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, Khatry 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-μmol (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 (Vβ) 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 $V\beta2^+$ cells in patients with Kawasaki disease[3]; 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 $V\beta2^+$ 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 Vβ family repertoire and T cell activation markets 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-alpha (TNF-α) by $V\beta2^-$ or $V\beta8^-$ 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 Vβ 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 Vβ 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 Vβ2 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 Vβ2 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 Vβ2 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 Vβ repertoire.

The effect of immunoglobulin on Vβ repertoire is uncertain. Therefore the demonstration of Vβ changes after administration of immunoglobulin early in the disease may be difficult. In the UK, Kawasaki disease is unfortunately still often diagnosed late outside paediatric centres, and treatment with immunoglobulin may therefore be delayed beyond the tenth day of illness. This has enabled us to study patients referred up to 21 days after disease onset *before* the administration of immunoglobulin.

In contrast to Leung *et al* we have found a variety of different staphylococcal toxins in throat and nose swab culture supernatants from patients with Kawasaki disease and their relatives.[2] In addition we have found activity suggesting the presence of one or more novel superantigen toxin or toxins. We propose that Kawasaki disease is either caused by more than one toxin or is caused by a novel superantigen toxin.

We disagree that we may have misled readers to conclude that superantigen involvement in Kawasaki disease is a proved fact. We concluded that our data 'supports the hypothesis that a superantigen is involved in the pathogenesis of Kawasaki disease'; a hypothesis that remains to be tested in further studies.

1 Choi Y, Lafferty JA, Clements JR, *et al*. Selective expansion of T cells expressing V beta 2 in toxic shock syndrome. *J Exp Med* 1990; **172:** 981–4.
2 Curtis N, Chan B, Levin M. Toxic shock syndrome toxin-secreting Staphylococcus aureus in Kawasaki syndrome [Letter]. *Lancet* 1994; **343:** 299.

Burkholderia cepacia and ΔF508 homozygosity in cystic fibrosis

EDITOR,—Colonisation by *Pseudomonas aeruginosa* has long been recognised as a common trait in cystic fibrosis. Lately also *Burkholderia cepacia*, formerly known as *Pseudomonas cepacia*, has emerged in cystic fibrosis as a significant, although not so widespread, pathogen.[1] As it has been suggested that homozygotes for ΔF508, the commonest cystic fibrosis mutation, could be more often and earlier colonised by *P aeruginosa*,[2 3] we decided to evaluate the correlation between ΔF508 homozygosity and *B cepacia* colonisation in cystic fibrosis.

All patients attending the Verona Cystic Fibrosis Centre between November 1991 and November 1994 were examined for *B cepacia* airway infection, and most of them genetically tested for ΔF508. *B cepacia* colonisation was considered chronic after at least two positive cultures a year for one or more years, or three consecutive positive cultures over a four to 12 month period.[4] Fourteen out of the 40 (35%) chronically colonised and 84 out of the 469 (22%) non-colonised patients were homozygotes for ΔF508. A significant difference in frequencies was shown between subjects chronically colonised by *B cepacia* who were homozygous for ΔF508 and patients chronically colonised carrying other genotypes (2×2 contingency table analysed by Fisher's exact test; p value=0·0123; odds ratio=2·468; confidence interval=1·236 to 4·927). Clinical evaluation of patients showed in ΔF508 homozygotes no signs of a more severe pulmonary disease, which could have explained the different colonisation rates, and the comparison of two investigations showed no significant difference (forced expiratory volume in one second p value=0·8985; *x* ray score p value=0·7277). Furthermore we could not find an evident early colonisation by *B cepacia* in ΔF508 homozygotes: there is no significant age difference at *B cepacia* first isolation in the two genotype groups (two tailed p value=0·2876).

Our ΔF508 homozygous patients show a higher prevalence of *B cepacia* chronic colonisation, and have more than double the chance of colonisation, compared with those carrying different genotypes. Surely environmental factors influence the colonisation rate, but apparently genotype is involved as well. If further studies in different populations and environments confirmed these results, the determination of chronic colonisation by *B cepacia* could be extensively included in studies on the genotype/phenotype correlation, considering also mutations less frequent than ΔF508.

