

Letters and Replies

A man from Surinam ...

Sir,

We have several problems with the *Nephroquiz for the Beginner*, (*Nephrol Dial Transplant* 1998; 13: 209–210) submitted by ter Wee and Gans.

1. The clues for the beginners are few. The examination does not include a test for orthostatic hypotension (sitting the patient up) to test for tachycardia or a decrease in diastolic blood pressure.
2. Furthermore, the given blood gas values: pH 7.50 pCO₂ 18 mmHg, HCO₃⁻ 20.5 are suspect. Every beginner should tackle acid–base disorders by first ‘checking the numbers’ as follows: $H = 24 \times pCO_2 / HCO_3^-$, which according to our arithmetic yields: $24 \times 18 / 20.5$ or 21.07. This value corresponds to a pH of 7.66, not 7.50. This observation is most puzzling, since the HCO₃⁻ is calculated by the microprocessor of the blood gas analyzer.
3. More importantly, the authors do not provide the beginners with the pivotal lesson of acid–base balance problems, namely considering the anions in the relationship [1]. No chloride concentration is given and thus, no anion gap can be calculated. This handicap makes speculations regarding primary disturbance and secondary responses extremely difficult. Let us assume that the pH value and the pCO₂ are correct. In that case, the HCO₃⁻ was actually 14 mmol/l. This finding would indicate the presence of a severe mixed disturbance, respiratory alkalosis and metabolic acidosis. Since we can not calculate the anion gap from the information given, we can not separate ‘gain of acid’ from ‘loss of bicarbonate’ problems. This maneuver is vitally important in this chronic drug abuser who may have ingested aspirin or sniffed glue. On the other hand, if the HCO₃⁻ value is correct, then the real pCO₂ must have been 25 mmHg. This value would be consistent with a respiratory alkalosis that is incompletely compensated, perhaps because insufficient time had passed. The reduced renal function provides a mechanism for metabolic acidosis; however, laboratory support for such a diagnosis under these circumstances is absent.
4. The authors measured osmolarity in urine (very reasonable), but failed to measure UNa, UK, UCl, or Urea. Thus, they miss out on the opportunity to calculate urine net charge or urine osmolar gap. This deficit forces them to speculate on whether the patient can adequately secrete H⁺ ions. They could have demonstrated this ability instead. Incidentally, what was the urine pH?
5. Sick cell trait can explain the haematuria, but according to the reference cited by the authors [2], can not explain metabolic acidosis. In that study, Oster *et al.* [2] examined nine adults with sickle cell trait and nine control subjects. The sickle cell trait patients indeed could not concentrate their urine properly, but exhibited normal acidification.

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A man from Surinam ... (Hyperventilation after drug abuse: how are the observed acid–base and electrolyte abnormalities interpreted?)

Sir,

We have read the article entitled ‘A man from Surinam ...’ which recently appeared in *Nephrology Dialysis Transplantation* as a nephroquiz for the beginner [1].

In the answers the authors make some points on which we would like to comment.

It is stated that during a hyperventilation attack serum HCO₃⁻ concentration would have been expected to be unchanged. However, in cases of acute respiratory alkalosis H⁺ ions derived from the protein, phosphate and hemoglobin cellular buffers, and from the alkalemia-induced increase in cellular lactic acid production move rapidly into the extracellular fluid, where they combine with HCO₃⁻ causing an appropriate fall in the serum HCO₃⁻ concentration [2]. It has been calculated that for each 10 mmHg decrease in the pCO₂, serum HCO₃⁻ concentration can decrease by 2 mmol/l [3]. This means that the presented HCO₃⁻ concentration of 20.5 mmol/l is compatible with an acute respiratory alkalosis. Taking into account the patient’s history, the patient is likely to exhibit a triple acid–base disorder; i.e. an acute respiratory alkalosis with an appropriate decrease in serum HCO₃⁻ concentration, a mild degree of vomiting-induced metabolic alkalosis, which could have been disclosed by the determination of serum Cl⁻ levels as well as by the serum Na⁺/Cl⁻ ratio [4], and a high anion gap metabolic acidosis mainly due to prerenal azotaemia. The high anion gap metabolic acidosis could have been detected by calculating the serum anion gap.

