LETTERS TO THE EDITOR

Urea and its bioavailability in newborns

EDITOR,—Jackson suggests that colonic salvage of urea N – that is, its return to the body N pool and contributing to the effective supply of N – is an important component in the handling of urea N in the newborn.¹ Although of interest for nitrogen economy during growth, pregnancy, low protein intake or during hibernation in bears, such an hypothesis, at least in the newborn child, is not based on compelling evidence.

The estimates of urea N salvage are based on incomplete excretion in urine of the total urea synthesised in the body.² The discrepancy could result not only from the hydrolysis of urea in the gut but also from excretion of urea in the skin. A significant proportion of N released from hydrolysis of urea in the gut is also known to be recycled into urea or excreted as ammonia in the breath. In healthy adults with a normal protein intake about 20% of synthesised urea is not excreted in urine, and an insignificant amount of urea N is incorporated into protein.³

Whether such a salvage of N occurs in newborns is not known. Data on breast fed infants, both pre-term and full term, have shown that most of the urea ingested is not bioavailable – that is, it is not hydrolysed in the gut.⁴ Studies in healthy pre-term and full term newborns show that the rate of urea synthesis measured by isotopic tracers ranges between 3 mg and 6 mg N/kg/hour, which is similar to the rate of urinary urea N excretion measured in a number of balance studies.^{5,6} In contrast, Wheeler *et al* observed very high rates of urea N synthesis (about 17.3 mmol N/kg/day or 20 mg N/kg/hour) in six neonates after major abdominal surgery.⁷ However, the rate of urinary urea N excretion was similar to that reported by others. Thus the discrepancy between synthesis and excretion was astronomical (80%). Interestingly, the recycled N was only a small component of urea synthesis. Several concerns can be raised regarding the validity of measurements in their study – route of tracer administration, the catabolic state of the infant, the accuracy of urine collection, etc. All question the conclusion regarding the salvage of urea N in these infants.

Thus published data on newborn babies do not support the concept that 'urea production and salvage appear to be normal features of early infancy'. It may be important only when protein intake is marginal or only in certain animal species.

SATISH C KALHAN

Department of Pediatrics,
Case Western Reserve University School of Medicine,
Cleveland, Ohio 44106, USA

- 1 Jackson AA. Urea as a nutrient: bioavailability and role in nitrogen economy. *Arch Dis Child* 1994; 70: 3–4.
- 2 Walser M, Bodenlos LJ. Urea metabolism in man. *J Clin Invest* 1959; 38: 1617–26.
- 3 Richards P. Nutritional potential of nitrogen recycling in man. *Am J Clin Nutr* 1972; 25: 615–25.
- 4 Fomon SJ, Bier DM, Matthews DE, Rogers RR, *et al*. Bioavailability of dietary urea nitrogen in the breast-fed infant. *J Pediatr* 1988; 113: 515–7.

- 5 Kalhan SC. Rates of urea synthesis in the human newborn: Effect of maternal diabetes and small for gestational age. *Pediatr Res* 1993; 34: 801–4.
- 6 Battista MA, Price P, Kalhan S. Effect of pediatric parenteral amino acid mixture on leucine and urea kinetics in preterm infants. *Pediatr Res* 1994; 35: 307A.
- 7 Wheeler RA, Jackson AA, Griffiths DM. Urea production and recycling in neonates. *J Pediatr Surg* 1991; 26: 575–7.

Dr Jackson comments:

Dr Kalhan's comments revisit a longstanding controversy which simply underlines the need for good data in a difficult area of investigation. There are three points of importance: whether salvage of urea-nitrogen has functional importance under any circumstance; whether it is important in infancy; and the nature of the importance. We have formally addressed the methodological criticisms raised.¹ Based on an extensive series of investigations we know for adults that normally 25% of daily urea-nitrogen production is salvaged.² In infants and children the major factors which influence the rate of salvage are the overall metabolic demand, determined in part by energy intake, the absolute protein intake relative to the magnitude of the metabolic demand for protein, and the presence of a functional colonic microflora.³

The data indicate that for infancy three phases for urea kinetics can be identified: (i) shortly after birth before the microflora are properly established, little or no salvage; (ii) up to 6 weeks of age, with an established flora, salvage is very high in response to the intense metabolic demand; and (iii) after 6 to 8 weeks of age, when salvage is moderate. For each phase there are clear differences in nitrogen metabolism, as identified by other investigators. These considerations adequately explain the different results obtained by different groups. There is no good reason simply to dismiss the data of Wheeler *et al*,⁴ as we have found considerable salvage in free living infants aged 3 to 6 weeks who were breast fed. These data confirm that at least 50% of the nitrogen salvaged from urea is retained within the system. Although the nature of the retention remains an open question at this point in time, we have early evidence which traces the label into essential amino acids.

