LETTERS TO THE EDITOR

Fragile X syndrome

EDITOR,—Our experience in a special school in Newcastle upon Tyne lends support to the proposal by Slaney *et al* to screen for fragile X syndrome.¹ Many individuals with special educational needs have not had recent investigation. In a preliminary survey of records for the year 1992/3, of the 58 individuals (44 male and 14 female) who had statutory reassessment of special educational needs in Newcastle upon Tyne, 48 were considered to have mild learning difficulties, 10 severe. All those having severe learning difficulties had been fully investigated by this stage. Among those with mild learning difficulties, one individual was already known to have fragile X syndrome but in 41/48 there was neither known diagnosis nor record of genetic investigations. Over half of these children, 21/41, had a family history of learning difficulties.

On the basis of these findings, chromosome analysis and molecular investigations for the fragile X syndrome was offered at one special school as a part of the medical review undertaken for the statutory reassessment of special educational needs during the period September 1993–July 1994. None of the 34 children, aged 13–14 years, had a recognised diagnosis, although two had had previous genetic investigations. There were 32 pupils with no known diagnosis to whom testing was offered, after full discussion of the details and implications of such investigations with each family. Blood samples were obtained from three girls and 23 boys: the remaining six pupils declined testing on account of fear of venepuncture. One boy with fragile X syndrome, one boy with Klinefelter's syndrome 47,XXY, and one chromosomal deletion 46,XY del (18) (q22?2) were detected. A satellite Y chromosome was observed in one boy, which was thought to be a normal variant.

The families were referred for specialist genetic counselling. In the three cases where a diagnosis was given, parents were relieved to have an explanation for their child's learning difficulty. Liaison with educational and community provision was facilitated. Thus, in three out of 26 children tested, a previously unrecognised diagnosis was made. Not only did we detect previously unrecognised fragile X syndrome but, with the inclusion of cytogenetic analysis as recommended in screening of populations selected on the basis of learning difficulties (unlike the restricted study by Slaney *et al*), also detected other important abnormalities. In their study, counselling was retrospective. In practice, we found that the opportunity to counsel families before testing could easily assimilated by a school doctor within the procedure required for medical input associated with the Education Act 1981, when parental concerns about the aetiology and implications of their child's problems often need to be readdressed. We believe that the offer of genetic screening in this way is feasible, within both the existing community health and regional genetic service resources, and welcomed by those involved. The findings of our study would support an argument to retain medical input into the 'transitional review' (Education Act 1993) of

children who have statements of special educational needs, at least until the cohort of younger children, who are more likely to have been investigated, is reached.

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1 Slaney SF, Wilkie AOM, Hirst MC, *et al*. DNA testing for fragile X syndrome in schools for learning difficulties. *Arch Dis Child* 1995; 72: 33–7.

Do children with hepatic cirrhosis complicating cystic fibrosis receive too much pancreatic enzyme?

EDITOR,—Colonic strictures^{1 2} and thickening of the bowel³ have recently been recognised in children with cystic fibrosis receiving high doses of pancreatic enzymes. We are concerned that some children with the complication of hepatic cirrhosis in cystic fibrosis are receiving excessive doses of pancreatic enzyme supplements in an attempt to control their steatorrhoea.

In the past 4.5 years we have assessed 13 children with cystic fibrosis complicated by hepatic cirrhosis for liver transplantation. Twelve were malnourished with median body mass index 16.5 (range 13.4–23.3) and upper arm circumference measurements all under the 5th centile. Seven gave a history of steatorrhoea and six required regular laxatives to prevent distal intestinal obstruction. There was wide variation in the daily intake of pancreatic enzymes (table) but the mean for the group was 16 653 units/kg/day of lipase and 544 units/kg/day of protease. In a recent study Sweeney *et al* found that a daily protease intake of more than 265 units/kg was a risk factor for bowel wall thickening and that the risk rose 10 times if laxatives were taken in addition.³ Six of the children we report here had high daily intakes of protease (410–3688 units/kg/day), five received high strength pancreatic enzyme preparations, and three of these also required regular laxatives.

We did not assess the bowel wall thickness in these children, but, when investigated for abdominal pain by abdominal computed tomography, patient 6 was found to have 3 mm thickening of the walls of both the small and large intestine. Patient 5 developed a haemorrhagic colitis which resolved when his pancreatic enzyme intake was reduced. Both

these patients had received high strength enzyme preparations.

Nine of these children have now received liver grafts and their daily enzyme intake is greatly reduced (table). The average daily protease intake has fallen by 56% and the daily lipase intake by 61%. In spite of this reduction in pancreatic enzymes fat absorption has improved and none of the children now have steatorrhoea. All except one now receive normal strength pancreatic enzyme preparations.

In children with cystic fibrosis and hepatic cirrhosis steatorrhoea may be a symptom of both the hepatic disease and pancreatic insufficiency. There is little benefit to be gained from increasing the enzyme doses beyond the recommended amounts of 265 units/kg/day of protease³ and doing so may be associated with considerable risk of gut complications.

