Letters

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

Secondary distal renal tubular acidosis in association with urological abnormalities

Sir,

Distal renal tubular acidosis (RTA) is a hyperchloremic type of metabolic acidosis characterized by the inability of the distal nephron to maximally acidify the urine pH to less than 5.5 despite spontaneous or induced metabolic acidosis [1,2]. This study is the first report of association of vesico-ureteric reflux and bladder outlet obstruction with distal RTA.

Thirteen patients presented with resistant rickets, dwarfism, and myopathy. They were found to have urological abnormalities and DRTA. The diagnosis of distal RTA was based on: (i) normal anion gap metabolic acidosis and (ii) basal urine pH above 5.5 in the absence of urinary tract infection; (iii) an inability to lower urine pH after ammonium chloride and/or frusemide test in patients who did not have spontaneous metabolic acidosis; (iv) absence of advanced renal failure (GFR > 25 ml/min/1.73 m²); (v) good hydration.

Distal acidification tests included the ammonium chloride loading test (0.1 g/kg) and urine pH measurement for the next 5 h with one blood pH after 2 h; the frusemide test (1–2 mg/kg or 80 mg frusemide and urine pH hourly for 5 h); and urine anion gap. Plasma concentrations of sodium, potassium, chloride, bicarbonate, calcium, phosphate and alkaline phosphatase were measured with an automated analyser. GFR was assessed by creatinine clearance and radionuclide study (using 99mTc-DTPA). Ultrasound of kidneys, intravenous urogram, and micturating cystourethrogram were performed to identify the urological abnormalities.

All thirteen patients had urological abnormality associated with secondary distal RTA. Only one was an adult, who had primary vesico-ureteric reflux. Of the 12 children with distal RTA secondary to urological problems, five had primary classic renal tubular acidosis. six had a posterior urethral valve and one had a neurogenic bladder.

The mean age at diagnosis was 12 ± 5.2 years. The mean interval between the onset of symptoms and diagnosis was 6.2 ± 2.2 year. The children had non-specific symptoms resulting in delayed recognition of the problem. They presented with failure to thrive, inability to run from muscle weakness, voiding dysfunction and rheumatic bone pain. Nine presented with primary complaint of failure to thrive and short stature. Only three had symptoms of obstructive voiding, while four had a palpable bladder. Hyperkalaemia was seen in four children. There were five patients with a GFR above 60 ml/min. Eight patients (all children) had mild renal impairment (GFR 24–60 ml/min). All these children had florid rickets with evidence of secondary hyperparathyroidism (subperiosteal bone resorption on X-ray).

Renal insufficiency in these patients could be due to interstitial nephritis resulting from a variety of factors, such as obstruction, infection, nephrocalcinosis or immune injury [3,4]. Reflux nephropathy with proteinuria and renal impairment was present in 12 out of the 13 patients with secondary distal RTA with urological disease. Four children with reflux nephropathy and distal RTA developed end-stage renal disease during the follow-up.

Vesico-ureteric and other urological conditions could secondarily be associated with distal RTA resulting in growth retardation and other metabolic derangements. Early recognition and adequate treatment of distal RTA with alkali can reverse growth failure in children [5]. Obstruction causes a voltage-dependent distal acidification defect with reduced H-ATPase activity [1]. Associated interstitial renal disease would produce rate-dependent distal RTA. Children presenting with short stature should also be evaluated for distal RTA and underlying urological disease if there is any suggestion of obstructive voiding. In children, distal RTA can often be a clue for underlying urological diseases, such as reflux nephropathy, calling for early diagnosis and surgical management in order to prevent end-stage renal disease. Simple tests of urinary acidification and high index of suspicion could detect RTA in patients presenting with growth failure.

Lipids and lipoproteins alteration after renal transplantation

Atherosclerosis and cardiovascular diseases are the leading causes of death among renal transplant recipients [1] and hyperlipidaemia is considered as a major risk factor in the development of atherosclerosis.

In this study, conducted from 1993 to 1995, we included 65 patients (40 male and 25 female). The age of the patients ranged from 11 to 60 years. Fifty-seven patients (87.6%) received kidneys from live donors, and the rest were from proclaimed brain-dead donors.

None of the patients had received drugs curtailing blood lipid levels. After transplantation all patients received cyclosporin, prednisolone, and azathioprine.

We determined cholesterol, triglyceride, creatinine, HDL-C and LDL-C prior to the transplant and at 3- and 12-week intervals after the transplant.

After having precipitated VLDL-C and LDL-C by means

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Table 1. Lipids (mg/dl)

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<th>Cholesterol</th>
<th>Triglyceride</th>
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<td>Before transplantation</td>
<td>182.6 ± 45.3</td>
<td>150 ± 68.5</td>
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<tr>
<td>12 weeks after transplantation</td>
<td>240.9 ± 75.6</td>
<td>203.6 ± 95.8 mg%</td>
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Table 2. Lipoproteins (mg/dl)

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<th>LDL-C</th>
<th>HDL-C</th>
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<tr>
<td>Before transplantation</td>
<td>114.5 ± 40.3</td>
<td>38.4 ± 13.1</td>
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<tr>
<td>12 weeks after transplantation</td>
<td>149.7 ± 70.1</td>
<td>50.9 ± 20.5 mg%</td>
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of dextran sulphate, HDL-C was determined and LDL-C was calculated employing the Friedewald formula.

