LETTERS TO THE EDITOR

Long term follow up of children born to mothers with periconceptual multivitamin supplementation

EDITOR,—Before recommending periconceptual folic acid-containing multivitamin supplementation universally for the prevention of neural tube defects one would also want to be sure that it was doing no harm. A UK study showed the over-representation of worries and anxiety among children at age 7-10 years born to mothers with periconceptual multivitamin supplementation.¹ In our previous study based on a short term postnatal follow up of 3356 infants (mean age 11 months) born to mothers supplemented with multivitamin or placebo-like trace element² in the periconceptual period, the results of the tests of mental and behavioural development were similar in the two groups. However, atopic dermatitis was found more often in the multivitamin group. We now summarise the results of long term follow up to the ages of 2 and 6 years with respect to the occurrence of atopic dermatitis (and other allergies) and anxiety.

The children were born to mothers who had been supplemented with multivitamin (including 0.8 mg of folic acid) or trace elements in the Hungarian randomised, double blind, controlled trial.³ Altogether 200 case and 200 control children were randomly selected with equal sex distribution for each age group (2 and 6 years) and they were examined by a double blind method. Of the 800 invited children, 625 (78%) took part in the study, 336 (84%) in the 2 year and 289 (72%) in the 6 year age groups. Parents of 120 children did not want to participate, 44 families had a new unknown address, three children died after the short term follow up study, four had severe congenital abnormalities, and four were unable to cooperate at the psychometric behavioural examinations. The occurrence of atopic dermatitis based on a medically documented case history did not differ significantly between the two nutritional groups at 2 years (32/176 (18.2%) in the multivitamin and 19/160 (11.9%) in the trace element group) and at 6 years (12/147 (8.2%) v 11/142 (7.7%)). The occurrence of other allergies including bronchial asthma, obstructive bronchitis, pseudocroup and food allergies were similar in the two nutritional groups at 2 years (21.0% in the multivitamin and 29.4% in the trace element) and at 6 years (30.6% v 33.8%).

At 2 years of age, developmental quotient was measured by the Brunet-Lezine method, while at 6 years intelligence quotient was measured by the Budapest Binet and Raven tests. In addition, the Goodenough man drawing test was used. There was no significant difference in the mental development of children between the multivitamin and trace element groups. Anxiety was measured by the child version of thematic aperception test⁴ in 6 year old children. Five levels of anxiety were examined but 'extremely low' did not occur, while 'extremely high' was found only in two children of the trace element group. The proportion of chil-

dren scoring 'above average' levels of anxiety was not higher in the multivitamin group and we were thus unable to confirm the previous UK finding.

In conclusion, no adverse effect was observed in children whose mothers had received periconceptual multivitamin supplementation.

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- 1 Holmes-Siedle M, Dennis J, Lindenbaum RH, Galliard A. Long term effects of periconceptual multivitamin supplements for prevention of neural tube defects: a seven to 10 year follow up. *Arch Dis Child* 1992;67:1436-41.
- 2 Czeizel AK, Dobó M. Postnatal somatic and mental development after periconceptual multivitamin supplementation. *Arch Dis Child* 1994;70:229-33.
- 3 Czeizel AK, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptual vitamin supplementation. *N Engl J Med* 1992;327:1832-5.
- 4 Schroth ML. The relationships between motives on the children's aperception test. *Journal of Psychological Genetics* 1979;134:219-24.

Gastro-oesophageal reflux and cows' milk protein allergy

EDITOR,—In their very stimulating paper, Cavataio *et al* reported their experience concerning gastro-oesophageal reflux (GOR) associated with cows' milk protein allergy (CMPA).¹ In a series of 47 cases of GOR, they found a very high prevalence of CMPA: 14 cases (30%); they also stressed the possibility of recognising these cases from characteristic 'phasic' pH tracing.

We evaluated a series of 112 infants (65 boys and 47 girls; median age 3.7 months) with GOR confirmed by oesophageal 24 hour pH monitoring. Using the results of an elimination diet followed by an open challenge test, we found CMPA dependent GOR in 18 patients (16%), a rate significantly lower than that found by Cavataio *et al*, but similar to that of other authors.² Moreover, we failed to find any characteristic oesophageal pH-metric pattern distinguishing patients with GOR plus CMPA from patients with GOR only: one out of 18 cases with CMPA dependent GOR showed the oesophageal 'phasic' pH monitoring reported by Cavataio *et al*, and this pattern was also present in three out of 67 cases with GOR only.

It is difficult to explain the difference in these two sets of results. The increase in pH subsequent to feeding found by Cavataio *et al* ('phasic' tracing) may have been an non-specific event, evident for some reason only in those patients in whom CMPA was diagnosed. Besides, such a high prevalence of CMPA in patients with GOR is truly surprising and has never been found by us or other authors in Southern Italy,² or by others in Europe.³ Staiano *et al* showed that in cases with CMPA dependent GOR, there is a significant increase in intestinal permeability² that suggests an involvement of the entire intestinal tract. As a matter of fact, 10/18 of our cases with CMPA dependent GOR showed failure to thrive: a significantly higher number, than in cases with GOR only (55% v 14/67=20%; $p<0.05$). Cavataio *et al* found difference neither in clinical symptoms, nor

in the prevalence of failure to thrive between patients with GOR and/or CMPA, and this can cast doubts on whether CMPA was correctly diagnosed. We think that other studies are necessary to further evaluate the prevalence of CMPA in infants with GOR and to investigate the possibility of recognising these cases by a characteristic oesophageal pH monitoring pattern.

