LETTERS TO THE EDITOR

Pancreatic enzyme supplementation in cystic fibrosis

SIR,—Pharmacological advances in pancreatic enzyme supplementation have produced a dramatic improvement in nutritional status of cystic fibrosis patients, contributing to ever improving life expectancy.[1] Compliance is sometimes problematic due to the large number of capsules required by some patients. For these individuals the introduction of higher strength enteric coated microsphere preparations (for example Creon 25000, Duphar) is particularly welcome. One group which has not been previously considered where improved acceptability is concerned is the younger child. In our clinic 76% of children under 5 years and 29% of children aged 5–10 years are unable to swallow conventional enteric coated microsphere preparations. To overcome this problem capsules are opened and the free granules taken with food.

We have performed an open, prospectively randomised, crossover study to compare the preference of a group of cystic fibrosis patients for two different presentations of enteric coated microspheres of pancreatin (Creon): the conventional gelatin capsule and a foil sachet. Patients who had been taking Creon capsules for a minimum of four weeks were invited to participate. Each child was randomised to receive either capsules or sachets for the initial six week block after which they crossed over to the second preparation. On entry to the study and at the six and 12 week intervals parents completed a questionnaire detailing their response to each preparation and in the final assessment stated their preference.

Seventeen patients were recruited, 11 girls and six boys (mean age 4·1 years, range 4 months–12 years). Their average daily intake of Creon was 30 capsules (range 10–45). In the final assessment 10 pateints preferred the foil wrapped preparation, five preferred the capsules, and two expressed no preference. Comments made about the preparations highlighted flaws that the practitioner may overlook. Most found conventional capsules too large to swallow and found the quantities of medication required excessive. Problems were also encountered with the disposal of empty capsule shells and the tendency of capsules to dissolve when wet. The consensus (10 of 17 patients) was that sachets were more easily manipulated and easier to dispose of.

Cystic fibrosis management demands of the child and his family a lifetime of rigorous treatment schedules. Pancreatic supplements are a constant companion and compliance and ease of administration must be priorities if treatment is to succeed. While the ultimate objective must be for children to learn to swallow capsules whole, for the substantial group who through age or idiosyncrasy cannot achieve this, a non-capsule preparation offers several advantages in administration.

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Clinical relevance of raised soluble serum interleukin-2 receptor concentrations in cystic fibrosis

SIR,—Dagli *et al* reported raised soluble serum interleukin-2 receptor (sIL-2R) concentrations in patients with cystic fibrosis.[1] Our own results—using an immunoenzymometric assay (Immunotech, France) with a precision comparable with the assay used by the authors—also showed significantly increased sIL-2R concentrations (see table) in 56 patients with cystic fibrosis (age 0·75–28 years) compared with 26 healthy non-atopic patients (age 1–27 years). A breakdown of these data into the same age groups as Dagli *et al* showed similar results (see table). In addition, patients with cystic fibrosis demonstrated significantly increased blood lymphocyte numbers compared with the controls with a mean (SD) 2590 (725) cells$\times 10^6$/l *v* 1740 (347) cells$\times 10^6$/l ($p=0·0005$), which were not related to the sIL-2R concentrations. Furthermore, no correlations with accompanying allergic diseases, immunoglobulins (A, E, G, M) and the Shwachman–Kulczycki score, pulmonary function, and blood gases were observed. However, in contrast to Dagli *et al*, we did not see differences between patients with cystic fibrosis with and without acute infections. To emphasise our results, no changes in the sIL-2R concentrations were observed in eight patients with acute bacterial infections before and after 2–3 weeks of antibiotic treatment: mean (SD) 3973 (2918·6) *v* 3625 (1966·0) pg/ml.

One reason for differences might be that our patients presented with bacterial infections only. Dagli *et al* did not clearly define 'acute infection'—that is bacterial or viral. It is well known that viral infections result in increased sIL-2R concentrations. In addition, in patients with cystic fibrosis with *Pseudomonas aeruginosa* colonisation lymphocyte hyporesponsiveness has been noted,[2] which is characterised by decreased T cell IL-2 production and has prevented IL-2R expression on lymphocytes. Like Dagli *et al* we were not able to demonstrate different sIL-2R concentrations in patients with cystic fibrosis with and without *P aeruginosa* colonisation. As lymphocytes are the major source of macrophage activating factors increased sIL-2R concentrations—as markers of lymphocyte activation[3]—should result in raised macrophage activation. But in cystic fibrosis lymphocyte as well as macrophage hyporesponsiveness have been reported.[4] Consistent with Dagli *et al* we thus confirm increased sIL-2R concentrations in patients with cystic fibrosis. In the light of a lack of any correlation between sIL-2R concentrations and clinical parameters and with regard to the above comments, raised sIL-2R concentrations should be seen in a more critical light. As Dagli *et al* hypothesis, raised sIL-2R concentrations could be the first indicator of the developing inflammatory process, which increases even more during acute infections.