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- 1 Smyth RL, van-Velzen D, Smyth AR, Lloyd DA, Heaf DF. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. *Lancet* 1994; 343: 85–6.
- 2 Taylor CJ. Colonic strictures in cystic fibrosis. *Lancet* 1994; 343: 615–6.
- 3 Sweeney EJM, Oades PJ, Buchdahl R, Rosenthal M, Bush A. Relation of thickening of colon wall to pancreatic-enzyme treatment in cystic fibrosis. *Lancet* 1995; 345: 752–6.

Monoclonal IgA gammopathy in a well infant

EDITOR,—We report on an unusual case of monoclonal gammopathy in an infant with no evidence of an underlying disorder. A 15 month old girl was referred because of raised serum IgA concentration (3.50 g/l) and λ IgA paraprotein. The indication for the investigation had been recurrent upper respiratory tract infections: five to six per year since attendance at day school. Her perinatal and previous medical history were unremarkable, with no suggestion of immunodeficiency, serious infections, or malignant disorder.

Her physical examination was normal (weight: 25th centile, height: 50th centile). On follow up at 20 months she had remained well and had developed varicella at 19 months with no complications, suggestive of intact T cell function.

The λ IgA paraprotein was confirmed at 18 and 20 months by serum electrophoresis and immunofixation of the α and λ chain (1–2 g/l on both occasions). Investigations showed a haemoglobin concentration of 120 g/l, white

Details of children studied

Patient No	Sex	Age (years)	Before transplant			After transplant		
			Lipase (units/kg/day)	Protease (units/kg/day)	Steatorrhoea	Lipase (units/kg/day)	Protease (units/kg/day)	Steatorrhoea
1	F	14.3	7385	194	—	4634	122	—
2	M	11.5	7385	194	—	5538	145	—
3	M	14.0	4900	129	—	4000	264	—
4	F	8.4	22 727	425	+	5533	145	—
5	M	5.8	73 765	3688	+	15 238	400	—
6	F	16.4	19 286	360	+	8378	545	—
7	M	19.0	5263	98	+	2631	49	—
8	F	12.9	17 931	471	+			
9	F	13.4	5000	131	+			
10	F	15.8	8000	210	—			
11	F	13.0	6824	179	—			
12	M	10.5	22 400	588	—			
13	M	11.4	15 625	410	+			
Mean			16 653	544		6565	239	

cell count $8.6 \times 10^9/l$, serum IgA 3.15 g/l (18 months) and 2.65 g/l (20 months), antinuclear antibody titre 1:80. There was no IgG or IgM to Epstein-Barr or cytomegalovirus, no urinary light chains, a normal number and proportion of T and B cells, and normal whole blood proliferation to mitogen. Chest radiography and abdominal ultrasound were normal.

The pathogenesis of the paraprotein in our patient is unclear. The adult entity of benign monoclonal gammopathy has not been described in the paediatric population, and previous reports of monoclonal gammopathy in children have consistently associated such gammopathies with serious disease. Additionally, there are no reports of a monoclonal gammopathy as an incidental finding in an otherwise healthy child. In a 10 year review of 4000 highly selected children, 155 (3.9%) were found to have paraproteinaemia.¹ These children were suffering from primary and secondary immunodeficiency, malignancy, autoimmune disease, asthma, serious infection, and aplastic anaemia. In contrast, none of the 120 healthy paediatric controls used in this study (donors for bone marrow transplantation) had paraproteins identified.

Our case is also unusual in that her paraprotein is of the IgA type, as there are only four reports of IgA monoclonal gammopathy in the paediatric population. Two of these children had a severe combined immunodeficiency,¹ one had an unspecified malignancy,¹ and the other an unspecified chromosomal disorder.² Of the 155 children with monoclonal gammopathy in the 10 year study previously referred to, no IgA paraproteins were identified.

It is possible this abnormal production of IgA is related to a subtle T cell dysregulation. Such dysregulation of T cells has been implicated in another paediatric disorder associated with raised IgA, IgA nephropathy. In this condition abnormal T cell function and signalling is thought to be responsible for the aberrant B cell activity, where respiratory pathogens or common environmental antigens stimulate excessive production of IgA, in the presence of increased helped T cell activity³ and decreased suppressor T cell numbers.⁴

We are following up this infant, with much interest, for any alteration in her IgA paraprotein or immune function, and for the possible development of disease.

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- 1 Gerritsen E, Vossen J, Van Tol M, Jol Van Der Zijde C, Van Der Weijden-Ragas R, Radl J. Monoclonal gammopathies in children. *J Clin Immunol* 1989; 9: 296-305.
- 2 Danon F, Seligmann M. Serum monoclonal immunoglobulins in children. *Arch Dis Child* 1973; 48: 207-11.
- 3 Lai KN, Ho RTH, Lai W, Chan CHS, Li PKT. Increase of both circulating Th1 and Th2 lymphocyte subsets in IgA nephropathy. *Clin Exp Immunol* 1994; 96: 116-21.
- 4 Sakai H, Miyazaki M, Endoh M, Nomoto Y. Increase of IgA specific switch T cells in patients with IgA nephropathy. *Clin Exp Immunol* 1989; 78: 378-82.