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Drs Cavataio, Iacono, and Carroccio comment:

Milocco and colleagues base their comments on the results recorded in a group of infants that is not comparable with the one we studied. It is relevant to underline that all our CMPA diagnoses had been made after an elimination diet and double blind cows' milk challenge; furthermore, in 31/39 patients with clear positive clinical reaction to cows' milk challenge, we documented intestinal mucosa damage which did not exist 24 hours before the challenge. As we followed rigorous criteria in making the diagnosis of CMPA and as these criteria are the only ones accepted in the literature,⁴ we are surprised that there are doubts about this diagnostic procedure. On the contrary, Milocco and colleagues have based their CMPA diagnosis on a single open challenge and this creates great uncertainty as to the correctness of the diagnosis.

Moreover, the age of the infants studied by Milocco and colleagues is not specified, but on the single datum we have (median age), it does not seem comparable with that of the patients we studied, in fact, 50% of their infants were <3.7 months old and we think that in such young infants it is very probable that there are many cases of 'physiological GOR', without any clinical relevance⁵ and, obviously, without any relation to CMPA.

They reported a low number of 'phasic' pH-metric tracings (4/85, but what about the remaining 27 patients with GOR? Is 112 really the total number?), but we think that they examined a majority of normal infants, probably with excessive physiological GOR and without GOR disease (did any of these infants undergo oesophageal endoscopy?).

Finally, it is noteworthy that another Italian group carried out a prospective study on GOR-CMPA association and found that 13/18 patients with GOR+CMPA and only 3/37 with GOR had a typical phasic pattern of the pH-monitoring tracing.⁶

1 Cavataio F, Iacono G, Montalto G, Soresi M, Tumminello M, Carroccio A. Clinical and pH-metric characteristics of gastro-oesophageal reflux secondary to cows' milk protein allergy. *Arch Dis Child* 1996;75:51-6.

2 Staiano A, Troncone R, Simeone D, *et al*. Small bowel permeability in the evaluation of infants with persistent vomiting. *Proceedings of Fourth Joint Meeting NASPGN-ESPGAN*. Houston, 1994: 348.

3 Déleze G, Nusslé D. L'intolérance aux protéines du lait de vache chez l'enfant. *Helv Paediat Acta* 1975;30:135-49.

4 ESPGAN Working Group for the diagnostic criteria for food allergy: diagnostic criteria for food allergy with predominantly intestinal symptoms. *J Pediatr Gastroenterol Nutr* 1992;14:108-12.

5 Carré IJ. Clinical significance of gastroesophageal reflux. *Arch Dis Child* 1984;59:911-2.

6 Di Stefano G, Violante M, Traverso G, Oddo S, Marino V, Cataldo F. Usefulness of 24-h

pH-metry and other laboratory investigations in the differential diagnosis between cow's milk allergy and GER in the first year. *3rd Joint Meeting of the British and Italian Societies of Pediatric Gastroenterology*. Naples 11-14 September 1996. Abstract book: 114.

Chromosomal and clinical features in an infant with Hallermann-Streiff syndrome

EDITOR.—Hallermann-Streiff syndrome (HSS) is a disorder of unknown origin rarely diagnosed in neonatal period. The early diagnosis of HSS is important for management because many complications, that are often life threatening, may occur early in this syndrome.¹ We report an infant with clinical and radiological findings of HSS, a spontaneous fracture of the left arm, and with chromosome variant 46, XX, 16qh+. She was a girl born at term after a normal pregnancy. Her family history was unremarkable. During pregnancy there was no exposure to known teratogens. Birth weight was 2700 g and length was 44 cm. Physical examination showed frontal prominence and cutaneous atrophy of the forehead and over the nose, which was thin, pointed and curved, micrognathia with relative macroglossia, microphthalmia, and a cataract in the right eye. Arms and legs were short in comparison to the body. Abdomen, thorax, genitals, neurological examination, cardiac structure and function were normal. Skeletal radiography showed thin ribs, clavicles, and long bones (ulna and radius). Chromosomes were 46, XX, 16qh+ by R banding and C banding techniques. Because of micrognathia and macroglossia the infant was fed by gavage in the first weeks. No respiratory problems occurred in the first month of life. At the age of 3 months the patient had a spontaneous fracture of the left radius and at 10 months (fig 1) she returned to our department because of a severe pneumonia; examination revealed growth retardation (her weight was 4050 g), hypotonia, squinting, and a cataract in the left eye.

Few chromosome anomalies have been found in previous cases, with only Carones reporting some discrepancy in the size of two members of pair of D group chromosomes,² and Jalbert *et al* describing a del(Bp).³ In our patient we found a well known polymorphism, 16qh+. The meaning of this chromosome finding in HSS is not clear and does not explain the features of this syndrome. Slender long bones with fractures have been described in a fetus with facial appearance of HSS.⁴ We think that fractures of long bones should be considered a possible complication in HSS related to the bone abnormalities described in these patients.

