving L-carnitine in both groups showed no significant differences in the levels of both CPT and LCAC/FC ratio. In group A, L-carnitine withdrawal resulted in a significant decrease in CPT activity, and a concurrent non-significant increase in the LCAC/FC ratio (Table 1).

As demonstrated by the increase in the LCAC/FC ratio, the reduction in RBC CPT activity alters acyl trafficking in RBC membranes, which impedes the repairing of fatty acids damaged by free radicals, and can lead to accumulation of lysophospholipids. The latter may be involved in anaemia and haemolysis in HD patients. L-carnitine, by inducing RBC CPT activity, restores the equilibrium between acyl CoA pools in RBC, thus allowing normal acyl trafficking and proper repair of RBC membrane PL. These mechanisms may underlie the beneficial effects of L-carnitine in treating anaemia in HD patients.

In addition, because of its stabilizing effect on RBC membrane, L-carnitine administration may bring about a reduction in the dose of erythropoietin required for the correction of anaemia, which may represent significant cost-saving. Recently we read two papers which described the

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**Table 1. Levels of CPT and LCAC/FC ratio in red blood cells from controls and from treated and untreated patients**

<table>
<thead>
<tr>
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<th>Controls</th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td></td>
<td>+L.Car.</td>
<td>−L.Car.</td>
<td>+L.Car.</td>
</tr>
<tr>
<td>CPT</td>
<td></td>
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<tr>
<td>0.42 ± 0.14</td>
<td>0.58 ± 0.18</td>
<td>0.42 ± 0.19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.32 ± 0.17</td>
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<tr>
<td>n=25</td>
<td>n=15</td>
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<td>(P&lt;0.01)</td>
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<tr>
<td>LCAC/FC</td>
<td>0.15 ± 0.04</td>
<td>0.11 ± 0.04</td>
<td>0.17 ± 0.11</td>
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<td>n=20</td>
<td>n=15</td>
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LCAC and FC are in nmol gH<sub>B</sub>⁻¹, and CPT is in nmol min⁻¹ mg protein⁻¹. Data indicated are mean ± SD. Significant differences vs controls are expressed in parenthesis. +L.Car., patients who have previously received L-carnitine; −L.Car., patients who have not previously received L-carnitine.

<sup>a</sup>Significant differences between +L.Car. and −L.Car. in group A (P<0.05). <sup>b</sup>Significant differences between +L.Car. and −L.Car. in group B (P<0.001). <sup>c</sup>Significant differences between +L.Car. and −L.Car. in group B (P<0.01).
L-carnitine treatment improvement in the response of anemia to rHuEpo treatment in patients on haemodialysis [7,8]. This effect is probably increased in haemodialysis patients with a deficit of carnitine, which is possible to predict in patients with a low protein intake, PCR <1 g/kg/day and a Kt/V >1, especially with high-flux dialysers [9].

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7. Boran M, Dalva I, Go¨nenc F, Cetin S. ... absence of right-sided endocarditis in these patients may human erythropoietin (r-HuEPO) and L-carnitine combination thus exposing patients with valvular diseases to IE. The most common infecting organisms. Local signs of inflammation at the vascular access site was associated significantly with staphylococcal IE. Surprisingly, there was no right-sided endocarditis in this series. Mortality was high, particularly among the older patients.

This survey shows that incidence of endocarditis in long-term dialysed patients may be 21 to 54 times higher than in the general population (Table 1, data drawn from a pilot study conducted by Delahaye in France in 1991 [5]). Higher risk factors for IE may account for this very high incidence. Mitral annular calcification and calcific aortic stenosis is more common in patients with chronic renal failure than in other patients of similar age, due to abnormal calcium–phosphorus homeostasis in the setting of secondary hyperparathyroidism [6]. Repeated vascular puncture expose dialysis patients to bacteraemia or vascular access site infection [7], thus exposing patients with valvular diseases to IE. The absence of right-sided endocarditis in these patients may simply reflect the high frequency of anatomically abnormal

### High risk of severe endocarditis in patients on chronic dialysis

Sir,

There are few studies of infective endocarditis (IE) in patients on chronic dialysis, except for those dating back to a time when the characteristics of dialysed patients, vascular access devices, and diagnostic procedures were different from those prevailing today [1,2]. We conducted an extensive national retrospective survey of IE in patients on chronic dialysis to determine its incidence and characteristics.

