LETTERS TO THE EDITOR

Randomised trial of early tapping in neonatal post haemorrhagic ventricular dilatation: results at 30 months

EDITOR,—In reporting the results of follow up from questionnaires to the clinicians involved in the care of children randomised after the official end of this multicentre trial, Johnson *et al* have highlighted an important issue.¹ Major functional loss can be identified at the age of 30 months by questionnaire, particularly when there is an unbiased comparison group. The primary question in this trial was whether early tapping carried an advantage over conservative treatment in the prevention of major functional loss detectable at the age of 2 years. What may be missed, however, are impairments which, at that age, are not perceived as major deviations from the norm. Abnormalities and asymmetries of tone may escape notice in a routine examination and become obvious only at a later stage. It is therefore not surprising that there are large differences between the proportions of children reported as being 'normal' and those having neuromotor impairment without functional loss, in children randomised before 31 January 1987 compared with those randomised after this date.

There may also be difficulties in categorising children as multiply or singly impaired without more formal testing. Silence or poor expression of language at this age is often attributed to shyness – particularly in the unfamiliar context of a short clinic visit.

However, for secondary questions concerned with the relationship between ultrasound findings and neurodevelopment at 30 months, the nature of the impairment matters. As always, the method to be used does depend on what question is being asked.

I do not share the view of Johnson *et al* that refining the questionnaire will succeed in identifying all the impairments which are unaccompanied by functional loss at 2 years, unless the respondents are prepared to undertake a more detailed and structured assessment. By 4 years, it may well be possible to devise questionnaires which focus on these problems. I would strongly support their initiatives to evaluate alternative strategies for measuring health status in children.

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1 Johnson A, Wincott E, Grant A, Elbourne D. Randomised trial of early tapping in neonatal post haemorrhagic ventricular dilatation: results at 30 months. *Arch Dis Child* 1994; 71: F147.

Dr Elbourne *et al* comment:

EDITOR,—All methods of ascertainment have advantages which need to be set against their potential problems for addressing particular questions. The advantages of a questionnaire to paediatricians asking them to provide information recorded previously in clinic records were largely pragmatic: it was cheap (trial funding had ended); did not require any special investigations; nor, in the context of a randomised controlled trial, was it likely to

lead to a biased comparison between the treatment groups. However, as we and Dr Mutch point out, the method is probably not sensitive enough to detect impairments without functional loss in 2 year old children.

One way in which the sensitivity of this approach might be improved is by prospective completion of the questionnaire by the paediatrician at the time of a routine hospital check up. This may prompt a more detailed and structured assessment. Additional questions, which cannot normally be answered retrospectively from case notes, can also be included. For instance, in the questionnaire used in the follow up of babies entered into a multicentre trial of the use of acetazolamide and frusemide in post-haemorrhagic ventricular dilatation, we added questions about limb and axial tone and reflex changes. This is completed by the paediatrician at the time of an outpatient clinic visit.

The most appropriate method for assessing groups of children will depend on the questions being addressed. In order to assess, disability at particular ages, simple questionnaires may not only be sufficiently robust, but may be the only method feasible in the context of follow up for large groups of geographically scattered children. The resulting increase in statistical power may more than offset the gains in accuracy which are made by using a more 'sensitive' test. It is these sorts of issues that we are exploring in our research assessing the advantages and disadvantages of questionnaires completed by paediatricians in clinics, health visitors, GPs and parents (and teachers for school age children).

Pro- or antioxidant activity of vitamin C in preterm infants?

EDITOR,—It is with great interest that we read the paper by Silvers *et al*¹ describing plasma ascorbic acid concentrations and plasma antioxidant activity in premature infants at birth, and potential implications for reactive oxygen species induced injury. The antioxidant activity of plasma was tested by measuring its ability to inhibit lipid peroxidation in rat brain homogenate, expressed as D_{max} (plasma volume in μ l required for maximum inhibition of auto-oxidation). In this *in vitro* system, as mentioned by the authors,¹ lipid peroxidation is iron dependent.² It is therefore not surprising that plasma with low concentrations of caeruloplasmin (which has ferroxidase activity) and high concentrations of ascorbic acid (which can reduce free iron and initiate the formation of hydroxyl radicals through Fenton chemistry) has a low D_{max} .¹

Although ascorbic acid can act as a pro-oxidant in the presence of free transition metal ions, it is a powerful antioxidant under other oxidative stress conditions.³ Ascorbic acid scavenges directly a variety of reactive oxygen species, including superoxide and hydroxyl radicals, suppresses the inactivation of antiproteases by oxidants generated by the myeloperoxidase-halide system, neutralises oxidants released from stimulated neutrophils in a dose dependent manner, and can regenerate membrane bound vitamin E.^{2,3} Ascorbic acid also has important metabolic roles – for example, in the biosynthesis of collagen, carnitine, and catecholamines.

The question, therefore, is whether *in vitro* observations such as the ones made by Silvers and colleagues¹ are relevant to the *in vivo* situation. The detection of non-transferrin bound iron in plasma of preterm and

term infants⁴ seems to support the authors' concerns regarding a potential pro-oxidant effect of ascorbic acid *in vivo*.¹ However, the various antioxidant and metabolic properties of ascorbic acid also have to be considered, and the integrated effect of high plasma ascorbic acid concentrations on the health status of premature infants is not known. Therefore, we caution readers not to conclude that ascorbic acid is harmful to premature infants and that ascorbic acid intake needs to be restricted in these infants. Only carefully designed and performed *in vivo* studies of vitamin C depletion or supplementation will be able to answer these important questions.

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- 1 Silvers KM, Gibson AT, Powers HJ. High plasma vitamin C concentrations at birth associated with low antioxidant status and poor outcome in premature infants. *Arch Dis Child* 1994; 71: F40–4.
- 2 Halliwell B, Gutteridge JMC. The antioxidants of human extracellular fluids. *Arch Biochem Biophys* 1990; 280: 1–8.
- 3 Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. *Proc Natl Acad Sci USA* 1989; 86: 6377–81.
- 4 Evans PJ, Evans R, Kovar IZ, Holton AF, Halliwell B. Bleomycin-detectable iron in the plasma of premature and full-term neonates. *FEBS Lett* 1992; 303: 210–12.

Dr Powers *et al* comment:

There is no doubt that ascorbic acid has several important biochemical functions in the body, including, under most physiological conditions, that of antioxidant. Under the particular conditions associated with premature birth, however, which include a low plasma concentration of plasma transferrin and caeruloplasmin, and possibly the presence of non-transferring bound iron, ascorbic acid present at high concentration would be expected to act as a pro-oxidant. Our published data suggest that this is indeed the case and show that a high plasma vitamin C concentration at birth is associated with poor outcome. As further support for this argument we have recently demonstrated that at ratios of vitamin C:caeruloplasmin which we observe in premature babies at birth, vitamin C strongly inhibits the ferroxidase activity of caeruloplasmin.¹

We have not suggested that vitamin C *per se* is harmful to premature babies, but it is difficult to ignore the fact that vitamin C concentrations in infant formula are higher than those measured in human milk, and that formulas for premature babies are even more generously supplemented. The traditional argument is that premature babies need high intakes of vitamin C to catabolise tyrosine completely, but our stable isotope studies of tyrosine metabolism in preterm infants suggest that this is not the case.² Whereas there is no good evidence that high vitamin C intakes are beneficial, there are indications that they may be harmful. We would therefore advocate a thorough re-evaluation of present recommendations for vitamin C intakes of preterm infants rather than a reassurance that current intakes are appropriate.