

LETTERS TO THE EDITOR

Vitamin A supplementation in developing countries

EDITOR,—I was frustrated by the recent annotation on vitamin A supplementation in developing countries.¹ My main complaint is the inability of Dr Filteau and Professor Tomkins to endorse vitamin A supplementation among children living in poverty.

The authors are concerned that 15 mg (50 000 IU) of supplemental retinol given at about 1.5, 2.5, and 3.5 months has been associated with an 11% excess incidence of bulging fontanelle among young infants.² However, the infants in this study received more frequent doses of vitamin A than is likely necessary for clinical benefit^{3 4}; there was a higher chance of having unnecessary side effects among those treated. A similar trial, using a single dose of 50 000 IU retinol among neonates, failed to demonstrate any significant adverse effects.⁵ Furthermore, Filteau and Tomkins incorrectly state that the bulging fontanelle represents vitamin A 'toxicity' when, in fact, this phenomenon is transient, and has no proved adverse effect on a baby (or parents for that matter). Do fever and injection site erythema represent toxicity from the diphtheria, pertussis and tetanus vaccine, or are they simply acceptable side effects of a beneficial treatment?

Most importantly, Filteau and Tomkins failed to cite two recent rigorous cumulative meta-analyses that demonstrated clear cut benefits of vitamin A supplementation.^{3 4} Both publications showed reduced childhood morbidity and mortality related to respiratory and diarrhoeal diseases among children in 'developing' countries. These data prove, through trial consensus, that supplemental vitamin A is safe, efficacious, and cost effective. Retinol supplements *should* be a part of the Expanded Programme on Immunisation (EPI). The longer we sit on the fence of inconclusiveness, the more children will suffer and die from preventable illness.

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- 1 Filteau SZ, Tomkins AM. Vitamin A supplementation in developing countries. *Arch Dis Child* 1995; 72: 106-7.
- 2 de Francisco A, Chakraborty J, Chowdhury HR, et al. Acute toxicity of vitamin A given with vaccines in infancy. *Lancet* 1993; 342: 526-7.
- 3 Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and childhood mortality. A meta-analysis. *JAMA* 1993; 269: 898-903.
- 4 Glasziou PP, Mackerras DE. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* 1993; 306: 366-70.
- 5 West KP, Khatri SK, LeClerq SC, et al. Tolerance of young infants to a single, large dose of vitamin A: a randomized community trial in Nepal. *Bull World Health Organ* 1992; 70: 733-9.

Dr Filteau and Professor Tomkins comment:
We regret that Dr Joel Ray interpreted our recent editorial to mean that we do not endorse vitamin A supplementation among

children living in poverty. On the contrary, we are strongly supportive of improving vitamin A status of children but believe that giving capsules to infants is not the only, or necessarily the best, means of doing this. We feel that more attention needs to be paid to improving the vitamin A content of the diet – through fortification, nutrition education, or food processing – and to supplementing mothers which would have the added benefit of reinforcing crucial messages about the importance of breast feeding.

High dose vitamin A capsules, in association with the EPI or otherwise, continue to have a place in public health nutrition but have some drawbacks. Firstly, there are legitimate concerns about the medicalisation of a nutritional problem and the ensuing reliance on drugs imported with foreign currency, rather than on local initiative and technology. Secondly, we maintain that issues of safety of capsules for infants have yet to be satisfactorily addressed. Although available evidence suggests that bulging fontanelle is indeed harmless and should be of little concern to parents,¹ we consider that the ongoing follow up research on these children into the possibility of prolonged adverse effects is essential. An additional area of concern was suggested in a recent report, namely, that vitamin A dosing at the time of vaccination may decrease the antibody response to measles in a subpopulation of children.² Therefore, we believe that the best way forward is that of the World Health Organisation which is coordinating a multicentre trial to evaluate efficacy, acute side effects, and longer term morbidity associated with vitamin A given at the time of EPI vaccinations.

Finally, we are aware of the meta-analyses Dr Ray cites but chose to mention only one such analysis, that by Beaton and colleagues,³ as the reports are all much in agreement.

- 1 Agoestina T, Humphrey JH, Taylor GA, et al. Safety of one 52- μ mol (50 000 IU) oral dose of vitamin A administered to neonates. *Bull World Health Organ* 1994; 72: 859-68.
- 2 Semba RD, Munasir Z, Beeler J, et al. Reduced seroconversion to measles in infants given vitamin A with measles vaccination. *Lancet* 1995; 345: 1330-2.
- 3 Beaton GH, Martorell R, Aronson KJ, et al. Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries. Geneva: ACC/SCN, 1993.