A first questionnaire was mailed to all 230 French metropolitan chronic dialysis centres, in order to record all the cases of IE among French patients who had been on chronic dialysis for at least 3 months either on haemodialysis in a centre or at home, or on peritoneal dialysis, and whose IE has been diagnosed between the 1 January 1988 and the 31 December 1994. Next, a detailed patient-oriented questionnaire was mailed to all the centres that reported IE. Patients were included in the analysis if they had definite or possible IE, according to the Duke Endocarditis Service Criteria [3].

Of the 230 dialysis centres contacted, 153 (66.5%) returned the first questionnaire, reporting 56 cases of IE. Thirty-two patient-oriented questionnaires were returned, two cases were rejected, and 30 patients reported by 22 centres were included in the analysis (definite IE for 22, and possible IE for 8). Twenty-three cases (77%) were reported between 1992 and 1994. We therefore estimated the annual incidence of IE from the figures for these 3 last years of the survey. The minimum and maximum estimations of the annual numbers of incident cases of IE in France are 8 and 21. On 31 December 1992, the European Dialysis and Transplant Association (EDTA) reported 16 527 patients alive on different forms of dialysis in France [4]. This permitted the annual incidence rate to be estimated at 5–13 cases of IE per 10 000 dialysed patients. Characteristics of validated cases of IE are reported in Table 1. The vascular access site was the most frequently identified portal of entry. Staphylococci were the most common infecting organisms. Local signs of inflammation at the vascular access site was associated significantly with staphylococcal IE. Surprisingly, there was no right-sided endocarditis in this series. Mortality was high, particularly among the older patients.

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| Table 1. Characteristics of infective endocarditis in a series of French dialysed patients and in the general French population |
|-----------------|-----------------|-----------------|
|                  | Dialysed patients (n = 30) | General population (n = 415)* |
| Annual incidence (per 10 000) | 5 (7–13) | 0.24 |
| Age | 62 (27–76) | 50 ± 19 |
| Sex ratio (female/male) | 1.5 | 0.56 |
| Known valvular lesion (%) | 60 | 55 |
| Prosthetic valve IE (%) | 13 | 22 |
| Endocarditis site (%) | | |
| Aortic | 40 | 36 |
| Mitral | 43 | 39 |
| Aortic and mitral | 17 | 13 |
| Right heart | 0 | 12 |
| Aetiological agent (%) | | |
| Staphylococcus sp (aureus) | 63 (53) | 23 (18) |
| Streptococcus sp (group D) | 17 (13) | 58 (23) |
| Other | 7 | 11 |
| Culture negative | 13 | 8 |
| Portal of entry (%) | | |
| Presumptively identified | 60 | 67 |
| Vascular access site (identified) | 37 | 8 |
| Surgery (treatment) (%) | 33 | 24 |
| Mortality (8 weeks after diagnosis) | 43% | 17% |

*Data from [5].
left-sided cardiac valves in patients on chronic dialysis. Right-sided endocarditis could also have been overlooked in dialysis patients with staphylococcal bacteraemia, as in these patients the frequency of valvular involvement may be higher than clinical or echocardiographic analysis would suggest [8]. The very high incidence of staphylococcal IE in dialysis patients is not surprising as Gram-positive cocci, especially Staphylococcus aureus, have been reported throughout the literature to be the predominant causative agent for bacteraemia in haemodialysis patients, and to be involved in 47–72% of cases [9]. The portal of entry was very different in dialysis patients and the general population, because the vascular access site was the identified source of IE for at least 37% of the dialysed patients, whereas only 8% of the general population patients had IE as a consequence of endovascular procedures. In the patients on dialysis, mortality was much higher than in the general population. This may be due to the general condition of dialysed patients, which is worse than in the general population, or to the predominance of staphylococcal IE. This organism might lead to higher mortality than other causative organisms, as already shown [5,10].