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- 1 Cohen MM Jr. Hallermann-Streiff syndrome: a review. *Am J Med Genet* 1991;41:488-99.
- 2 Carones AV. Syndrome dyscephalique de François. *Ophthalmologica* 1961;142:519-8.
- 3 Jalbert P, Gilbert Y, Leopold P, Mouriquand C, Beaudouin A. Syndrome d'Hallermann-Streiff-François, a propos d'une nouvelle observation associée à une anomalie cariotypique 4P. *Pediatr* 1968;23:703-5.
- 4 Dennis NR, Fairhurst J, Moore IE. Lethal syndrome of slender bones, intrauterine fractures, characteristics facial appearance, and

Figure 1 Infant at 10 months of age.

cataracts, resembling Hallermann-Streiff syndrome in two sibs. *Am J Med Genet* 1995;59: 517-20.

Neutral lipid storage disease—response to dietary intervention

EDITOR.—Neutral lipid storage disease (NLSD) is an autosomal recessive metabolic disorder characterised by a multisystem accumulation of neutral lipids (triglycerides). The patients with NLSD have congenital ichthyosis and variable systemic manifestations.¹ The storage of cytoplasmic triglycerides in NLSD patients results either from a severe defect in the degradation of cytoplasmic triacylglycerols containing long chain fatty acids² or rapid triacylglycerol resynthesis.³ Based on these biochemical data, one might expect that a low fat diet poor in long chain fatty acids could be beneficial to these patients. We report a boy with NLSD with emphasis on his response to dietary intervention.

CASE REPORT

An 8 year old boy was born as a collodion baby to unrelated parents. Examination at the age of 22 months revealed ichthyosiform erythroderma, hepatomegaly (11 cm below the right costal margin), and diffuse bilateral cataracts. Liver enzymes were raised (aspartate aminotransferase (AST): 177 IU/l, alanine aminotransferase (ALT): 179 IU/l, γ -glutamyltransferase: 42 IU/l. Liver histology showed gross fatty infiltration of the hepatocytes with lobular fibrosis. Leucocyte neutral lipid vacuolation was detected in the peripheral blood smears. Lipid thin layer chromatography from skin tissue showed increased accumulation of triglycerides.

The boy was put on a low fat diet (table 1) and at the end of the first year of treatment the size of the liver decreased by 50% and the liver function improved. The skin also became less erythematous and less scaly.

At the age of 3.5 years the boy was operated for cataracts. At the age of 8 years, still on the special diet, his skin condition improved fur-

ther and the liver size was normal (AST: 60 IU/l, ALT: 70 IU/l). There was no hearing or muscle power impairment and he made good progress in school.

In our patient a low fat diet, poor in long chain and enriched with medium chain fatty acids, led to regression of liver size, improvement of his skin condition, and possibly prevention of other organ involvement. In 1980 Angelini *et al* also reported improvement in liver size with a medium chain triglyceride diet in a 5 year old girl with NLSD.⁴ As in other metabolic disorders the special diet did not restrain the progress of the patient's cataracts.⁵ It is conceivable that by starting the special diet before cataract initiation, this complication might be totally prevented. This observation indicates that in cases of NLSD, an early initiation of a diet poor in long chain fatty acids might improve the skin condition and prevent systemic disturbances.

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- 1 Chanarin I, Patel A, Slavin G, Wills EJ, Andrews TM, Steward G. Neutral lipid-storage disease: a new disorder of lipid metabolism. *BMJ* 1975;i:553-5.
- 2 Hilaire N, Negre-Salvare A, Salvoyre R. Cellular uptake and catabolism of high-density-lipoprotein triacylglycerols in human cultured fibroblasts: degradation block in neutral lipid storage disease. *Biochem J* 1994;297:467-73.
- 3 Igal RA, Coleman RA. Acylglycerol recycling from triacylglycerol to phospholipid, not lipase activity, is defective in neutral lipid storage disease fibroblasts. *J Biol Chem* 1996;271:16644-51.
- 4 Angelini C, Philippart M, Borroni C, Bresolin N, Cantini M, Lucke S. Multisystem triglyceride storage disorder with impaired long chain fatty acid oxidation. *Ann Neurol* 1980;7:5-10.
- 5 Nelson L. Abnormalities of the lens. In: Behrman R, Kliegman RM, Arvin AM, eds. *Nelson textbook of pediatrics*. 15th Ed. Philadelphia: WB Saunders, 1996:1783-9.

Primary manifestation of Henoch-Schönlein purpura during immunosuppressive treatment

EDITOR.—Although numerous investigations suggest an immunological process involving a disturbance of the regulatory mechanism for IgA synthesis,¹ the aetiology of Henoch-Schönlein purpura are still unresolved.