As far as hypokalaemia is concerned, the authors claim that it is due to hypovolemia-induced secondary aldosteronism resulting in enhanced kaliuria. However, in such cases despite stimulation of the renin–aldosterone axis, significant changes in serum K⁺ concentrations are rare. This is because hypovolaemia is associated with both a low glomerular filtration rate and enhanced proximal Na⁺ and H₂O reabsorption leading to a marked decrease in distal fluid delivery, thereby diminishing K⁺ secretion [5,6]. Additionally, it should be mentioned that metabolic alkalosis, which has been implicated as a cause of hypokalaemia, can increase K⁺ excretion only when there is a significant elevation in serum HCO₃⁻ concentration, so that the excess filtered HCO₃⁻ exceeds the reabsorptive capacity resulting in an enhanced delivery of NaHCO₃ and H₂O to the distal nephron. In this setting, the ensuing reabsorption of some of this Na⁺ in the cortical collecting tubules is accompanied by an increased K⁺ excretion, since HCO₃⁻ acts as a non-reabsorbable anion [7]. In this case, however, serum HCO₃⁻ concentration was not increased. Hypokalaemia could have been the result of respiratory alkalosis. Although acute respiratory alkalosis is initially accompanied by an increase in serum K⁺ levels due to hyperventilation-induced enhance-

ment of alpha-adrenergic activity mediated by a fall in serum HCO_3^- concentration, this increase is followed by a fall in serum K^+ levels primarily due to changes in serum acid–base composition and modulated by adrenergic activity [8]. Thus, it would be of value to estimate the urine K^+ excretion indices (such as FEK^+ or TTKG) to better delineate the underlying pathogenetic mechanisms of hypokalaemia.

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Reply

Sir,

As pointed out by Luft *et al.*, this patient should have been tested for the existence of orthostatic hypotension, as we have mentioned in the answer to our case.

We agree with Luft *et al.* and Elisaf and Siamopoulos that determination of the anion gap is critical for evaluation of acid–base balance problems. As such we should have mentioned in the answer to our case that the anion gap should have been determined. This patient, however, was treated in the emergency room for dehydration. As the attending emergency-room physician inappropriately considered the acid–base disorder to be based on a 'simple' hyperventilation attack, no additional laboratory data were ordered. Thus, neither serum chloride concentration nor urinary sodium, potassium, chloride or pH were measured. Therefore, we could only speculate on the underlying cause of the acid–base disorder in this patient. Initially, hyperventilation does not result in a fall in bicarbonate. If the hyperventilation continues for several minutes, H^+ ions start to move from the intracellular into the extracellular fluids where they will bind to bicarbonate resulting in a fall in serum bicarbonate levels as pointed out by Elisaf and Siamopoulos. As stated in our case, we also concluded that hyperventilation had contributed to the acid–base disorder of this patient, but we felt that the serum bicarbonate level of 20.5 mmol/l could not be explained by hyperventilation alone. Especially, as the pre-existing nausea and vomiting would have induced a loss of HCl resulting in a metabolic alkalosis. The acid–base problem is further complicated by the renal failure of this patient, which would result in metabolic acidosis. Thus, with the lack

of additional laboratory data this patient's acid–base disorder can only be speculated upon.

In patients with sickle-cell disease and nephropathy, an incomplete form of type 1 renal tubular acidosis can be present [1,2] as stated in our case. Indeed, Goossens *et al.* [1] and Oster *et al.* [2] were unable to demonstrate such a defect in patients with sickle-cell trait, as pointed out by Luft *et al.* Whereas patients with sickle-cell disease had a pronounced loss of their concentrating capability, in the study by Goossens *et al.*, maximal urinary osmolality of the sickle-cell trait patients ($n=6$) was still 757 mosmol/kg H_2O (range 583–1051 mosmol/kg H_2O) and in the study by Oster *et al.* 593 ± 35 mosmol/kg H_2O . This might indicate that in several of the investigated sickle-cell trait patients the concentrating capability was not yet impaired, which might have prevented the demonstration of renal tubular acidosis in these patients.

In our patient the hypokalaemia was most likely caused by the initial vomiting. The resulting metabolic alkalosis and dehydration could result through several mechanisms in hypokalaemia. As pointed out by Elisaf and Siamopoulos, dehydration does not usually result in severe hypokalaemia as the increased action of aldosterone, induced by activation of the renin–angiotensin system, is offset by the decrease in glomerular filtration rate, which reduces distal tubular flow. However, in sickle-cell disease, sickling of red blood cells interferes with the counter-current mechanism resulting in an impaired concentrating capability early in the disease. Goossens *et al.* [1] were able to demonstrate that dehydration in a patient with sickle-cell disease and nephropathy was associated with an inappropriately high urinary sodium loss. These authors concluded, therefore, that the sickle-cell kidney was a sodium-losing nephropathy despite the existence of increased proximal tubular function for sodium conservation. In patients with sickle-cell trait the loss of concentrating capacity occurs at a later time. Although we have not been able to find studies in which sodium wasting has been investigated in patients with sickle-cell trait, it is feasible that this also exists in these patients. Thus, hypokalaemia may occur easier in dehydrated sickle-cell trait patients as inappropriately high delivery of sodium to the distal tubule may exist owing to the impaired counter-current mechanism.

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Contrast-associated nephropathy—old clinical problem and new therapeutic perspectives

Sir,

I have read with great interest Kolonko's article [1] on contrast-media nephrotoxicity. I agree with most of its content but would like to make several comments.

Among the risk factors mentioned, several, including proteinuria, hyperuricaemia, hypertension, and advanced age, are not yet considered as being independent [2].

