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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1 Elborn JS, Shale DJ, Britton JR. Cystic fibrosis: current survival and population estimates to the year 2000. *Thorax* 1991;**46**:881–5.

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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1 Dagli E, Warner JA, Besley CR, Warner JO. Raised serum soluble interleukin-2 receptor concentrations in cystic fibrosis patients with and without evidence of lung disease. *Arch Dis Child* 1992;**67**:479–81.
2 Sorensen RV, Stern RC, Polmar SH. Lymphocyte responsiveness to Pseudomonas aeruginosa in cystic fibrosis: relationship to status of pulmonary disease in sibling pairs. *J Pediatr* 1978;**93**:201–5.
3 Nelson DL, Kurman CC, Fritz ME, Boutin B, Rubin LA. Production of soluble and cellular interleukin-2 receptors by cord blood mononulcear cells following in vitro activation. *Pediatr Res* 1986;**20**:136–9.
4 Chartrand SA, Marks MI. Pulmonary infections in cystic fibrosis: pathogenesis and therapy. In: Pennington JE, ed. *Respiratory infections: diagnosis and management*. New York: Raven Press, 1988:276–97.

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