The aforementioned parameters did not show significant alterations in the triglyceride, LDL-C, 3 weeks after transplant; however, the total cholesterol, LDL-C, HDL-C, and triglyceride showed significant changes \( (P<0.01) \) 12 weeks after the transplant. (Tables 1, 2)

The study conducted by Vathsala [2] shows an increase in cholesterol and a reduction in triglyceride following successful transplantation and/or a reduction in triglyceride and increase in cholesterol, HDL-C, LDL-C were seen at 3 months after the transplant [3].

According to Ilbes et al’s claim, immunosuppressive drugs cause various abnormalities such as decreased clearance of triglyceride and increased hepatic synthesis following corticosteroid therapy [4]. Similarly cyclosporin, being lipophilic, alters lipoprotein metabolism especially when concomitant beta blockers are being taken, and it thereby causes severe hyperlipidaemia.

Hypercholesterolaemia is also observed when patients receive cyclosporin and prednisolone [2]. This is in contrast to our patients who receive a combination of cyclosporin, prednisolone, and azathioprine. Since our patients showed a voracious appetite following successful transplant and as saturated lipids and carbohydrates form our staple diet, the differences in the results obtained in Iran and those in European countries and USA could be attributed to diet.

In conclusion we may state that periodic measurement of lipids and lipoproteins in transplant recipients is essential, and hyperlipidaemia should be managed by pharmacological agents, dietary regimen, and exercise.

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Antiproteinuric effect of Losartan in patients with chronic renal diseases

Sir,

In the recent editorial on the AIPRI trial [1], Mann gives an excellent account of the potential of ACE inhibitors for retarding the evolution of renal failure in chronic nephropathies. Angiotensin II antagonists produce effects very similar to those of ACE inhibitors and have a beneficial effect on renal function in various animal models of chronic renal disease. Since these agents interfere with the renin–angiotensin system at a level (AII receptors) different from that of ACE inhibitors, they may allow a more complete counteraction of this system when used in association with ACE inhibitors. We have recently completed a pilot study aimed at providing information for designing a randomized trial comparing the effect on renal function of ACE inhibitors given alone and in combination with Losartan. This was an open trial in 11 patients with various renal diseases (chronic glomerulonephritis in eight, diabetic nephropathy in two, chronic pyelonephritis in one) who had been treated with ACE inhibitors for more than 3 months (Benazepril in two, Enalapril in three, Lisinopril in two, and Fosinopril in two). Each patient had arterial pressure, creatinine clearance and 24 h protein excretion measured on two consecutive days while on ACE inhibitors, after 2 weeks of combined treatment ACE inhibitor plus Losartan (50 mg/day) and again after 1–2 weeks after stopping Losartan.

Losartan caused a 30% reduction in proteinuria in patients on ACE inhibitors, did not modify creatinine clearance and produced a 6 mmHg decline (NS) in mean arterial pressure (Table 1). Such a decline almost entirely depended on a marked hypotensive response observed in a diabetic patient (−46/−22 mmHg) after 2 weeks of treatment. Proteinuria in this patient was little affected by Losartan and in the aggregate there was no relationship between changes in protein excretion and in mean arterial pressure (\( r = −0.10, P=0.769 \)). One patient developed a malar skin rash of mild degree 1 week after the introduction of Losartan which promptly subsided after stopping the drug. Such phenomenon occurred on rechallenging.

These preliminary data in man are in line with recent work [2] showing that the association Losartan + Lisinopril is more effective than Lisinopril or Losartan given alone in reducing proteinuria and glomerulosclerosis in rats with passive Heymen nephritis. It seems plausible that angiotensin II antagonists combined with ACE inhibitors allow a more complete counteraction of the effects of angiotensin II on the kidney. ACE inhibitors retard the progression of diabetic nephropathy as well as of non-diabetic renal diseases [3]. The antiproteinuric effect of Losartan was independent on changes in the GFR and in arterial pressure. Proteinuria is a key pathogenetic factor in the progression of renal disease [4] and Losartan may potentiate the nephroprotective effect of ACE inhibitors in chronic renal diseases. These data offer a sound basis for a controlled study. However, at this stage the marked hypotensive response we found in one patient and the mild skin rash observed in another patient demand caution when Losartan is used in association with ACE inhibitors.

Angiotensin II antagonists in association with ACE inhibitors may potentiate the nephroprotective effect of this class of drugs. The AIPRI study undoubtedly represents a breakthrough for the pharmacological treatment of progressive renal diseases. Our preliminary data suggests that pharmaco-
logical interference with the renin–angiotensin system beyond ACE inhibition might add further benefit in patients with chronic renal diseases.

