

- 2 Brash AR, Hickey DE, Graham TP, Stahlman MT, Oates JA, Cotton RB. Pharmacokinetics of indomethacin in the neonate: relationship of indomethacin plasma levels to response of the ductus arteriosus. *N Engl J Med* 1981;305:67-72.
- 3 Seyberth HW, Muller H, Willie L, Pluckthun H, Wolf D, Ulmer HE. Recovery of prostaglandin production associated with reopening of the ductus arteriosus after indomethacin treatment in preterm infants with respiratory distress syndrome. *Pediatric Pharmacology* 1982;2:127-41.

### The incidence of renal calcification in preterm infants

SIR,—In the report by Short and Cooke, the 21 infants who developed renal calcification all had bronchopulmonary dysplasia.<sup>1</sup> While Short and Cooke recorded details of steroid usage the relationship between steroid use and renal calcification was not explored. Their failure to do so is indeed surprising as nephrocalcinosis may be one of the side effects of the now widespread use of steroids for bronchopulmonary dysplasia.<sup>2</sup>

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- 1 Short A, Cooke RWI. The incidence of renal calcification in preterm infants. *Arch Dis Child* 1991;66:412-7.
- 2 Kamitsuka MD, Peloquin D. Renal calcification after dexamethasone in infants with bronchopulmonary dysplasia. *Lancet* 1991;337:626.

### Drs Short and Cooke comment:

We thank Dr Blumenthal for his interest in our recent article, and note his comments regarding the use of steroid treatment. The hypercalcaemic effects of steroids have been utilised for many years in the treatment of hypercalcaemia in adult patients. We certainly considered the possible effects of such treatment in our own patients, and recorded dosage and duration of dexamethasone treatment.

The small number of patients with dexamethasone (two infants with bronchopulmonary dysplasia who developed calcification, and one who did not), however, preclude any useful comment upon the effects of such treatment in our study. In the two patients with renal calcification who received dexamethasone, renal ultrasound scans were normal before treatment, but we would be reluctant to postulate a direct causal relationship between steroid therapy and calcification. We would agree, however, that the increasing use of steroids provides an additional argument for close evaluation of the renal tract in all preterm infants at risk of renal calcification.

### Who pioneered the use of alternative donors (and stem cells from peripheral blood) in bone marrow transplantation?

SIR,—Dr Hows writes her opinion that 'The Seattle group has pioneered the use of partially matched family donor transplants . . .' and perhaps that reflects her own experience, mainly in adult transplantation.<sup>1</sup> As far as is known to us, the first successful bone marrow transplant from a father to a son was inspired by Professor J R Hobbs and undertaken on 29 August 1972 by the Westminster Bone Marrow Team for Mark Pegram who had severe combined immune deficiency; the late Dr Iain Anderson was the consultant paediatrician and the late Professor James G

Humble was the haematologist. Despite a stormy graft-versus-host disease (GVHD) in which bilirubin concentration rose to 118  $\mu\text{mol/l}$ , Mark has survived to the present day with no evidence of chronic GVHD and has enjoyed a normal healthy life and currently plays rugby. He was probably the first human to be treated after bone marrow transplantation with antilymphocyte globulin.<sup>2</sup> In 1985 the team published a series of 50 patients engrafted from genetic haplotype-sharing donors,<sup>3</sup> and these were mostly for paediatric patients with longer survivals than the 40 in the Seattle paper.<sup>4</sup>