Long term follow up to determine the prognostic value of imaging after urinary tract infections

EDITOR,—I read with interest the two papers by Merrick *et al* on the prognostic value of imaging in children with urinary tract infections (UTIs).^{1 2}

It would be helpful if the authors could tell us what proportion of the initial cohort of children with UTI, during 1975 to 1990, underwent initial imaging and later follow up imaging. We have shown that in an area of very good standard for general practice only a small minority of children with UTI had been referred for radiological investigations.³ The fact that this 'denominator' figure is not provided casts doubt on how representative their results are. The true natural history and prognostic value of different radiological abnormalities, further UTIs, etc, can only be determined on a large scale, prospective, hospital and community based study.

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- 1 Merrick MV, Notghi A, Chalmers N, Wilkinson AG, Uttley WS. Long term follow up to determine the prognostic value of imaging after urinary tract infections. Part 1: reflux. *Arch Dis Child* 1995; 72: 388-92.
- 2 Merrick MV, Notghi A, Chalmers N, Wilkinson AG, Uttley WS. Long term follow up to determine the prognostic value of imaging after urinary tract infections. Part 2: scarring. *Arch Dis Child* 1995; 72: 393-6.
- 3 Jadresic L, Cartwright K, Cowie N, Witcombe B, Stevens D. Investigation of urinary tract infection in childhood. *BMJ* 1993; 307: 761-4.

EDITOR,—Merrick *et al* recommend micturating cystourethrography (MCU) be restricted to females who have not achieved bladder control.¹ Based on their data that suggest vesicoureteric reflux (VUR) is not a risk factor for progressive renal damage in boys less than 1 year of age, the authors excluded males.² As there is a possibility of type II statistical error with a sample size of only 205 children, basing evaluation strategies on such a small sample size warrants careful scrutiny.

The risk of renal damage due to pyelonephritis is considered greatest in the first few years of life.^{3 4} The most common indication for antibiotic prophylaxis to prevent pyelonephritis in infancy is the presence of VUR. We are concerned that the recommendation by Merrick *et al* might restrict the prescription of antibiotic prophylaxis in infant boys and thereby increase the risk of potentially avoidable episodes of pyelonephritis with attendant renal damage.

The indications for MCU and antibiotic prophylaxis are evolving. Since pyelonephritis and renal scarring can develop in infants who do not have VUR, perhaps an episode of pyelonephritis in infancy justifies antibiotic prophylaxis, regardless of the presence or absence of VUR.

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- 2 Merrick MV, Notghi A, Chalmers N, Wilkinson AG, Uttley WS. Long term follow up to determine the prognostic value of imaging after urinary tract infections. Part 2: scarring. *Arch Dis Child* 1995; 72: 393-6.

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- 4 Jacobson SH, Eklöf O, Eriksson CG, Lins LE, Tidgren B, Winberg J. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow-up. *BMJ* 1989; 299: 703-6.

Dr Uttley comments:

I would like to thank Dr Jadresic for her interest in the two papers by Merrick *et al*. The vast majority of children referred to the Edinburgh hospitals with UTI, either acutely or after treatment, would have undergone imaging of their urinary tract in some form. This has been standard hospital practice and teaching throughout the period of the review. Indeed the need for investigation after a single UTI has been the formal recommendation to undergraduates, postgraduates, and general practitioners throughout. Needless to say we have no information regarding children not referred by their general practitioners and we agree with Dr Jadresic that some patients may not have been referred. Large scale prospective hospital and community based studies are indeed required, and perhaps the impending era of national guidelines and audit will help to answer these thorny questions in the future.

With regard to the letter of Drs Robson and Kelley we do not recommend MCU to be restricted solely to females who have not achieved bladder control. Although it has not emerged as an independent variable for progression of renal disease in young boys, an MCU is clearly an important part of their work-up, particularly after febrile UTI and where abnormalities other than VUR could well be present. However, we do feel the indirect voiding study to be a more sensitive, and a substantially less invasive and traumatic way of assessing the presence or absence of VUR in all children who have achieved bladder control and that this now should be seen as the initial test for reflux.

The data presented reaffirm the importance of reflux as a risk factor for progressive renal damage generally and particularly so when associated with infection.

The fact that VUR did not come out as a risk factor for progressive renal damage in boys under 1 year of age, must be due in part to the fact that this particularly vulnerable group did in general receive appropriate antibiotic prophylaxis. A further issue is that renal damage identified at presentation in these young males will represent renal dysplasia, sometimes profound, and for which evidence of progression was difficult to elucidate.

Overall it would be a pity if debate over appropriate investigation was to overshadow the importance of appropriate clinical follow up and antibiotic treatment and prophylaxis and to that extent we are in total agreement with the final paragraph of Drs Robson and Kelley's letter.

Non-accidental fracture occurring in hospital

EDITOR,—Recent reports have implied that fractures occurring to infants in hospital are due to natural causes, whereas those occurring out of hospital may be due to non-accidental injury. The inference is that fractures occurring within a place of safety cannot be non-accidental. We report a case of a child who sustained a non-accidental fracture of the left radius and ulnar while in hospital.