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Biocompatible membranes in acute renal failure: prospective case-controlled study

Sir,

It is not the purpose of this letter to address the much discussed topic of the times, namely should cuprophan membranes be banned from the treatment of patients with acute renal failure. Nor is it its purpose to discuss the dismal fact that the mortality of acute renal failure has remained remarkably constant over the past three decades since I last wrote on the subject [1], despite the technical progress made with continuous therapies using highly biocompatible membranes [2]. It is rather to recount a personal experience which has involved me in a considerable amount of work and relates to the topic.

On August 24th 1994, the *Lancet* published a paper entitled ‘Biocompatible membranes in acute renal failure: prospective case controlled study’ [3]. In this published study according to the authors, 52 consecutive critically ill patients, all from the same hospital, with acute renal failure secondary to cardiac surgery were recruited and dialysed with either a cuprophan (26) or AN69 (26) dialyser. Initially, it had been planned to recruit 212 patients, however, the authors felt obliged to stop the study for ethical reasons after 26 pairs had been enrolled. This dramatic decision was based upon the fact that 12 deaths from lethal sepsis had occurred in the cuprophan group and only 4 in the AN69 group. This difference was significant for the subset of septic patients by $x^2$-testing. The number of patients with sepsis are not given, nor is any objective evidence as to how lethal sepsis was diagnosed. Apparently, mortality as a whole (cuprophan: 17 deaths; AN69: 10 deaths) did not reach statistical significance between the groups, so subset data dredging was necessary to justify the ‘Procrustean’ [4] hypothesis that cuprophan dialysis potentiated lethal sepsis. No confidence limits were given and the statistical power of this observation was too small to be measured. Nevertheless, the *Lancet* published this article, allowing a sweeping conclusion that cuprophan should not be used in the treatment of acute renal failure and published a favourable editorial endorsing the findings [5]. Three months later, in November 1994, two letters appeared in the correspondence columns of the *Lancet* protesting about the sweeping claims of Schiffl et al [6,7]. His reply was about the deep concern he felt about the fate of patients where a statistically significant difference of 31% in a lethal complication was not a ‘misplaced argument’ [8]. I was surprised when I read his reply as he had sent in an abstract to ASAIO meeting for 1995, 6 weeks before the *Lancet* correspondence was published where an identical study to the *Lancet* was reported, except that the numbers had increased from 52 to 76 and the total deaths on cuprophan from 17 to 25 (needless to say, these numbers now become significant for the cuprophan group as a whole) and in addition a full manuscript detailing the 76 patients which clearly included all the *Lancet* patients although the *Lancet* reference is not given [9,10]. How could his institutional review board have allowed him to continue with this study when he had already stated publicly that it was unethical to do so? and why did he not refer to these data in his reply to the letters attacking him on small numbers and sweeping conclusions? Only Dr Schiffl can answer these questions, and to date, he has refused to do so even though he has been questioned yet again in the correspondence columns of the *Lancet* by myself [11]. This story could continue through various other publications and presentations of Schiffl in the last 2 years where serial additions and subtractions to the data would shock opponents of redundant or serial publications [12], but I prefer to close this anecdote with the news that after much prodding by me, the previous Editor of the *Lancet*, was finally persuaded to start an investigation of Schiffl’s data which required him and all other authors to sign the letter of reply. In this, Schiffl admitted in writing to the *Lancet* that he had performed a meta-analysis of two studies and portrayed it as a single randomized prospective study, but that anyhow he was so convinced of his results that this

<table>
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<th>Protein excretion (g/day)</th>
<th>Creatinine clearance (ml/min)</th>
<th>Mean arterial pressure (mmHg)</th>
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<tr>
<td><em>Baseline</em> ACE inhibitors</td>
<td>4.7±2.1</td>
<td>62±26</td>
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<tr>
<td>ACE inhibitors + Losartan</td>
<td>3.3±2.5 ($P=0.013$)</td>
<td>61±25</td>
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<tr>
<td><em>Post-control</em> ACE inhibitors (n=9)</td>
<td>3.8±2.8</td>
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Data are mean ± SD.
minor misdemeanour really did not alter his conclusions that cuprophan should not be used in the treatment of acute renal failure. Subsequently, the new Editor of the *Lancet* allowed me to write a letter which pointed out the various discrepancies that have been published and presented, exposing myself to a blistering attack from Schiffl whilst he still refused to admit his error in public [13].

At last, I decided, perhaps tardily to seek the opinion of a relative of Gaus. I sent the written admission of Schiffl to the *Lancet* to Professor Wilhelm Gaus of the University of Ulm, Germany, a well known biometrician, who has permitted me to quote his opinion on the subject. He says ‘Offering a meta-analysis as a study with one’s own data is not only trickery and incorrect, but also cheating. This is not only a biometrical view. Every sound researcher and clinician will understand that partially offering old and published data as a new study is unacceptable’ [personal communication].

Nevertheless, one must agree with Mills [4] that the results of Procrustean data torturing are more believable and more destructive as they start with a popular hypothesis and are viewed as definitive proof of the hypothesis.

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