There is no clear evidence that tubular obstruction should be still considered as one mechanism of contrast-media nephrotoxicity. Indeed contrast medium increases urate

excretion in the initial hours following exposure [3]. In the presence of dehydration, such an increase could contribute to urate precipitation and intratubular obstruction. This mechanism was probably more relevant in the past when hydropenic conditions were often used to enhance the radiographic quality of urographic studies. Accordingly patients with multiple myeloma have a very low risk of contrast-media nephrotoxicity provided their hydration status is carefully monitored [4].

More importantly, the choice of one of the low osmolar contrast media radiocontrast agents available is, I agree, essential in high-risk patients, in whom low osmolar contrast agents should be used. In this regard I wish to point out that Ioxaglate is not a high- but a low-ionic contrast medium. Therefore, this contrast medium the safety of which has been assessed in transplanted [5] and other subjects with renal insufficiency [6] should clearly also be considered in high-risk patients.

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Reply

Sir,

In our article recently published in NDT [1] we summarized the basic knowledge on the pathogenesis, risk factors, and clinical picture of contrast-associated nephropathy (CAN) and some prophylactic procedures in order to avoid this complication in patients undergoing radiological examinations. Therefore we listed both proven independent risk factors of this condition and some other factors, which might increase the incidence of CAN, as for example hypertension, advanced age, proteinuria etc. Considering the need for radiological procedure with radiocontrast in such patients, one should analyse every known and even minor risk factor to properly evaluate a total cumulative risk of developing CAN. It is important to remember, that the total risk of CAN rises as the number of risk factors increases [2].

Taking into account Dr Deray's comment about tubular obstruction, numerous review articles exist considering a possible mechanism of massive intratubular cast forming after contrast material administration. The pathomechanism of this process may be explained by the precipitation of radiocontrast molecules, together with Tamm–Horsfall protein and other pathological proteins, especially in the presence of nephrotic-range proteinuria [3,4]. Other possible constituents of these tubular casts are tubular epithelial cells damaged and desquamated due to ischaemia, direct radiocontrast toxicity, and disturbed function of integrins [3,5]. Moreover,

the Tamm–Horsfall protein presents the amino-acid sequence called RGD (Arg-Gly-Asp), which seems to be recognizable by several integrins [6]. Massive tubular casts formation can increase the intratubular pressure and urine back-leak into the interstitial tissue, worsening its oedema, ischaemia, and further mechanical damage.

In our article, Ioxaglate was listed as a high-osmolar contrast medium [1]. The range of osmolality of presently used contrast media is quite broad (between 290 mOsm/kg H₂O for Iohexol 140 and 1090 mOsm/kg H₂O for Uropolinum 60%). According to the physiological range of plasma osmolality, which is 285–295 mOsm/kg H₂O, osmolality of Ioxaglate (580 mOsm/kg H₂O) seems to be high, and for sure is not physiological. Therefore it is only arbitrary and depends upon the view of different authors to call Ioxaglate low- or high-osmolar radiocontrast material. From the clinical point of view, it is most important to provide evidence that the given radiocontrast substance exerts or does not exert some toxic effect. Dr Deray provides such evidence for Ioxaglate based only on results obtained in very small numbers of patients (21 patients in paper [7] and 8 in paper [8] respectively).

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Daily variations of protein intake in haemodialysed patients

Sir,

We read with extreme interest the article by Movilli *et al.* [1] on the independent role of metabolic acidosis on nutritional status in chronic haemodialysed patients. It was pointed out that, in the presence of moderate to severe metabolic acidosis, nPCR does not reflect the real dietary protein intake, probably as a result of increased catabolism of endogenous proteins.

We would like to emphasize that the real protein intake in chronic haemodialysed patients may be influenced by many conditions, such as clinical, social, economics and pharmacology factors [2]. Moreover, also acute daily variations in

Table 1. Urea generation (NG), protein catabolic rate (nPCR), weight gain (Δ BW), serum urea nitrogen (SUN), bicarbonates (HCO_3^-) and creatinine (sCrea) in the 3 days after HD

	Day 1	Day 2	Day 3	P
NG (g/day)	8.79 \pm 3.07	8.31 \pm 3.57	5.80 \pm 2.89	0.024
nPCR (g/BW/day)	1.24 \pm 0.37	1.18 \pm 0.37	1.04 \pm 0.30	0.050
Δ BW (kg)	1.51 \pm 0.67	1.05 \pm 0.55	0.99 \pm 0.69	0.047
SUN (mg/dl)	52.7 \pm 12.7	73.8 \pm 19	87.9 \pm 21.8	0.000
HCO_3^- (mEq/l)	25.7 \pm 2.6	23.2 \pm 2.4	21.1 \pm 2.7	0.001
sCrea (mg/dl)	7.24 \pm 1.51	9.19 \pm 1.99	10.5 \pm 2.27	0.000

ANOVA for repeated measures.