Mean (SD) sIL-2R concentrations in pg/ml in patients with cystic fibrosis and controls according to age

Age group (years)	*Cystic fibrosis patients*	*Controls*	*p Value**
0–28	4410 (2140·8) [n=56]	2556 (991·2) [n=26]	0·0001
0–3·9	6359 (3336·5) [n=7]	3688 (155·0) [n=4]	0·058
4–7·9	4675 (1997·4) [n=8]	2142 (954·0) [n=6]	0·0095
8–11·9	4141 (1993·7) [n=8]	2449 (903·8) [n=6]	0·0525
12–28	4007 (1732·5) [n=33]	2415 (1029·4) [n=10]	0·0042

*p Value by Kruskal-Wallis test.

There is a need for further studies to confirm that sIL-2R concentrations have a predictive value for the clinical outcome in cystic fibrosis. We agree with the authors as to the need for anti-inflammatory treatments in cystic fibrosis but only when substantiated by evidence of increased granulocyte activity (unpublished observations).

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The value of proximal small intestinal biopsy in the differential diagnosis of chronic diarrhoea

SIR,—We would like to respond to the comment of Bell and Marcovitch concerning our paper on the value of small intestinal biopsy in chronic diarrhoea.[1 2]

The apparent controversy in our paper is the recommendation that a child with chronic diarrhoea of more than 14 days' duration should have a small intestinal biopsy in order to expedite diagnosis and management. This philosophy is based on our experience as both a secondary referral centre in the east end of London, and as a tertiary referral centre receiving cases from home and abroad.

Bell and Marcovitch comment that referral of a child with two weeks of diarrhoea is extremely unusual in their experience, and imply that this is due to GP action in placing children on cows' milk free diets. In fact, it is probable that different areas of the country with different work loads/referral patterns require different courses of action. It is not disputed that small intestinal biopsy is safe in experienced hands and is required to diagnose coeliac disease and other permanent states, such as microvillous atrophy; what is disputed is the clinical selection of the patients and the timing of the biopsy.

Let us strongly say that *we are not* recommending that the diagnosis of toddler's diarrhoea requires a small intestinal biopsy. We had hoped that it was clearly stated in the paper that the differential diagnoses in these cases included coeliac disease and cows' milk sensitive enteropathy, and the purpose of the biopsy (as in all cases) was to establish the presence or absence of an enteropathy. Concerning coeliac disease—many of the cases are

referred from GPs and general paediatricians requesting us to investigate the suspected diagnosis of coeliac disease. Coeliac disease has a broad clinical spectrum, and, as Bell and Marcovitch state, antigliadin, antireticulin, and antiendomesial antibody tests are not perfect, although they are used as screening tests in epidemiological surveys. Therefore, on an individual patient basis, we choose to perform a small intestinal biopsy as the most efficient means of investigation. Clearly there is a difference between children who have a permanent disorder and those with a temporary condition such as cows' milk sensitive enteropathy. In centres where small intestinal biopsy is not available a therapeutic trial of milk elimination may be in order, but this will lead to the over diagnosis of the condition and overuse of milk substitutes.

It was certainly our aim to add to the body of knowledge on chronic diarrhoeal disease in childhood, and trust that other centres, both national and international, would view our experience in the light of the context of their own work situation.

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Positive hepatitis serologies with treatment for Kawasaki syndrome

SIR,—Intravenous immune globulin (IVIG) is currently the treatment of choice for Kawasaki syndrome in that it shortens the duration of symptoms and lowers the incidence of coronary artery aneurysms associated with this disorder. We describe a 3 year old boy who had hepatomegaly and raised hepatic transaminases associated with Kawasaki syndrome and transiently developed false positive serologies to hepatitis B and hepatitis C after treatment with IVIG.