The first intended HLA matched mixed lymphocyte culture negative transplant from a volunteer unrelated donor to produce an engrafted survivor was conceived by Professor J R Hobbs and undertaken on 13 April 1973 for Simon Bostic who had chronic granulomatous disease; Dr Kenneth Hugh-Jones was the consultant paediatrician, Dr David James was responsible for the HLA tissue typing, and (now) Professor Masaichi Yamamura perfected the mixed lymphocyte culture method<sup>5</sup>; the case was not reported in full until 1977.<sup>6</sup> Cyclophosphamide only was used for the induction to avoid total body irradiation which has more unpleasant sequelae for children, and it was thus discovered that this could only displace some 12% of the human host marrow, so that there was only engraftment of some 12% of the healthy female donor's neutrophils. Neutrophil counts, nevertheless, were  $0.7-1.5 \times 10^9/\text{l}$  and were identified by Professor Humble as they not only contained female 'clubs' but could be shown by double staining to be strongly nitroblue tetrazolium positive in contrast to the majority of the totally negative host cells. An almost identical result has since been reported.<sup>7</sup> Such a good neutrophil count kept Simon completely free of life threatening infections and off all antibiotics for some six years, by which time the chimeric state had petered out and the nitroblue tetrazolium positive cells could no longer be detected. During that period, Simon flourished and grew normally and his lymphocytes remained mixed lymphocyte culture negative against his donor when tested on seven occasions. With the final disappearance of the donor cells, Simon relapsed to his former severe illness developing liver and lung abscesses which responded to the introduction of intensive antibiotic treatment and subsequent prophylaxis, but thereafter his growth rate deteriorated and never again reached normal. He has gained adulthood with modern care but when recently tested did not show much evidence of inducibility of increased staphylococcal killing capacity by the use of interferon gamma.<sup>8</sup> His donor, Mrs Joan Macfarlane, went on to add two further children to the one she had at the time she volunteered, and, presumably as a result, she became mixed lymphocyte culture positive against Simon so was not used for a second graft.

A second boy with severe chronic granulomatous disease engrafted for three months after a transplant on 19 February 1975 from another matched volunteer unrelated donor and also derived immense benefit from the procedure to enjoy seven years of childhood before dying of cor pulmonale, and an adult similarly had correction of his severe aplastic anaemia after a transplant in November 1975. A fuller account of the introduction of volunteer unrelated donors appears in *Correction of Certain Genetic Diseases by Transplantation, 1989* a symposium report distributed by the Westminster Medical School

Research Trust, 17 Horseferry Road, London SW1P 2AR. It gives the true credit for the initiation of the first volunteer unrelated donor panel to the mother of Simon Bostic, Mrs Elisabeth Bostic, after the near miss when Professor Hobbs had proved a mixed lymphocyte culture negative matched unrelated donor from Holland for her first affected son, Andrew, who died just a few days before the graft could be undertaken in 1972. After Elisabeth's death, full credit should then be maintained for the stoic work of Mrs Shirley Nolan who took up the fund raising to enable Dr James to build it up to its world famous size. On the above evidence, surely credit for pioneering the use of alternative donors belongs to Professor John R Hobbs and the Westminster Bone Marrow Team, who still enjoy the world's best survivals from children so treated.

Incidentally, Hobbs was also responsible for the first transplant using stem cells of the peripheral blood, taken from a 4 year old donor in June 1970 to treat a boy with type I mucocutaneous candidiasis (migration inhibition factor is completely absent) a disease which has proved fatal in all our other cases who were not transplanted. The treated patient remains alive and well as the longest living survivor of a matched sibling transplant in Britain and Dr Hows might have noted that this transplant was done at the Hammersmith Hospital<sup>9</sup> before she arrived.

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- 1 Hows JM. Paediatric bone marrow transplantation using donors other than HLA genotypically identical siblings. *Arch Dis Child* 1991;66:546-50.
- 2 Hobbs JR, Humble JG, Anderson IM, James DCO, Yamamura M. The elective treatment of graft-versus-host disease following a bone marrow graft from a father to a son with severe combined immunodeficiency. *Postgrad Med J* 1976;52(suppl 5):90-4.
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- 9 Valdimarsson H, Moss PD, Holt PJJ, Hobbs JR. Treatment of chronic mucocutaneous candidiasis with leucocytes from HL-A compatible sibling. *Lancet* 1972;i:469-72.

### Dr Hows comments:

I am grateful to Drs Hughes-Jones, Selwyn, and Riches for their account of the pioneering role of Professor Jack Hobbs and other members of the Westminster Bone Marrow Transplant Team in the use of alternative marrow donors in paediatric bone marrow transplantation.

I tried to write a short 'state of the art'