Table 2. Univariate correlation among urea generation (NG) and protein catabolic rate (nPCR), body-weight (BW), weight gain (Δ BW), serum urea nitrogen (SUN), bicarbonates changes (HCO_3^-) and creatinine (sCrea)

	R	P
nPCR	0.838	0.000
BW	0.233	NS
Δ BW	0.376	0.01
SUN	0.283	NS
HCO_3^-	-0.021	NS
ΔHCO_3^-	0.101	NS
sCrea	0.103	NS

protein intake may occur; therefore, making critical also the timing of nPCR evaluation as a measure of protein intake. With the aim of adding further information on this issue, we studied 18 anuric patients (10 M, 8 F, mean age 57 \pm 12 years) on chronic haemodialysis from 84 \pm 18 months. Two hours after the last haemodialysis of the week, a blood sample was drawn. Thereafter each patient was daily monitored for three consecutive non-dialytic days: body-weight (BW), serum urea nitrogen (SUN), serum bicarbonates (HCO_3^-), serum creatinine (sCrea) were measured and urea generation (NG) and nPCR were calculated.

As reported in Table 1, urea generation and nPCR progressively and significantly decreased in the 3 days after haemodialysis. Interestingly, the reduction of urea generation was coupled with a similar significant decline in the extent of daily body-weight increment. Overall, these findings suggest a progressive reduction of whole nutrient intake, protein intake and, consequently, urea generation during the time between two haemodialyses. As a further support, urea generation did correlate with interdialytic weight gain (Table 2). As predictable, also serum levels of bicarbonate decreased after haemodialysis, reaching 21.1 \pm 2.7 mEq/l,

that is, a condition of mild acidosis, on the third non-dialytic day. To note, serum bicarbonate levels detected during interdialytic time did not correlate with urea generation or nPCR, thus excluding the influence of metabolic acidosis of mild degree on acute changes of both urea generation and nPCR.

In conclusion, these data suggest that in the interdialytic period, chronic uraemic patients do experience a progressive day-to-day reduction of whole nutrient and protein intake. nPCR seems not to be influenced by mild metabolic acidosis, thereby accounting only for the real protein intake. Thus, protein intake in chronically haemodialysed patients is characterized by a wide interday variability, and the timing of nPCR measurement in such patients may be a confounding factor when assessing protein intake.

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1. Movilli E, Bossini N, Viola F *et al.* Evidence for an independent role of metabolic acidosis on nutritional status in haemodialysis patients. *Nephrol Dial Transplant* 1998; 13: 674-678
2. Di Iorio B, Terracciano V, Gaudiano G, Altieri C. Factors affecting nPCR in hemodialyzed patients. *Int J Artif Organs* 1995; 18: 131-140

Reply

I agree with the observation made by Dr Di Iorio of a wide variation in day-to-day dietary protein intake in HD patients. However, the conclusion drawn by the Author that PCRn is not influenced by metabolic acidosis is not supported by his data. In fact, the data presented here show that there is a progressive downward trend in urea generation rate, and consequently in PCRn, in the 3 days after dialysis treatment. There is also a decrease in body-weight gain in the 3 days after dialysis.

What can be concluded is that HD patients voluntarily adapt their protein intake to meet with dialysis restrictions in terms of weight gain, particularly in the long dialysis interval. This fact probably hides the influence of metabolic acidosis on PCRn separately evaluated in the 3 days after dialysis.

These observations are not in contrast with ours and further stress the need for a great prudence in interpreting kinetically derived data.

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Letters

Bromate intoxication due to the ingestion of a dose prescribed by a homeopathist

Sir,

Bromate is used by hairdressers as neutralizers for permanent waves. Most of the acute bromate intoxication cases reported are suicides attempted by hairdressing professionals and

accidental ingestion by children. Some cases of food intoxication are also described [1]. No case of chronic bromate intoxication through medication has been reported till now. The clinical evolution is generally dominated above all by digestive signs and then by an acute renal failure and irreversible auditory disorders. Haemolytic anaemia, central nervous system disorders and reversible polyneuropathy also

show after some weeks. Deaths have also been reported. For animals, the lethal dose is between 160 and 500 mg/kg, while for man it is estimated at 240 mg/kg [1,2]. The treatment is based on the gastrointestinal decontamination, thiosulphate intravenous administration (reducer of bromate into bromide) and haemodialysis [1].