We report a 4 year old boy who received a liver transplant at the age of 3 years after developing a fulminant liver failure due to intoxication with α -amanitin. After transplantation, immunosuppressive treatment with cyclosporin (Neoral, Sandoz) and prednisone was carried out. During later care the cyclosporin trough serum concentrations

Table 1 Diet given to the patient with NLSD

Frequent meals (every 4-6 hours) to avoid lipolysis
Normal protein (15% of total energy)
High carbohydrate (65-70% of total energy) mainly in the form of starchy foods and one or two glucose 10% polymer drinks during the night (Maxijul, Scientific Hospital Supplies)
Low fat (20% of total energy) 18% derived from medium chain fat (MCT Oil, Mead Johnson) and 2% from essential long chain fat. The MCT Oil was added at the end of the cooking into the meal (optimum cooking temperature < 160°C)
Supplement of vitamin and mineral mixture (Seravit Paediatric, Scientific Hospital Supplies)

always exceeded 100 ng/ml, while simultaneously the dose of corticosteroids was reduced to 1 mg/day. Eight months later, after a short minor infection of the upper respiratory tract, the boy developed the clinical signs of Henoch-Schönlein purpura with a typical purpuric skin rash and ecchymotic areas particularly on the lower legs and the feet, joint involvement with periarticular pain, tenderness and swelling, and abdominal pain without melena, but guaiac positive stools. During the subsequent course, renal involvement manifested with one episode of macrohaematuria and intermittent proteinuria, but without impairment of renal function (glomerular filtration rate 144 ml/min/1.73 m²) and no hypertension. As a complication, localised swelling of the left testis developed. The symptoms lasted for four weeks; no urinary abnormalities were noted afterwards.

During the acute stage, laboratory data showed the following results: normal values for haemoglobin, red and white blood cell count, platelet count, blood coagulation parameters (partial thromboplastin time, prothrombin time, fibrinogen, factor XIII, bleeding time), C3, C4 according to the age of a 4 year old boy; negative anti-DNA and P/C-antineutrophilic cytoplasmic (ANCA) antibody serology; raised plasma concentrations of IgA (2.8 g/l), IgG (18.1 g/l), and IgM (2.7 g/l). Three weeks later, Epstein-Barr virus (EBV) serology showed raised titres of IgG antibodies to virus capsid antigen (VCA 1:320) and EBV early antigen (1:160), but negative VCA-IgM serology and positive titre for anti-EBV nuclear antigen-1 IgG. In addition, EBV-DNA was detected in peripheral blood leucocytes, presumably reflecting a reactivated EBV infection.

Henoch-Schönlein purpura is considered to be a vasculitic disorder with immune pathogenesis. Raised serum IgA concentration, circulating IgA immune complexes, IgA rheumatoid factor, an increased percentage of IgA bearing peripheral blood lymphocytes, etc, were demonstrated.¹ Triggering infectious mucosal stimuli are responsible for development of Henoch-Schönlein purpura and circulating dimeric IgA are distinctly involved in this process.^{2,3} Whereas isolated cases of recurrent Henoch-Schönlein purpura nephritis in adults after renal transplantation have been observed,⁴ this is to our knowledge the first report on a patient, who, despite of receiving regular immunosuppressive treatment after liver transplantation, developed a primary manifestation of Henoch-Schönlein purpura eight months later. This event confirms the assumption of an initial infectious triggering agent for Henoch-Schönlein purpura (for example EBV), rather than a primary immunological process. This is supported by the failure to prove the presence of autoantibodies (for example anti-DNA, ANCA).⁵

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1 White RHR. Henoch-Schönlein nephritis. A disease with significant late sequelae. *Nephron* 1994;68:1-9.

- 2 Knight JF. The rheumatic poison: a survey of some published investigations of the immunopathogenesis of Henoch-Schönlein purpura. *Pediatr Nephrol* 1990;4:533-41.
- 3 Coppo R, Amore A, Gianoglio B, et al. Macromolecular IgA and abnormal IgA reactivity in sera from children with IgA nephropathy. *Clin Nephrol* 1995;43:1-13.
- 4 Crown AL, Woolfson RG, Griffiths MH, Mansell MA, Neild GH. Recurrent systemic Henoch-Schönlein purpura in an adult following renal transplantation. *Nephrol Dial Transplant* 1994;9:423-5.
- 5 Robson WMLM, Leung AKC, Woodman RC. The absence of anti-neutrophil cytoplasmic antibodies in patients with Henoch-Schönlein purpura. *Pediatr Nephrol* 1994;8:295-8.

Thyroid morphological findings in the mothers of infants with congenital hypothyroidism

EDITOR,—Little information is available on the aetiology of primary not transient congenital hypothyroidism due to thyroid malformations. Usually it is considered to be a sporadic disease; however, to date, there are no reliable studies to identify some possible family risk factors for the disease.^{1,2} Therefore between April and September 1996, during therapeutic follow up of affected children, we examined the mothers of 19 consecutive infants with congenital hypothyroidism (group A) screened through our regional newborn screening program (Emilia-Romagna, Italy) and 17 age matched volunteer mothers of unaffected children (group B). At the time of this examination the chronological age of the infants with congenital hypothyroidism was 5.5±3.8 years; in all cases the diagnosis of congenital hypothyroidism was confirmed and all had malformations (15 ectopic thyroid glands, three athyrosis, one hypoplasia). All the mothers examined were resident in our region, clinically euthyroid, and had not previously had any thyroid investigations. In all subjects a thyroid ultrasound was performed by the same blind operator using a 10 MHz probe and blood samples were taken to determine serum concentrations of thyroid stimulating hormone, free triiodothyronine, and free thyroxine and antithyroid antibodies.