Physicians must maintain a high index of suspicion for endocarditis in dialysed patients. Patients on long-term dialysis should be considered at very high risk of severe IE, irrespective of recognized or unrecognized underlying valve disease. Consequently, procedures that may cause bacteraemia [11] require antibiotic prophylaxis. Especially intensive care must be given to the skin at the vascular access site, and patients with dermatitis near or at that site should receive antistaphylococcal antibiotics until the dermatological disease is cured. Empiric antimicrobial treatment of IE in dialysed patients should include provision for Staphylococcus sp.

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calcium infusion in patients with primary hyperparathyroidism was found to be comparable to the percentage suppression of PTH secretion of the cells prepared from their removed adenoma by a comparably high ionized calcium concentration in the medium. In its report of 1988 the team of Brown (Brent et al. [8]) even reported that the in vivo Ca set point of healthy controls was somewhat higher (1.15–1.2 mmol/l) than in their previous ex vivo studies (1.0 mmol/l) performed on other controls. Likewise, no direct comparison has ever been made in the same uraemic patients. Only the ex vivo Ca set point, measured with the definition of Brown, has been found higher than 1.0 mmol/l in 13 of 15 hyperplastic glands from six uraemic patients. Therefore we do not agree with Goodman and Salusky [2,3] that the Ca set point according to Brown has been validated by direct in vivo-ex vivo comparison. However, we agree with them that the alternative definition of Felsenfeld has never been validated.

Our main concern about the physiological and clinical relevance of measuring the Ca set point by these definitions is that in vivo, the Ca set point is dependent upon basal concentration of ionized calcium and not necessarily related to the changes in basal, maximal or minimal PTH concentrations. This has been shown by the following three studies:

1. Caravaca et al. [9] reported that the Ca set point increased in parallel with an increase in basal plasma ionized calcium, whereas PTH max decreased significantly after 10 weeks of intravenous calcitriol in patients dialysed throughout the study with a constant dialysate calcium of 1.25 mmol/l.

2. The same phenomenon has been observed by Pahl et al. [10] in dialysis patients with hyperparathyroidism. They intentionally increased the basal plasma calcium (measured only as total calcium) by intravenous administration of calcitriol associated with a calcium dialysate concentration of 1.75 mmol/l, or by increasing the dialysate concentration from 1.75 to 2.0 mmol/l, as well as the dose of oral calcium. This resulted in a decrease in PTH max with an increase in the calcium set point, whereas discontinuation of the plasma calcium increasing measures resulted in a return of all parameters to their baseline value.

3. Hardy et al. [11] briefly treated 13 euparathyroid haemodialysis patients with three intravenous injections of 4 µg of alfalcacidol over a 1-week period. A slight hypercalcemia and a significant decrease in basal, maximal, and minimal PTH was observed with a significant increase in the Ca set point measured either with the definition of Brown or that of Felsenfeld.

In conclusion, whatever the definition of the Ca set point, we think that the major problem in measuring it in vivo is that it has little physiological and clinical relevance. In contrast with Brown’s initial assumption, it does not actually measure an intrinsic functional property of the parathyroid cells which conditions their secretion rate.

Therefore we agree with Felsenfeld [12] that set point of calcium, as applied to human studies, is somewhat of an artificial concept with respect to disordered PTH secretion.

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11. Hardy P, Shenouda M, Moriniere Ph, Fournier A. Shift of calcium set point in uremia does not explain PTH hypersecretion nor 1 alpha OH vitamin D suppressive effect on PTH secretion. ISN XIII International Congress of Nephrology. Madrid 1995; 413