A 64-year-old female was rushed to hospital due to the alteration of her general condition, confusion and equilibrium disorders evolving over 8 days. Her past history included depression for over 20 years, cholecystectomy 6 years previously, neurological accident 14 months previously, non-documented and labelled vascular accident, 11 day-hospitalization due to loss of equilibrium, pain in lower limbs, lack of appetite, epigastric pains, and loss of weight 11 months previously, which would indicate a functional origin. She was exclusively treated with homeopathic drugs prescribed and sold in Germany. The clinical examination showed a well-hydrated, calm, but confused patient. Her speech was incoherent and rambling. Weight 55.600 kg, height 149 cm, BP 150/90 mmHg, HR 68/min, T° 35.9°C. The general, neurological, cardiac, vascular, pulmonary and abdominal examination was quite normal. The urgent biology examination showed a normal haemogram, fibrinogen 4.28 g/l, Na 152, K 4.4, Cl 100 and bicarbonate 23.2 mmol/l, normal renal function, the thyroid function was also normal and there was no inflammatory syndrome. The patient was hospitalized with the diagnostic of melancholic depression and a possibility of hysteric conversion and she was perfused with citalopram 40 mg/d. On days 3 and 4, she developed a progressive coma without lateralization. She was given antibiotics (amoxy-clav 3 × 2 g/d) and mucolytics (acetylcystein 3 × 300 mg/d) due to a right basal pneumopathy. On day 5, the patient was better. The biology examination showed a better PaCO₂ at 43 mmHg, a frank inflammatory syndrome, Na 140, K 3.6, Cl 168, HCO₃ 26.5 mmol/l. The anion gap was calculated at -50.9. On each following day, hyperchloraemia was found, and confirmed (ion selective electrical method and dry chemistry). Chlorurorachia was also high at 158 mmol/l (norm: 115-132). On day 8, we found among her homeopathic medications a 250 cc bottle containing, among other things, 30 g of Na bromate/100 cc and 1.5 g of K bromate/100 cc. The patient received two 4-h haemodialysis sessions due to bromate intoxication and left hospital without any sequel on day 15. The bromaeemia results (day 6) came in later: 9.5 mmol/l.

A diagnosis of bromate intoxication usually poses no problem in cases of attempted suicides or accidental absorption by children. This is not the same when bromate is consumed without the patient or the patient's family knowing it, as in this case. Moreover, probably due to the chronic background of the intoxication (45 g bromate over 2 months) neurological symptomatology was predominant, and there was neither acute renal failure nor auditory disorder. Finally, homeopathic medications are not considered as drugs by the patients and usually neglected by medical anamnesis as their innocuous reputation has been established. Here, the diagnosis was suggested by the hyperchloraemia and the hyperchlorurorachy, associated with a negative anionic gap. Bromate, which is impossible to dose in clinical routine is slowly reduced into bromide in the plasma and there is a positive interference between chloride and bromide for the chloraemia determination methods (at least ISE and dry chemistry), with a selective response of bromide against chloride of 15.03/1 [3]. Direct dosage of bromide is possible, but the result is not quickly known. Moreover in bromate intoxication, this dosage represents only the quantity of the reduced product and is thus not correlated with poisoning [1].

In this case, the hyperchloraemia appeared suddenly on day 5. It was probably due to the reducing effect of acetylcystein which was administered from day 4 to day 8 at the dose of 900 mg/d. *In vitro* and *in vivo* tests on animals showed that this product potentially resulted in the reduction of bromate into bromide and that is why it was proposed for the treatment of bromate intoxication, as bromide is far less toxic [4]. The use of sulfhydryl-carrying molecules had never been reported in humans before [1]: in this case, the acetylcystein unmasked the bromate intoxication, favoured the reduction into bromide and helped improve the patient's clinical condition.

The product under discussion is a syrup sold in 250 ml flask, called 'Nerventonikum' by Hanauer Apotheke Zopff & Reuther. Its composition is printed on the label: Extr. Faecis spiss. 0.2 g; Extr. Taraxaci aquos. Spiss (Droge: Extr. = 2.2:1) 0.5 g; Extr. Valerianae aquos. Spiss (Radix: Extr. = 3:1) 0.5 g; Kalium bromatum 1.5 g; Natrium phosphoric. 9 g; Natrium bromatum 30 g; Corrigentia et aqua ad 100 ml. This product is thus sold freely, the instructions for use being 3 × 5 ml/d for 'nervous disorders, sleeping troubles, depression, agitation, anxiety'.

It is likely, although not sure, that the previous hospitalization of the patient (for loss of equilibrium and of weight, pain in the lower limbs, etc.) is of the same toxic origin, as she has been taking this product for several years. One may question whether such a patent medicine, without any proven therapeutic use and containing enough bromate to kill four 80 kg adults should remain at the disposal of people, without any prescription. Other cases of chronic or acute intoxication of this type should be expected. In cases of confusion and obtundation without any obvious cause, it may be interesting to consider bromate, to look for homeopathic medicine absorption and to dose chloride repetitively, if possible after administration of acetylcystein.

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Crossover comparison of intravenous and subcutaneous recombinant human erythropoietin in a small haemodialysis unit

Sir,

Parenteral administration of human erythropoietin (rHuEpo) is now a standard of care in the management of ESRD patients with anaemia. A target haematocrit between 32% and 38% is associated with improvements in cardiovascular

performance and overall quality of life [1]. There is increasing interest in maximizing the effectiveness of rHuEpo in the treatment of anaemia in haemodialysis patients. Numerous factors affect rHuEpo responsiveness in haemodialysis patients [2]. One factor recently under increased scrutiny is the route of administration. Subcutaneous rHuEpo administration has a longer half-life than intravenous administration, and several studies have suggested that lower doses may be used successfully to maintain haematocrits in some dialysis populations [3,4]. Prompted by these studies, we performed a crossover comparison of the two routes of administration in a stable haemodialysis unit population.