At the ultrasound examination three mothers in group A (15.8%) showed congenital thyroid abnormalities that were pathological asymmetries of the gland (agenesis of the left lobe and of the isthmus in one case and severe hypoplasia of the left lobe in the other two cases). Their incidence was 33.4% (1/3 cases) in the mothers of athyrotic children and 13.3% (2/15 cases) in the mothers of children with ectopic glands. None of the mothers in group B showed the same abnormalities. Thyroid enlargement on ultrasound examination was found in 8/19 cases in group A and in 7/17 cases in group B; the percentage of nodular goitres was 75.0% and 85.7% respectively.

All subjects examined showed thyroid hormone values within the normal range; positive antithyroid antibody titres were found in 2/19 subjects of group A and in 1/17 subjects of group B.

Congenital thyroid hemiagenesis is thought to be a rare developmental anomaly of the gland and its exact incidence is unknown as the data are usually skewed toward selected patients.³ The only data in literature from a large necropsy series reported a prevalence of 0.34%.⁴ The preliminary results of our study seem to indicate that the ultrasound findings of a pathological thy-

roid asymmetry represent a possible risk factor for fetal congenital hypothyroidism. Further family studies are needed to evaluate the thyroid transcription factor-1 gene which is probably responsible for thyroid development. In our region (Emilia-Romagna, Italy) we have observed an elevated incidence of 'asymptomatic' goitres in women of fertile age. This disease, however, does not appear to be related to a higher risk for thyroid malformation in the offspring.

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- 1 Goujard J, Safar A, Rolland A, Job JC. Epidemiologie des hypothyroïdies congénitales malformatives. *Arch Fr Pediatr* 1981;38:875-9.
- 2 Khoury MJ, Becerra JE, Almada PJ. Maternal thyroid disease and risk of birth defects in offspring: a population-based case-control study. *Paediatr Perinat Epidemiol* 1989;3:402-20.
- 3 Bough ID Jr, Greco T, Romanczuk B. Thyroid hemiagenesis. *Ann Otol Rhinol Laryngol* 1994; 103:328-30.
- 4 Williams ED, Toyn CE, Harach HR. The ultimobranchial gland and congenital thyroid abnormalities in man. *J Pathol* 1989;159:135-41.

Investigating children with mild to moderate learning difficulties

EDITOR,—Dr Corrigan and colleagues ask important questions about the value of diagnostic screening for children with mild to moderate developmental delay.¹ Unfortunately, their study has many of the methodological weaknesses highlighted in a recent review on this field.²

The vital issue of clear case definitions is not adequately addressed mainly because no standardised cognitive or developmental assessment tools were employed. Furthermore to meaningfully evaluate the performance of the diagnostic tests examined in this study requires not only accurate prevalence data, but also a knowledge of the individual tests' sensitivities and specificities.

Most of the known organic causes of mild to moderate developmental delay are of a low prevalence, limiting the usefulness of small studies. In the specific case of fragile X screening it is worrying that the authors conclude 'The failure of this study to detect any cases of the fragile X gene would suggest that until larger studies are completed on similar populations fragile X screening of children with mild to moderate learning difficulties should not be recommended'. The prevalence of fragile X syndrome in the general population is currently estimated at around about 0.2/1000 and in boys with learning difficulties nearer 5/1000.³ It is not therefore surprising that no cases of fragile X were detected in this study's sample of 95 children. Perhaps a more appropriate conclusion would be that although they have not yet found any affected children, they should keep looking. DNA testing for fragile X has a high sensitivity and specificity, and testing is not only for the child's benefit but also for the mother and extended family.

Choosing medical investigations in developmentally delayed children remains a diffi-

cult area, but there are well described protocols for critically appraising medical investigations which should be followed before making recommendations on the performance of diagnostic investigations.⁴

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Drs Corrigan and Stewart comment:

As has been correctly pointed out research into children with mild to moderate learning difficulties is plagued by difficulties in case definition. In our study we used operational criteria based on school placement and provision of remedial assistance to define learning difficulties. This reflects the clinical reality and outlines the extent of the problem.

The majority of these children were maintained in mainstream education and did not have formal educational assessment. They represent a large number of children (16% of population in our study) that are becoming an increasing focus for paediatricians with a remit in educational medicine. At present there are no formal recommendations regarding medical assessment or investigation in this group.

Any decision to institute a regular screening programme for these children would have significant implications for both the child and health resources. We feel therefore that the benefits of a programme such as screening for fragile X would first have to be proved. Studies should show positive results in an identifiable group of children using easily translatable operational criteria before recommending their inclusion.

