LETTERS TO THE EDITOR

N1303K mutation and diabetes mellitus in cystic fibrosis

EDITOR,—In the last two decades, 28 patients with cystic fibrosis (19 girls, nine boys) out of the 313 (160 girls, 153 boys) attending the Genova Cystic Fibrosis Centre developed diabetes mellitus. In all cases the diagnosis of diabetes was based on the National Diabetes Data Group criteria and patients were treated with insulin or oral hypoglycaemic agents.

In the 28 patients with diabetes two different groups (A and B) could be identified.

Patients in group A (12/28 patients) were characterised by earlier onset diabetes (14.4 v 22.5 years, $t = 4.09$, $p < 0.001$). They presented with overt diabetes and had not been previously tested by oral glucose tolerance tests. Insulin treatment was required at the onset in 6/12 patients in group A and after an average period of 1.2 years (range 0.2–2.1) in another 4/12; one patient died 12 months after diagnosis when she was still under treatment with oral hypoglycaemic agents.

In contrast, patients in group B (16/28 patients) were characterised by slowly progressive diabetes. The diagnosis was based upon two abnormal consecutive oral glucose tolerance tests and all the patients were treated at the onset of diabetes with oral hypoglycaemic agents. Eleven of the 16 are still being treated with oral hypoglycaemic agents; in the other five, insulin treatment was required after an average period of 3.03 years from the diagnosis (range 1.64–6.96 years). The average time between the diagnosis and the start of insulin treatment was longer in group B patients (3.0 years) than in group A (1.9 years) but the difference was not statistically significant ($t = 1.92$, $p = 0.091$).

Genetic analysis was performed in 23 out of the 28 patients. The most frequently found mutation was $\Delta F508$, with a frequency of 47% (slightly lower than that in the general Italian cystic fibrosis population: 51.05%). N1303K was the second most frequent mutation and its frequency was higher than in non-diabetic patients attending our cystic fibrosis centre (11.1% and 2.6% respectively; $\chi^2 = 5.083$, $p = 0.029$) (table 1). All the five diabetic patients with N1303K mutation were in the early onset diabetes group (group A). Among the six patients presenting with overt diabetes and who required insulin treatment at diagnosis, three were negative for islet cell antibodies and the others could not be examined for these antibodies.

The N1303K mutation is classified as a 'severe' mutation with respect to the exocrine pancreatic secretion, in that it is associated with pancreatic insufficiency. The frequency of the N1303K mutation varies between eth-

nic groups, being more common in southern than in northern Europe. The genotype/phenotype correlation for the N1303K mutation has already been evaluated, but diabetes was not taken into account among clinical manifestations^{1,2} and no apparent correlation emerged (but no information on the patients' age was reported).³ We are aware of only one study evaluating the incidence of the different cystic fibrosis gene mutations in diabetic cystic fibrosis patients, but in that series only 8/21 patients were diabetic, they were older than our diabetic patients and only one patient was heterozygous for N1303K.⁴

Our data support the possibility that two types of diabetes can be associated with cystic fibrosis and that there is a genotype/phenotype correlation between the early onset cystic fibrosis associated diabetes and the mutation N1303K. This suggests that the mutation N1303K is a possible risk factor for early onset insulin requiring diabetes in cystic fibrosis patients. The relevance of our results must be verified in different populations.

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Secondary cases of meningococcal disease

EDITOR,—Two thousand cases of meningococcal sepsis occur every year in the UK, predominantly in the winter, and 10% of these children die.^{1,2} Household contacts of cases of meningococcal disease have a 500–4000 times increased risk of developing the diseases^{3,4} and the incidence of secondary cases, as a percentage of the total number of cases of meningococcal sepsis, ranges from 0–4.5%.⁵⁻⁷ Antibiotic chemoprophylaxis effectively eliminates nasopharyngeal carriage of *Neisse-*

ria meningitidis in household contacts, and prevents contacts from acquiring the diseases.⁵⁻¹⁰ Guidelines for administration of chemoprophylactic antibiotics have recently been re-emphasised¹⁰ but failure of administration still occurs.

We are aware of five recent cases where there has been a failure of chemoprophylaxis which has led to secondary disease. Failure of prophylaxis was multifactorial. In four cases no prophylaxis was prescribed after admission of the index case in the family. In the fifth, prophylaxis was prescribed but not taken. Secondary cases occurred because the aetiology of the presenting illness in the index case was not recognised either clinically or microbiologically and chemoprophylaxis was not given; there was a delay in administering chemoprophylaxis; chemoprophylaxis was refused or overlooked; or because an alternative coincidental pathogen was identified leading to confusion.

Table 1 Antibiotic chemoprophylaxis

Rifampicin (twice daily for two days)	Ceftriaxone (single im injection)
<1 year	5 mg/kg per dose
1-12 years	10 mg/kg per dose
>12 years	600 mg per dose

Since a petechial rash occurs in 80% of children with meningococcal sepsis, recognition of disease and administering chemoprophylaxis (table 1) to contacts should be straightforward, particularly if clear protocols are to be established in paediatric units for the management of meningococcal sepsis which include recommendations for chemoprophylaxis. Further, since the likelihood that a child with bacterial meningitis in the UK has meningococcal infection is high after the virtual elimination of *Haemophilus influenzae* type b disease by vaccination, we believe prophylaxis should be offered to all household and kissing contacts of cases whenever bacterial meningitis is suspected, as early as possible, before culture results are available, and by the parenteral route in young children who refuse oral medication.

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Table 1 Frequency of the N1303K mutation in diabetic and non-diabetic cystic fibrosis patients

	No of CF alleles tested	No of N1303K alleles	% of N1303K in CF alleles
CF with DM	45	5	11.1
CF without DM	335	8	2.6
CF total	380	13	3.4

$\chi^2 = 5.083$, $p = 0.029$.

CF: cystic fibrosis; DM: diabetes mellitus.