Subjects were 56 ± 4 years of age and had received haemodialysis for an average of 7.2 ± 2.4 years. Causes of end-stage renal failure included diabetic nephropathy (5), hypertensive nephrosclerosis (2), membranous nephropathy (1), and unknown aetiology (2). All patients were African-American males. Data were obtained monthly for 3 months prior to starting subcutaneous rHuEpo and for the 3 consecutive months after 6 months of use of subcutaneous rHuEpo. The initial dose of subcutaneous rHuEpo was two-thirds of the dose of intravenous rHuEpo, and subsequent adjustment of dosing followed a standard paradigm. rHuEpo was given three times per week regardless of the route of administration. Target haematocrit was 34%. Data were analysed using Student's *t* test: paired two-sample for means, with significance set at $P < 0.05$. Initial and final parameters on each of the 10 patients in the study are listed (Table 1). Following our protocol, which was dictated by the haematocrit, dosing of subcutaneous rHuEpo progressively increased such that, by the conclusion of the study, total weekly dosing did not differ from that administered previously by the intravenous route.

Parker *et al.* [4] reported administration of one-third the weekly rHuEpo intravenous dose given subcutaneously over a 10-month period without a significant reduction in haematocrits. In that study, 179 patients on haemodialysis were screened according to their selection criteria. From this group, only 24.6% were entered into their trial and only 15% completed the protocol. In our small dialysis unit trial, fourteen of our patients had been on haemodialysis for at least 6 months. The only other selection criterion in our study were that the patients agreed to the switch to subcutaneous rHuEpo of which 71.4% did. We suggest that the cost savings of universal switching of an entire haemodialysis unit patient population to subcutaneous rHuEpo may not be appreciated.

In conclusion, subcutaneous rHuEpo administration was confirmed to be a safe and effective method for maintaining the haematocrit in stable, chronic haemodialysis patients. However, no reduction in total weekly rHuEpo administration was seen during our trial. Additional research is needed to determine factors controlling optimal response to exogenous rHuEpo in the haemodialysis population.

Table 1. Initial and final parameters of the patients during the study period

	Initial	Final	<i>P</i>
Hct, %	33 ± 1	31 ± 1	0.0930
Iron saturation, %	25.6 ± 2.1	20.0 ± 1.5	0.0135
Ferritin, ng/ml	134 ± 16	264 ± 68	0.1124
Albumin, g/dl	3.7 ± 0.1	3.9 ± 0.1	0.0384
PTH, pg/ml	403 ± 123	477 ± 135	0.4718
Urea reduction ratio	0.59 ± 0.03	0.62 ± 0.03	0.3652
rHuEpo dose, u/week	10223 ± 2097	9733 ± 2132	0.7924

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Tacrolimus and gingival hyperplasia

Sir,

Gingival hyperplasia is a known complication of cyclosporin therapy. Tacrolimus is a macrolide immunosuppressive agent. Its mechanism of action is similar to that of cyclosporin. It has been stated that it does not produce gingival hyperplasia [1,2].

We observed gingival hyperplasia in one of the four renal transplant patients of our centre who are on treatment with tacrolimus. She is a 43-year-old woman, transplanted 10 months previously, treated with 6 mg of tacrolimus (0.08 mg/kg body weight/day) and 4 mg of methylprednisolone per day. Blood levels of tacrolimus in the morning are 13 ng/ml (modified assay MEIA, Tacrolimus, Abbott). She is not taking any drug known to induce gingival hyperplasia, notably nifedipine. She had gingival bleeding after brushing her teeth and gingival overgrowth at the ninth month after transplantation; the latter could be ranked as degree I (mild overgrowth with blunting of marginal gingiva) according to the classification by Gomez *et al.* [3]. A single course of 500 mg/day per os for 3 consecutive days of azithromycin, an azalide antimicrobial agent, was able to stop gingival bleeding after 2 days and to reverse gingival hyperplasia after 1 week (degree 0 according to the classification by Gomez *et al.* [3]).

This clinical observation shows two points:

- (i) tacrolimus can induce gingival hyperplasia in renal transplant patients, to the best of our knowledge, this is the first report in the literature;
- (ii) azithromycin is effective in the treatment of tacrolimus-induced gingival hyperplasia.

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Interruption of the administration of cyclosporin after renal transplant: long-term results

Sir,

Cyclosporin A (CyA) was introduced in transplant programmes in the 1980s. Its greater immunosuppressive power improved the results of all transplant groups [1,2]. However, some authors advocated the post-transplant replacement of CyA by azathioprine (Aza), in order to prevent the long-term effects of nephrotoxicity.