- 1 Corrigan N, Stewart M, Scott M, Fee F. Fragile X, iron, and neurodevelopmental screening in 8 year old children with mild to moderate learning difficulties. *Arch Dis Child* 1997;76:264-7.
- 2 Roelvelde N, Zielhuis GA, Gabreels F. The prevalence of mental retardation: a critical review of recent literature. *Dev Med Child Neurol* 1997;39:125-32.
- 3 Murray A, Youings S, Dennis N, et al. Population screening at the FRAXA and FRAXE loci: molecular analyses of boys with learning difficulties and their mothers. *Hum Mol Genet* 1996;5:727-35.
- 4 Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical epidemiology: a basic science for clinical medicine*. Boston: Little, Brown and Company, 1991.

Increased incidence and prevalence of diabetes mellitus in Down's syndrome

EDITOR,—In 1968 Milunsky and Neurath reported an increased prevalence of diabetes mellitus in patients with Down's syndrome.¹ However, the response rate in their survey was low (<50%) and the authors did not distinguish between insulin and non-insulin dependent diabetes mellitus. In 1973, Jeremiah *et al* also reported an increased prevalence of diabetes mellitus in Down's syndrome patients.² Their observations, however, were based on the presence of glucosuria.

In the second Dutch nationwide study on the incidence of diabetes mellitus type I in children,³ five cases of Down's syndrome in the age range of 0–14 years were spontaneously reported. Taken into account a yearly incidence of 250 newborns with Down's syndrome, this results in an incidence of diabetes mellitus in Down's syndrome of 50/100 000/

year (95% confidence interval (CI) 16 to 116/100 000/year), whereas in the general population the incidence during the same period was 12.4/100 000/year (95% CI 12.1 to 12.7/100 000/year). These data suggest a threefold increased risk of diabetes mellitus in children with Down's syndrome. We also estimated the prevalence in a population based study among 893 children with Down's syndrome aged 0–9 years born between 1986 and 1994. Three of them had diabetes mellitus, giving a prevalence rate of 335/100 000 (95% CI 87 to 980/100 000), which is higher than the prevalence of diabetes mellitus type I in the age matched general population (40/100 000; 95% CI 35 to 45/100 000).

Our data confirm the suspicion that children with Down's syndrome are more prone to develop diabetes mellitus. All children were insulin dependent. However, it remains to be investigated whether these patients have type I or type II diabetes mellitus as both autoimmunity and signs of premature aging in Down's syndrome could predispose towards type I and type II diabetes mellitus.⁴ As the symptoms of diabetes mellitus in Down's syndrome children may be more difficult to detect and there is an increased risk of complications such as hyperosmolar coma,⁵ special attention has to be taken to symptoms as polydipsia and polyuria.

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- 1 Milunsky A, Neurath PW. Diabetes mellitus in Down's syndrome. *Arch Environ Health* 1968;17:372-6.
- 2 Jeremiah DE, Leyshon GE, Rose T, Francis HW, Elliott RW. Down's syndrome and diabetes. *Psychol Med* 1973;3:455-7.
- 3 Ruwaard D, Hirasings RA, Reeser HM, et al. Increasing incidence of type I diabetes in the Netherlands. The second nationwide study among children under 20 years of age. *Diabetes Care* 1994;17:599-601.
- 4 Rabinowe SL, Rubin IL, George KL, Adri MN, Eisenbarth GS, Trisomy 21 (Down's syndrome): autoimmunity, aging and monoclonal antibody-defined T-cell abnormalities. *J Autoimmun* 1989;2:25-30.
- 5 Stolz U, Saur F, Gugler E. Das hyperosmolare, nicht-ketogene Coma diabeticum beim Kind. *Helv Paediatr Acta* 1977;32:155-63.

UK paediatric clinical research under threat

EDITOR,—The message of your contributor(s) concerning prospects for clinical research in paediatrics was disturbing.¹ Two aspects cause me concern.

First, that the author(s) requested anonymity. Was this through reticence or self effacement? There seemed little in the article to cause offence. If the author(s) thought that they or their departments might be censured by their universities or grant giving bodies, this would be a serious enough matter to be taken up by national academic and representative bodies. Academic paediatricians need visible, resolute leadership and the unequivocal support of non-university paediatricians.

Second, your contributors offered no proposals to deal with the threat. It will not recede spontaneously and neither academic medicine nor clinical practice is immune from the laws of natural selection—adapt or perish. Those who lead our specialty and promote its academic underpinnings should be making plans individually and collectively (including other specialties) to meet and overcome the threat. These include your contributors, presumably, and our newly elected college Vice President who has declared his commitment to promoting paediatric research.

One tactic would be to expect that all trainees in paediatrics should undertake a period of research—not a series of audit projects. Some European countries specify that a number of papers in peer reviewed journals is required for the final certification process. The arguments for promoting research in the training of NHS consultants were set out by the President of the Royal College of Physicians a few years ago.² Practising evidence-based medicine without knowing how the evidence is assembled is as absurd as managing asthma without knowledge of respiratory physiology.

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- 1 Anonymous. UK paediatric clinical research under threat. *Arch Dis Child* 1997;76:1-3.
- 2 Turnberg L. *The place of research in the training of NHS consultant physicians*. London: Royal College of Physicians, 5 April 1993.

