Sir,

We thank Di Iorio et al. [1] for their interest in our paper. The findings of their study provide another piece of evidence to support the notion that l-carnitine (LC) treatment may improve the anaemic status of haemodialysis patients irrespective of EPO sensitivity. A more in-depth discussion of the potential mode of action of LC on uraemic anaemia may thus be worthwhile.

Uraemic red blood cells (RBCs) must survive a variety of chemical and physical insults (i.e. oxidative stress, haemodialysis (HD) sessions), which severely affect the biophysical properties of RBC membrane and, hence, contribute to a significant reduction of RBC life span [2]. LC has been shown to favourably affect key biophysical properties of normal erythrocytes [3]. In keeping with these actions, LC might improve renal anaemia by alleviating the deteriorated rheological properties of uraemic RBCs [4]. In addition to the biophysical intervention, LC is able to exert a favourable metabolic action in a cellular environment deprived of any sub-cellular organelle. LC is known for its role in facilitating the transport of long-chain fatty acids across the mitochondrial membrane. However, LC also plays a pivotal role in the membrane phospholipid fatty acid turnover [3], a metabolic pathway involved in the repair process of oxidatively injured membrane phospholipids. A large body of evidence indicates that uraemic RBCs are continuously exposed to oxidative stress, which may oxidatively damage their lipid and protein components [2]. Since oxidized phospholipids may severely impair membrane properties, repairing them could improve membrane integrity and potentially reduce haemolysis. Thus, despite the lack of mitochondria, evidence for a role of LC in red cell metabolism is suggested by the presence of LC and carnitine palmitoyl-transferase (CPT) in the RBC, and their involvement in membrane phospholipid fatty acid turnover.

If the above discussion argues that an important LC target is the mature, circulating RBC (peripheral action), one may not exclude the fact that the ameliorative action of LC on uraemic anaemia may be present at the level of erythropoiesis (central action). Recent evidence seem to support the latter hypothesis. Matsumura et al. [6] demonstrated that the addition of high amounts of LC (>200 μM) to erythroid colonies in cell cultures from fetal mouse liver, a major location of erythropoiesis during the embryonic period, resulted in a significant increase of such erythroid colonies. Some reports have also indicated that the elevation in inflammatory cytokines and oxidative parameters correlated with rhEPO resistance, and that LC treatment improved these impairments [7].

In an attempt to gain more definitive information on the potential action of LC on erythropoiesis, Kitamura et al. [8] investigated the erythropoietic effect of LC using cells from mouse bone marrow, where erythropoiesis takes place only after birth. The authors have clearly shown that in the presence of 0.5 or 1.0 IU/ml of rhEPO, LC at concentrations...
>200 μM significantly enhanced CFU-E colony formation in mouse bone marrow cell cultures.

Although these observations are still preliminary, some conjecture may be offered regarding the potential effect of LC on differentiation during RBC maturation. Programmed cell death is known to occur during the differentiation of progenitor cells. Erythropoietin contributes to RBC maturation by retarding apoptosis, thus allowing erythroid progenitors to complete their differentiation programmes. Indeed, a major negative regulation of erythropoiesis is the caspase-mediated cleavage of GATA-1 or other erythropoietic factors [9]. Mutomba et al. [10] reported that LC at millimolar levels inhibits the activation of caspses at various point in the Fas ligation pathway in Jurkat cells. Collectively, these reports suggest that LC influences erythropoiesis, possibly by inhibiting the apoptosis of progenitor cells.

A better understanding of the mechanisms involved in LC-mediated effect on uraemic anaemia, peripheral and/or central action, will help to clarify the role of LC in the treatment of renal anemia.

Conflict of interest statement: A.A. is currently the Director of the Research and Development Department of Iperboreal Pharma Srl.

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Impact of calcium and vitamin D therapy on arterial and cardiac disease in young adults with childhood-onset end stage renal disease

Sir,

In the discussion of their well-documented study on cardiovascular disease in young adults with childhood-onset of end-stage renal disease (ESRD), the Berlin paediatricians Briese et al. [1] pointed out interesting differences with a quite similar study reported 4 years ago by their colleagues of Heidelberg [2]: the prevalence of coronary calcifications (10 vs 92%) and of cardiac valve calcifications (0 vs 32%) was quite lower in the Berlin study than in the Heidelberg one, while the technique of evaluation was comparable (Table 1). This difference was all the more remarkable in that the population characteristics were quite the same regarding the proportion of transplanted patients. However, the age was slightly younger (23 vs 27 years) while on dialysis was shorter (2.9 vs 5 years) and that of transplantation longer (9.2 vs 7.8 years).

In spite of these differences, at the time of cardiovascular evaluation, the classical cardiovascular risks [body mass index (BMI), smoking, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol] were comparable (with the exception of mean blood pressure which was 11 mmHg lower), as well as the non-classic risk factors such as albumin and homocysteine, with the exception of CRP that was 11 mg/l higher in the Berlin study. Regarding the serum mineral parameters, although their evaluation in the Berlin study was only punctual and not time-integrated as in the Heidelberg one, it is remarkable to note that the Ca × PO4 product was similar while the serum parathyroid hormone (PTH) levels were twice lower in Berlin, despite the fact that the cumulative doses of both calcium oral phosphate binder (Ca-OPB) and ‘active’ vitamin D (alfacalcidol or calcitriol) were much lower (respectively by 7- and 35- folds). Since the Berlin authors did not comment on such differences between calcium and vitamin D therapy and clinical results, we would like to propose the following comments.

We have noted that in contrast to the Heidelberg group, the Berlin group mentioned the use of cholecalciferol i.e. plain vitamin D at a dose of 2.1–10^4 IU per year i.e. 5.750 IU (or 143 μg) per day i.e. a dose that would certainly secure a serum 25 OH vitamin D level well above the recommended thresholds of 30–40 ng/ml [3]. Even though the 3 year difference in age and the 2 years less time on dialysis may have contributed to the 2-fold difference in PTH suppression, we think that a causal relationship between lower PTH levels and lower prevalence of cardiovascular calcifications with cholecalciferol use cannot be excluded. Indeed, there is a rational to relate this better PTH suppression to cholecalciferol use since the Slatopolsky group [4] recently evidenced in bovine parathyroid cell cultures that at a concentration of 40 ng/ml 25 OH vitamin OH D was as efficient as calcitriol at a maximally PTH suppressive dose (40–80 ng/ml), for suppressing PTH. The reason for this efficiency is not only that the concentration of 25 OH vitamin D is about 10^3 higher, but that provided calcidiol concentration is sufficient, it can be taken up by the LR2-megalin receptor present in the parathyroid cells and presented to their mitochondrial 25 OH vitamin D-1α hydroxylase, in order to synthesize 1.25(OH)2 vitamin D [5]. This in situ synthesized calcitrocin can then suppress the

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