In 1985 we tested the therapeutic change some months after the transplant with a group of patients selected as being of low immunological risk, with good short-term results [3].

In this paper we present the long-term results for the same patients.

Study design: The group was made up of 24 patients, 15 male and 9 female, who had received a kidney from a deceased donor, and whose initial immunodepressive treatment was with cyclosporin A at doses of 14 mg/kg/day, subsequently adjusted according to blood levels, and 20 mg/day of prednisone, with a subsequent reduction to 0.15 mg/kg/day. Fourteen patients presented an acute rejection crisis but responded to the corticotherapy administered, except for two who suffered a relapse, requiring the administration of antilymphocytic serum.

Nine months (6–12 months) after the transplant the administration of CyA was abruptly interrupted, immediately beginning that of Aza at doses of 2 mg/kg/day.

Results: After the change of therapy only one patient presented an acute rejection crisis 8 years later, which abated with corticotherapy. Six patients remained normotensive and ten remained hypertensive, a further seven began arterial hypertension at some time during the evolution subsequent to the change and only one normalized hypertension on suspending the administration of cyclosporin A. Twelve patients presented an increase in the aminophosphatases at some time during their evolution, eight of whom had positive viral markers (7 VHC and 1 HBsAG). In three of the patients with VHC the increase in aminophosphatases was persistent, one of them suffering from hepatic cirrhosis. Two patients presented an episode of bacterial sepsis. A renal biopsy was performed on two patients due to proteinuria and/or renal insufficiency, chronic rejection and relapse of nephropathy due to IgA being diagnosed respectively. One patient presented a moderately differentiated epidermoid carcinoma of the vocal chord and another a vesical carcinoma. Four presented renal artery stenosis.

Three patients died: one from hepatic cirrhosis, one from acute myocardial infarction and one in the postoperative period after the resection of an aortic aneurysm. A graft was lost in a patient who presented sepsis originating in the transplanted kidney which made it necessary to perform transplantectomy.

The actuarial survival of the patient and graft 10 years after the transplant was 81% and 77%, respectively.

The plasma creatininaemia and proteinuria in urine 24 h prior to the change and at 1, 5 and 10 years are shown in Table 1.

Discussion: The introduction of the CyA visibly improved the results of all the transplant groups, but its nephrotoxic nature meant that it was administered according to different criteria which endeavoured to minimize its negative side effects.

Under the hypothesis that the chronic nephrotoxicity could potentiate the chronic nephropathy of the transplant and involve a high loss of grafts in the long term, different authors interrupted their administration at some time during the post-transplant evolution of their patients in order to continue treatment with Aza, obtaining conflicting results [4].

In 1985 we tested suspending the administration of CyA months after the transplant [3], obtaining bad results in a subgroup of patients with initial therapy with Aza and steroids, who had presented severe acute rejections and who began to take CyA for this reason. Its subsequent interruption was followed by new, also severe, episodes of rejection. We therefore decided to continue the change of immunosuppressors only in the patients considered as of low immunological risk: neither hypersensitized nor retransplanted, who had received induction treatment with CyA since the beginning of the transplant and who had not presented severe acute rejection crises.

Some authors warn of the risk of therapeutic change on obtaining a shorter survival of the graft in patients in which the administration of CyA was suspended, adducing that the improvement of the renal function normally observed after the change is counteracted by a higher incidence of acute rejection crisis which brings with it the loss of the graft or else facilitates the development of chronic rejection [5–7]. For other authors this negative effect would be observed even in the patients who had not presented acute rejection subsequent to the therapeutic change [8–10].

Some [11,12] observe a similar survival of the graft and of the patient in both groups, although they achieve a better renal function in those who did not receive CyA. On the other hand, after 8 years Hollander and Cols [13] observe a better survival of graft and patient in the group treated with azathioprine, on not observing an increase in the number of acute rejection crises after the conversion in comparison with the patients who continue with CyA, although they recognize that they do not manage to predict which patients will present it after the change.

We believe that CyA is an immunodepressant with which good results are obtained in the induction and short-term maintenance of the transplant [14] but we do not know the longer-term effects of its nephrotoxicity. The nephrotoxicity produced by the CyA could culminate in the establishment

Table 1. Plasma creatininaemia and proteinuria

	Before the change	Conversion	1 year	5 years	10 years
Plasma creatinine ($\mu\text{mol/l}$)	117		112	105	125
Proteinuria (g/24 h)	0.01		0.01	0.15	0.23

of a chronic nephropathy of the transplant, adversely affecting the survival of the graft. Therefore, in our opinion, the groups of patients considered as of low immunological risk could benefit from the therapeutic change, mainly if the graft comes from a donor considered as borderline, with the aim of improving their long-term survival prospects.