Clinical lecturer posts under threat

EDITOR,—Should anyone decide to scrap secondary school education, one effect would be to make it near impossible for anyone to go to university. To axe clinical lecturer posts, as discussed in the alarming January 1997 editorial in the journal,¹ would be an equally insane act, and would at a stroke virtually abolish recruitment into academic medicine.

The problem is that it is near impossible to get clinical lecturers to perform world class research (a) early in their research careers and (b) while needing to continue with clinical training. The situation is bizarre: it is like expecting an 11 year old to play cricket for England. The poor child needs to get further experience in the sport, as well as needing to continue with a general education. The solution is quite simply to forget about 11 year olds as being eligible for the national team, and to concentrate on their further development. By agreement with the Higher Education Funding Council for England (HEFCE), who make the rules, clinical lecturers should be excluded from the quinquennial research assessment exercise.

In commenting on the *Archives* editorial, an editorial in the *Lancet* has summed up the situation as 'a research culture that asks too much'.² Radical alternatives have been proposed, but are unlikely to work. One option, for which there is considerable pressure, is to make clinical lecturers wholly supernumerary to the clinical service, for approximately three years—sufficient time for a PhD. They would be engaged 100% of the time on research, and would have to spend additional years undergoing clinical training. However such an arrangement would require aspiring academics to take a very large salary drop, hardly a practical way to tackle the existing combined difficulties of recruiting into paediatrics

and into academic medicine. Another option would be for NHS trusts to take over the funding of HEFCE funded clinical lecturer posts, but this seems little more than a pipe dream given the existing difficulties of getting NHS trusts to fund ordinary training grade posts.

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- 1 Anonymous. UK paediatric clinical research under threat. *Arch Dis Child* 1997;76:1-5.
- 2 Anonymous. A research culture that asks too much. *Lancet* 1997;349:515.

Fashion victim: infective endocarditis after nasal piercing

EDITOR,—We report a case of infective endocarditis occurring after nasal piercing.

A previously well 14 year old girl presented three weeks after nasal piercing and metal stud insertion. After insertion she developed progressive 'flu' like symptoms with fever, myalgia, headache, nausea, and vomiting. Examination revealed a normally developed girl who was pyrexial (39.4°C) and uncomfortable, with suprapubic and epigastric tenderness.

Examination of her cardiovascular system demonstrated no abnormality.

Investigations showed a neutrophil leucocytosis, a raised C reactive protein and erythrocyte sedimentation rate. Blood and urine cultures were taken. Because of her persisting abdominal pain a laparoscopy and appendicectomy were performed and showed no abnormalities.

Despite treatment with flucloxacillin, cefotaxime, and metronidazole she proceeded to rigor. Nasal swabs and blood and urine cultures repeatedly grew *Staphylococcus aureus* despite appropriate antibiotic treatment.

Subsequently she developed signs of focal septic embolisation and an echocardiogram was performed, revealing a large vegetation on the anterior leaflet of the mitral valve with no evidence of valvular incompetence. The size of the vegetation¹ and the blood culture results indicating the likely infecting organism to be *S aureus*. A diagnosis of infective endocarditis was made and she was treated with high dose flucloxacillin and vancomycin. Subsequently she developed clinical signs of mitral regurgitation confirmed on echocardiography. She developed an allergic rash to flucloxacillin and treatment was changed to vancomycin alone for the last three weeks of her six week treatment. The mitral valve vegetation decreased in size after treatment but she was left with minor degree of mitral incompetence evident clinically and echardiographically.

Infective endocarditis due to *S aureus* in the absence of an underlying cardiac defect is uncommon.² In vitro studies have demonstrated the ability of *S aureus* to induce a tissue factor promoting adherence to valve endothelium, altering host responses and partially protecting from antimicrobial treatment resulting in a prolonged bacteraemia.

Initial treatment of infective endocarditis comprises intravenous benzylpenicillin and gentamicin. If staphylococcal infection is confirmed then flucloxacillin is added and treatment continued for six weeks, using vancomycin in cases of penicillin allergy.²

Nasal carriage of *S aureus* renders piercing of this area more likely to result in infective

endocarditis, however piercing of any mucous membrane may result in bacteraemia and infective endocarditis.

We report for the first time infective endocarditis arising after nasal piercing in a person with a structurally normal heart, and emphasise the importance in excluding this diagnosis in patients with a persisting pyrexia after recent invasive adornment.

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- 1 Saiman L, Prince A, Gersony WM. Pediatric infective endocarditis in the modern era. *J Pediatr* 1993;122:847-53.
- 2 Watanakunakorn C. Staphylococcus aureus endocarditis at a community teaching hospital, 1980 to 1991. An analysis of 106 cases. *Arch Intern Med* 1994;154:2330-5.

Needle injuries as a cause of non-accidental injury

EDITOR,—Carers of children need to be aware of the wide range of possible non-accidental injuries so that they may be recognised and managed appropriately. The insertion of sharp needles into body cavities or soft tissues is an uncommon form of child abuse and we wish to report three cases presenting to us during a four year period.

Case 1—A 4 week old infant of Asian parents died before being admitted to the emergency department. A necropsy confirmed the cause of death as bacterial pneumonia. Examination of the scalp revealed a healed 1 cm laceration posterior to the anterior fontanelle. Tracts led to three broken sewing needles embedded within the occipital lobes.