Given that growth is an important feature of infancy and that for most people the lowest protein diet they ever take is their mother's milk, the evidence in favour of the importance of urea-nitrogen salvage need not be compelling to justify full consideration of its potential importance.

- 1 Jackson AA, Picou D, Landman J. The non-invasive measurement of urea kinetics in normal man by a constant infusion of ¹⁵N¹⁵N-urea. *Hum Nutr Clin Nutr* 1984; 38C: 339–54.
- 2 Jackson AA, Danielsen MS, Boyes S. A non-invasive method for measuring urea kinetics with a single dose of [¹⁵N¹⁵N]urea in free-living humans. *J Nutr* 1993; 123: 2129–36.
- 3 Jackson AA, Wotton SA. The energy requirements for growth and catch-up growth. In: Schurch B, Scrimshaw, NS, eds. *Activity, energy expenditure and energy requirements of infants and children*. Switzerland: International Dietary Energy Consultative Group, 1990: 185–214.
- 4 Wheeler RA, Jackson AA, Griffiths DM. Urea production and recycling in neonates. *J Pediatr Surg* 1991; 26: 575–7.

Fresh frozen plasma and neonatal sepsis

EDITOR,—Acunas and colleagues conclude that fresh frozen plasma (FFP) is less effective than intravenous immunoglobulin as

adjunctive treatment for neonatal sepsis.¹ They also highlight the possible risk of viral transmission with its use.

FFP may also contain viable donor lymphocytes, exposing the recipient to potentially fatal transfusion associated graft versus host disease (TA-GvHD).² This usually occurs in those with defective cell mediated immunity. However, it may occur in the apparently immunocompetent,³ and preterm infants are also at risk.⁴ Although TA-GvHD may be prevented by irradiation of blood products,³ FFP is not routinely irradiated on most neonatal units and therefore TA-GvHD may be another potential disadvantage of the use of FFP in neonates.

DAVID BURGNER

Newborn Emergency Transport Service,
Royal Alexandra Hospital for Children,
Camperdown, Sydney, NSW 2050, Australia

- 1 Acunas BA, Fakman M, Liouss G, Davies ET, Bakoleas B, Costalos C, *et al*. Effect of fresh frozen plasma and gammaglobulin on humoral immunity in neonatal sepsis. *Arch Dis Child* 1994; 70: F182–7.
- 2 Wintergerst U, Meyer U, Remberger K, Belohradsky BH. Graft versus host reaction in an infant with DiGeorge syndrome. *Monatsschr Kinderheilkd* 1989; 137: 345–7.
- 3 Pelszynski MM, Moroff G, Luban NL, Taylor BJ, Quinones RR. Effect of gamma radiation of red cell units on T-cell inactivation as assessed by limiting dilution analysis: implications for preventing transfusion-associated graft-versus-host disease. *Blood* 1994; 83: 1683–9.
- 4 Berger RS, Dixon SL. Fulminant transfusion-associated graft-versus-host disease in a premature infant. *J Am Acad Dermatol* 1989; 20: 945–50.

EMLA and informed consent in neonates

EDITOR,—We were very interested in the account of the use of EMLA cream in 21 neonates,¹ following an earlier trial in seven babies.² There seem to be few direct reports of the safe use of EMLA in newborns, though Koren suggested that EMLA is in widespread unlicensed use in North America for circumcision of neonates, with no apparent harm.³ Use of EMLA is not recommended for babies under 1 year of age in the United Kingdom, but the use of EMLA in infants older than 1 month has recently been approved in the USA.

Neonates may be at increased risk of methaemoglobinaemia, due to their thin skin, low concentrations of methaemoglobin reductase in their blood, slow metabolism of lignocaine and prilocaine. Fetal haemoglobin is more readily oxidised to methaemoglobin than is adult haemoglobin.

We obtained ethical committee approval for a randomised, double blind trial of EMLA v placebo cream in newborn babies. Parents were warned verbally and in writing of the risks of methaemoglobinaemia and advised about our methods of ensuring safe use. Fully informed verbal and written consent was obtained. Exclusion criteria were clinically apparent anaemia, oxygen treatment, cyanotic congenital heart disease, weight of less than 1500 g or a baby taking aniline derivatives.

We restricted the dose of EMLA or placebo to 0.1 ml/kg/bodyweight applied once only to an area of skin measuring 2×1 cm for exactly one hour. Each baby was watched closely for 12 hours for signs of colour change or desaturation, if necessary using a pulse oximeter or other monitors. Blood tests for methaemoglobin, lignocaine, prilocaine and methaemoglobin reductase concentrations