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A successful pregnancy in a kidney recipient with tacrolimus (Prograf, FK 506) therapy

Sir,

About one in 50 women of childbearing age with a functioning renal transplant becomes pregnant [1]. Pregnancies after liver, pancreas, and kidney transplantations have been reported in patients with tacrolimus treatment [2–4]. Starzls group has the greatest experience and reported 27 pregnancies in 21 liver recipients [2].

We here report a successful outcome of a kidney recipient giving birth to a healthy child in the 33rd week of gestation, with tacrolimus and prednisolone as immunosuppressive treatment. The most remarkable thing was that the tacrol-

imus dosage had to be more than doubled during pregnancy. A slight increase of dose was described in a recent case of kidney–pancreas transplantation [4]; however, this was not found among the liver recipients [2]. The reason for this is discussed.

A 36-year-old woman with chronic pyelonephritis was referred to the Department of Renal Medicine in 1983 because of renal insufficiency. She became pregnant in 1989 and kidney function deteriorated during pregnancy. Due to pre-eclampsia and worsened kidney function, a caesarean delivery was performed in the 32nd week and a healthy girl was born. In 1993 the patient underwent kidney transplantation with a kidney from her mother. Immunosuppressive treatment was cyclosporin and prednisolone. No acute rejections occurred. The patient was switched to cyclosporin Neoral in 1995. Despite lowering the dosage of Neoral, the s-creatinine remained at a higher level, around 180–190 $\mu\text{mol/l}$, compared with before the change. A transplant biopsy performed in 1996 showed cyclosporin toxicity. The cyclosporin was changed to tacrolimus. The prednisolone dosage was unchanged at 10 mg daily. After a couple of months the daily dosage of tacrolimus 4.5 mg (0.07 mg/kg) gave a satisfactory s-creatinine around 160 $\mu\text{mol/l}$ and a trough level of tacrolimus around 6 ng/ml.

In August 1997 the patient informed us that she was pregnant. The dosage of tacrolimus had to be more than doubled during the pregnancy because of lowering trough levels from the 12th week of gestation (Figure 1). The serum creatinine showed good kidney function with serum creatinine around 130–140 $\mu\text{mol/l}$. After increasing the dosages of tacrolimus to 12 mg daily the trough levels stabilized around 6 ng/ml during the remaining period of the pregnancy. The blood pressure was normal throughout pregnancy with a low dosage of nifedipine. In the 30th week of gestation the serum urate and s-creatinine increased. In addition, proteinuria increased from 0.3 g/day to 0.6 g/day and slight ankle oedema was observed. In the 32nd week the s-creatinine was 180 $\mu\text{mol/l}$ and the s-uric acid 509 mmol/l. A decision was made to deliver the patient by caesarean section in the 33rd week. A normal girl was born weighing 2200 g. The weight was adequate for gestational age. The level of tacrolimus in cord blood was 5.6 ng/ml. The serum creatinine of the patient returned to 140 $\mu\text{mol/l}$ immediately after delivery.

During the following weeks the tacrolimus dose had to be reduced because of increasing trough levels. The blood pressure increased slightly but was normalized with increasing dosages of nifedipine. The s-creatinine levelled off at 158 $\mu\text{mol/l}$ and the original tacrolimus dose of 4.5 mg daily was given. The baby showed good progress and could be discharged after 16 days at hospital.

This case showed that the tacrolimus dosages had to be more than doubled during pregnancy. This was not necessary in the liver recipients reported [2]. One could speculate about enhanced drug elimination during pregnancy by the fetus, since the drug passes the placenta. Also there might be an increased metabolizing capacity of the maternal liver in the kidney recipients not observed in the liver recipients. In fact it has been demonstrated that the activity of the drug metabolizing enzyme cytochrome P450 increases during pregnancy [5]. However, this may not occur in transplanted livers.

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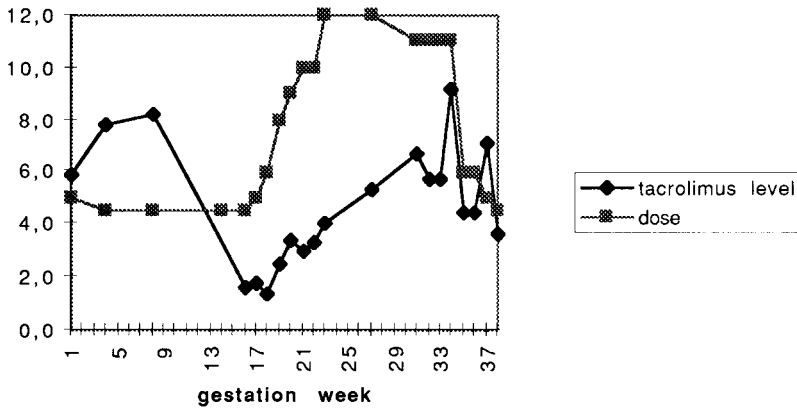


Fig. 1. Trough levels of tacrolimus (ng/ml) and daily dose (mg) of tacrolimus during pregnancy and after delivery in a transplant kidney recipient.

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