Case 2—A female sibling to case 1 had previously presented at the emergency department with bruises, abrasions, and burns. A skeletal survey demonstrated four needles in the soft tissues of the head, neck, and forearm. These were removed surgically and found to be sewing needles.

Case 3—A baby boy was born at 25 weeks' gestation after a concealed pregnancy in a young African mother. An abdominal radiograph at 3 weeks demonstrated two linear opaque objects in the abdomen. Repeat radiography after 10 days showed two further similar objects in the pelvis. At laparotomy four needles were removed.

The insertion of sharp needles through the skin or mucous membranes of young children is a rare form of non-accidental injury with only seven other cases having been reported.¹⁻⁴ We are not aware that this is a recognised part of African or Indian culture and this must be considered and managed as child abuse.

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- 1 Stone RK, Harawitz A, San Filippo A, Gromisch DS. Needle perforation of the liver in an abused infant. *Clin Pediatr (Phila)* 1976;15:958-9.

- 2 Swadia ND, Thakore AB, Patel BR, Bhavani SS. Unusual form of child abuse presenting as an acute abdomen. *Br J Surg* 1981;68:668.
- 3 Bhaskaran CK. Insertion of sewing needle as a form of child abuse. *Arch Dis Child* 1978;53:968.
- 4 Ameli NO, Alimohammadi A. Attempted infanticide by insertion of sewing needles through fontanelles. Report of two cases. *J Neurosurg* 1970;33:721-3.

Acknowledgment and authors

EDITOR,—I share Dr Moncrieff's¹ irritation at the number of requests for information which I receive and replying to the first request for information often invites further trouble. I agree with him that researchers should do their own research.

I also agree with him about authorship but I would point out that in a department which supports a serious number of research fellows, the head of department is quite likely to have had the idea and written the grant application, as well as having a substantial hand in writing the abstracts and reports. This is hardly guest authorship and five or six research fellows can easily generate 10 to 20 papers in a year if they are coming towards the end of their period of research.

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- 1 Moncrieff M. Acknowledgments and authors. *Arch Dis Child* 1996;75:366.

Height and weight achievement in cleft lip and palate

EDITOR,—We were interested to read the recent article by Lee *et al.*¹ Of course, it is not surprising that children with cleft lip and palate have growth failure in infancy, especially with their feeding difficulties. However, follow up in this study was only to a mean of 25.5 months.¹ Growth failure is common in children with cleft lip and palate and is related to the type of cleft, as well as age and sex.² Some children with cleft palate and especially those combined with an additional midline cleft lip may be part of holoprosencephaly complex and have hypothalamic pituitary deficiency, there being no other dysmorphic features.³ However, growth hormone secretion has little influence on growth in early childhood.⁴ Growth may be normal in children with pituitary deficiency until approximately 2 years of age. In addition, children with midline defects may have an evolving endocrinopathy with pituitary deficiencies only appearing in later childhood.⁵ Moreover, growth hormone deficiency has been described as 40 times more common in children with cleft lip and palate.⁶ We believe that although early catch-up growth is undoubtedly important, growth of children with cleft palate should continue to be monitored throughout childhood.

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- 1 Lee J, Nunn J, Wright C. Height and weight achievement in cleft lip and palate. *Arch Dis Child* 1997;**76**:70-2.
- 2 Bowers EJ, Mayro RF, Whitaker LA, Pasquariello PS, LaRossa D, Randall P. General body growth in children with cleft palate and related disorders: age differences. *Am J Phys Anthropol* 1988;**75**:503-15.
- 3 Roitman A, Laron Z. Hypothalamo-pituitary hormone insufficiency associated with cleft lip palate. *Arch Dis Child* 1978;**53**:952-5.
- 4 Karlberg J. A biologically-oriented mathematical model (ICP) for human growth. *Acta Paediatr Scand Suppl* 1989;**350**:70-94.
- 5 Stanhope R, Preece MA, Brook C. Hypoplastic optic nerves and pituitary dysfunction. *Arch Dis Child* 1984;**59**:111-4.
- 6 Rudman D, Davis T, Priest JH, Patterson JH, Kutner MH, Heymsfield SB, Bethel RA. Prevalence of growth hormone deficiency in

children with cleft lip palate. *J Pediatr* 1978;**93**: 378-82.

Aetiology of asthma

EDITOR,—Austin and Russell suggest that mobility of families may be more important in the aetiology of asthma than exposure to any one individual allergen or pollutant.¹ This ties in with the finding of Hughes and Baumer,² except that they failed to ask whether there is an emotional component to this. Most of us know that moving house is second only to divorce as a traumatic event in life, and considering the greater attachment that children have to their home (they after all

spend more time there than adults as a rule), it is no surprise that this could be the mechanism of the effect these authors describe. In some cases the move may be due to family break up.

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- 1 Austin JB, Russell G. Wheeze, cough, atopy, and indoor environment in the Scottish Highlands. *Arch Dis Child* 1997;**76**:22-6.
- 2 Hughes CH, Baumer JH. Moving house: a risk factor for the development of childhood asthma? *BMJ* 1995;**311**:1069-70.

Notice

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