Evidence for a superantigen mediated process in Kawasaki disease

EDITOR,—We read with interest the report by Curtis *et al* regarding T cell receptor variable beta ($V\beta$) chain repertoire in patients with Kawasaki disease.¹ We are concerned that readers may reach the premature conclusion that the involvement of superantigens in the aetiopathogenesis of Kawasaki disease is a proved fact. The authors ignored a substantial body of evidence that does not support this view. The results of Abe *et al* implicating a superantigen in Kawasaki disease could not be confirmed by two different series.² In our own study we found no increase in the percentage of $V\beta 2^+$ cells in patients with Kawasaki disease³; in addition, our analysis of T cell activation markers in Kawasaki disease paired samples collected at different intervals showed no changes in the expression of HLA-DR or interleukin-2 receptor. Thus, we could demonstrate no evidence that our patients had been exposed to a superantigen. Subsequently, a multicentre study confirmed our observations.⁴ Another recent study also

found no evidence of exposure to superantigen in patients with Kawasaki disease,⁵ and several groups reported their inability to reproduce the results of Leung *et al*⁶ regarding the isolation of a new, toxic shock syndrome toxin-secreting strain of *Staphylococcus aureus* in patients with Kawasaki disease.^{4 5 7} Even in the report by Curtis *et al* the majority of patients during the acute phase had a percentage of $V\beta 2^+$ cells in the normal range.

The possible involvement of superantigen in the aetiopathogenesis of Kawasaki disease is far from resolved, and a more balanced discussion of the evidence for and against it would have been helpful.

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- 1 Curtis N, Zheng R, Lamb JR, Levin M. Evidence for a superantigen mediated process in Kawasaki disease. *Arch Dis Child* 1995; 72: 308-11.
- 2 Abe J, Kotzin BL, Jujo K, et al. Selective expansion of T cells expressing T cell receptor variable regions V beta 2 and V beta 8 in Kawasaki disease. *Proc Natl Acad Sci USA* 1992; 89: 4066-70.
- 3 Pietra BA, De Inocencio J, Giannini EH, et al. T cell receptor $V\beta$ family repertoire and T cell activation markers in Kawasaki disease. *J Immunol* 1994; 153: 1881-8.
- 4 Melish ME, Parsonett J, Marchette M. Kawasaki syndrome (KS) is not caused by toxic shock syndrome toxin-1 (TSST-1)+staphylococci. *Pediatr Res* 1994; 35 (suppl): 187A.
- 5 Sakaguchi M, Kato H, Nishiyori A, et al. Characterization of CD4⁺ T helper cells in patients with Kawasaki disease (KD): preferential production of tumour necrosis factor- α (TNF- α) by $V\beta 2^+$ or $V\beta 8^+$ T helper cells. *Clin Exp Immunol* 1995; 99: 276-82.
- 6 Leung DYM, Meissner HC, Fulton DR, Murray DL, Kotzin BL, Schlievert PM. Toxic shock syndrome toxin-secreting *Staphylococcus aureus* in Kawasaki syndrome. *Lancet* 1993; 342: 1385-8.
- 7 Nishiyori A, Sakaguchi M, Kato H, et al. Toxic shock syndrome toxin-secreting *Staphylococcus aureus* in Kawasaki syndrome. *Lancet* 1994; 343: 299-300.

Dr Curtis and Professor Levin comment:

We agree that more studies are required to investigate the role of superantigens in Kawasaki disease. Since our paper was submitted, conflicting data has been published concerning selective $V\beta$ usage in the disease. We believe this conflict is due to methodological differences, in particular the different time at which samples were taken in other studies. We observed that the detection of increased $V\beta$ expression is critically dependent on the timing of the investigation with respect to the onset of disease. Our study suggests that it is not possible to detect the rise in $V\beta 2$ bearing cells in patients studied early in the disease.

A similar finding was observed in Choi *et al*'s original study of staphylococcal toxic shock syndrome in which peak $V\beta 2$ expansion was observed 10-14 days after onset of disease.¹ Choi *et al* proposed that the timing of sampling explained the inability to detect $V\beta 2$ expansion in three of the eight patients studied.

In none of the studies cited by De Inocencio and Hirsch were the results from the acute patients analysed with respect to time after disease onset. In Sakaguchi *et al*'s study, patients in the 'acute' group (defined as under nine days) may have been studied too early to detect a change in $V\beta$ repertoire.