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1 Anonymous. Pseudomonas cepacia – more than a harmless commensal? [Editorial.] *Lancet* 1992; **339:** 1385–6.
2 Johansen HK, Nir M, Hoiby N, Koch C, Schwatz M. Severity of cystic fibrosis in patients homozygous and heterozygous for ΔF508 mutation. *Lancet* 1991; **337:** 631–4.
3 Borgo G, Gasparini P, Bonizzato A, Cabrini G, Mastella G, Pignatti PF. Cystic fibrosis: the ΔF508 mutation does not lead to an exceptionally severe phenotype. A cohort study. *Eur J Pediatr* 1993; **152:** 1–6.
4 Thomassen MJ, Demko CA, Klinger JD, Stern RC. Pseudomonas cepacia colonization among patients with cystic fibrosis. *Am Rev Respir Dis* 1985; **131:** 791–6.

Birth weight in phenylketonuria

EDITOR,—The report by Verkerk *et al* of relatively low birth weight in Dutch infants with phenylketonuria[1] agrees well with our earlier finding of low birth weights in phenylketonuria in Ireland and west Scotland.[2] In agreement with other workers in the USA,[3] the UK,[4] and Poland,[5] we found that in our total sample of 62 infants with phenylketonuria and 53 unaffected siblings, and within families, there was no significant difference between infants with phenylketonuria and their unaffected siblings either in their unadjusted birth weights or in their birth weights adjusted for factors that affect this quantity. Moreover, the 115 birth weights in the combined sample lay on a normal distribution curve with no evidence of a bimodal or trimodal distribution. However, the mean unadjusted birth weight of the combined sample was 121 g less than the mean for a randomly selected sample of 819 control infants born in the same hospitals in the same years as the infants with phenylketonuria and their siblings ($p \leq 0{\cdot}02$); for the adjusted birth weights the difference between the means was 107 g ($p < 0{\cdot}02$). We concluded that, as the reduction in birth weight was the same for both infants with phenylketonuria and their unaffected siblings, the lower birth weight was not related to the pathogenesis of phenylketonuria or to the fetal genotype. It appears that the reduction in birth weight was a reflection of the maternal genotype affecting the intrauterine environment and was a previously unknown effect of the phenylketonuria gene in single dose.

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1 Verkerk PH, van Spronsen FJ, Smit GPA, Sengers RCA. Impaired prenatal and postnatal growth in Dutch patients with phenylketonuria. *Arch Dis Child* 1994; **71:** 114–8.
2 Crockett DJ, Woolf LI, McBean MS, Woolf FM, Cahalane SF. Birth weight and pathogenesis in phenylketonuria. *Int J Neurosci* 1990; **54:** 259–66.
3 Rothman KJ, Pueschel SN. Birthweight of children with phenylketonuria. *Pediatrics* 1976; **58:** 842–4.
4 Smith I, Carter CO, Wolff OH. Birthweight of infants with phenylketonuria and their unaffected siblings. *J Inherit Metab Dis* 1978; **1:** 99–100.
5 Cabalska B, Miesowicz I, Zorska K, Nowaczewska I, Duczynska N. Influence of the phenylketonuric heterozygote on the developing fetus. *J Inherit Metab Dis* 1982; **5:** 129–31.

Dr Verkerk comments:

Woolf and Crockett hypothesise that the reduced birth weight in phenylketonuria as found in some studies may be the result of maternal genotype affecting the intrauterine environment. This interesting hypothesis is based on their own findings and on a qualitative review of the literature. According to their theory no differences should be found in birth weight between infants with phenylketonuria and their healthy siblings. However, the findings of the first study on the relationship between phenylketonuria and birth weight are not in agreement with this theory.[1] The study by Saugstad found that mean birth weight of 49 infants with phenylketonuria was 356 g lower than mean birth weight of their 86 healthy siblings. After adjustment for differences in gestational age, the discrepancy in birth weight even increased to 530 g. I am therefore not yet convinced by the explanation offered by Woolf and Crockett. Perhaps a quantitative review of the literature (meta-analysis) may provide more information on this subject.

1 Saugstad LF. Birthweights in children with phenylketonuria and in their siblings. *Lancet* 1972; i: 809–13.

Diagnosis of mycobacterial lymphadenopathy

EDITOR,—Clark and colleagues recently reviewed 17 cases of non-tuberculous mycobacterium (NTM) lymphadenopathy.[1] As they conclude, it is important to differentiate *Mycobacterium tuberculosis* from NTM infection, although this is not always possible on clinical grounds alone. If mycobacterial infection is suspected, then definitive species group identification is essential, as the surgical management, and the antibiotic sensitivities, of NTM and *M tuberculosis* are very different.

Skin testing is a useful first line investigation of infective lymphadenopathy.[2 3] *Mycobacterium avian* purified protein derivative is available commercially in Australia (but not in the UK). Cross reactivity between this and the human Mantoux test is common. However, if a NTM is the causative organism, then the *M avian* hypersensitivity reaction is usually significantly larger than that caused by