Case report

Seven days before hospitalisation, this 3 year old boy developed fever, abdominal pain, and vomiting. During the next five days he developed a generalised maculopapular skin eruption sparing the palms and soles, diffuse tender cervical adenopathy, oedema of the hands and feet, non-purulent conjunctivitis, right upper quadrant abdominal tenderness with mild hepatomegaly, and a systolic ejection murmur. Serum alanine aminotransferase was 133 IU/l (normal 6–65), serum aspartate aminotransferase was 191 IU/L (normal 7–40), and serum lactate dehydrogenase was 775 IU/l (normal 232–619). Prothrombin time, alkaline phosphatase, and bilirubin values were normal, as was an abdominal sonogram. Past and family history were negative; he had received no transfusions nor been exposed to infectious hepatitis. A diagnosis of Kawasaki syndrome was made and IVIG administered. The child's symptoms resolved within 48 hours but serum transaminases remained raised. On the third hospital day, alanine aminotransferase was 164 IU/l and aspartate aminotransferase was 191 IU/l. Alkaline phosphatase and bilirubin values remained normal. Serum was obtained for measurement of hepatitis serologies. Antibodies to hepatitis C virus were detected (HCV Ab ELISA, Ortho Diagnostics), as were antibodies to core and surface antigens of hepatitis B virus. Clinically the child did well and was discharged from the hospital at the conclusion of IVIG treatment. In the year since hospital discharge he has remained asymptomatic and his serum transaminases have remained normal. Three months after discharge, antibodies to hepatitis C virus, and core and surface antigens of hepatitis B virus were detectable. However, at six, nine, and 12 months after discharge, all antibody studies were negative.

The history and serological findings in this case suggest antibodies to hepatitis B and C viruses were passively transferred by infusion of IVIG. The disappearance of detectable antibody to both viruses six months after the infusion is consistent with the 30 day half life of IVIG.[1] Passive transfer of antibody to hepatitis B virus has been described after infusions of IVIG.[2] Similarly, passive transfer of antibody to human immunodeficiency virus has been described after infusions of hepatitis B immune globulin,[3] tetanus immune globulin,[4] and IVIG.[2] A recent study indicates commercial preparations of immune globulin contain high titres of antibody to hepatitis C virus.[5]

The increases in serum transaminases in this case were likely to have been due to Kawasaki disease. Increases in serum transaminase and bilirubin values occur frequently in Kawasaki disease and correspond microscopically to cholangitis, periductitis, vasculitis, and portal perivasculitis.[6]

IVIG has become an important therapeutic agent with ever increasing uses. This patient demonstrates that infusion of IVIG may induce false positive serological and immunohaematological tests, and therefore the results of such studies must be interpreted with caution.

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Recurrent parotitis

SIR,—Cohen *et al* report 11 children with recurrent parotitis.[1] They state that immunological factors may be involved in the pathogenesis of this condition, although in general the immunological abnormalities described have been fairly subtle.[2 3] We report a recent case which supports the theory that autoimmune mechanisms are important.

We have recently seen an 11 year old girl who presented with a 12 month history of four episodes of right sided parotid swelling, without redness or tenderness, but associated with low grade fever. There was a history of recurrent, unexplained fevers from infancy until 7 years of age. She also gave a history of dry, sore eyes since infancy, recently diagnosed by an ophthalmologist as being allergic conjunctivitis. She had a chronic non-productive cough for four years. She had had recurrent ear infections from 5 years of age, for which adenotonsillectomy was performed and ventilating tubes inserted, and had a chronic non-productive cough since age 7 years.

Sialogram showed right sided sialectasia with a normal left parotid duct. Chest radiography was normal. Full blood count was normal, with no eosinophilia. Serum immunoglobulin concentrations that were performed on two occasions showed serum IgG 3·2 and 2·4 g/l (normal 6·5–15·0), serum IgA 0·07 and 0·09 g/l (normal 0·5–5·0), and serum IgM 0·13 and 0·23 g/l (normal 0·3–2·5). HIV antibodies were not detected. T cell numbers were normal but B cells were raised (CD19 27%, normal 1–15%). A diagnosis of common variable immunodeficiency (late onset hypogammaglobulinaemia) was made, and the patient was started on intravenous immunoglobulin replacement treatment.

It is well recognised that autoimmune phenomena may occur in common variable immunodeficiency, including non-suppurative parotitis. Conley *et al* described parotitis in two of eight children with common variable immunodeficiency, although did not state whether or not it was recurrent.[4] One of the two patients described by Friis *et al* had IgA deficiency, gluten enteropathy and high titres of antinuclear antibodies, all features of evolving common variable immunodeficiency.[3] As long ago as 1960, Mosbech and Kristensen felt that autoimmunity might play an important part in the pathogenesis of recurrent parotitis.[5] We believe the case we report here supports that theory. Our case shows the importance of measuring serum immunoglobulin concentrations on children with recurrent parotitis.

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