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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- Osborne L, Santis G, Schwarz, *et al.* Incidence and expression of the N1303K mutation of the cystic fibrosis (CFTR) gene. *Hum Genet* 1992;89:653-8.
- Gasparini P, Marigo C, Bisceglia G, *et al.* Screening of 62 mutations in a cohort of cystic fibrosis patients from North Eastern Italy: their incidence and clinical features of defined genotypes. *Hum Mutat* 1993;2:389-94.
- The Cystic Fibrosis Genotype-Phenotype Consortium. Correlation between genotype and phenotype in patients with cystic fibrosis. *N Engl J Med* 1993;329:1308-13.
- Hamdi I, Payne SJ, Barton DE, *et al.* Genotype analysis in cystic fibrosis in relation to the occurrence of diabetes mellitus. *Clin Genet* 1993;43:186-9.

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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- Jones D. Epidemiology of meningococcal disease in Europe and the USA. In: Cartwright K, ed. *Meningococcal disease*. Chichester: John Wiley and Sons, 1995:146-57.
- Havens PL, Garland JS, Brook MM, Dewitz BA, Stremski ES, Troshynski TJ. Trends in mortality in children hospitalised with meningococcal infections, 1957 to 1987. *Pediatr Infect Dis J* 1989;8:8-11.
- Meningococcal Disease Surveillance Group. Analysis of endemic meningococcal disease by serogroup and evaluation of chemoprophylaxis. *J Infect Dis* 1976;134:201-4.
- Olsen P, Kjellander J, Danielsson D, Lindquist BL. Epidemiology of *Neisseria meningitidis* prevalence and symptoms from the upper respiratory tract in family members to patients with Meningococcal disease. *Scand J Infect Dis* 1981;13:105-9.
- Kristiansen BE, Tveten Y, Ask E, *et al.* Preventing secondary cases of meningococcal disease by identifying and eradicating disease-causing strains in close contacts of patients. *Scand J Infect Dis* 1992;24:165-73.

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.

- 6 Cooke RPD, Riordan T, Jones DM, Painter MJ. Secondary cases of meningococcal infection among close family and household contacts in England and Wales, 1984-87. *BMJ* 1989;298: 555-8.
- 7 Olivares R, Hubert B. Clusters of meningococcal disease in France (1987-1988). *Eur J Epidemiol* 1992;8:737-42.
- 8 Ege PP, Samuelsson SI, Lind I. [Meningococcal disease 1987-1989. Outbreak of serogroup B:15:PI.16 in the county of Frederiksborg]. *Ugeskr Laeger* 1993;155:3456-9.
- 9 Public Health Laboratory Service Communicable Diseases Surveillance Centre Report. *BMJ* 1986;293:1293-4.
- 10 PHLS Meningococcal Infections Working Group and Public Health Medicine Environmental Group. Control of Meningococcal disease: guidance for consultants in communicable disease control. *Communicable Disease Report* 1995;5(13):R189-93.

Diphtheria: are we ready for it?

EDITOR.—The article by Begg and Balraj discusses the adequacy of current control and containment measures for diphtheria.¹ We agree with the authors that the diagnosis of *Corynebacterium diphtheriae* and *Corynebacterium ulcerans* has in the past often been delayed or missed altogether as many laboratories have ceased to culture throat swabs routinely for these organisms.

The Public Health Laboratory Service (PHLS) Standardisation of Clinical Bacteriology Methods Working Group recommends in their standard operating procedure (SOP) on the investigation of throat swabs that all throat swabs should be cultured routinely for *C diphtheriae* and *C ulcerans* using Hoyle's tellurite medium.²

Reasons for this include:

- Immunisation does not prevent asymptomatic carriage of the organism
- Vaccinated individuals may still be susceptible
- There is a risk of indigenous transmission
- A major outbreak is possible
- Early recognition of a case allows for containment of the patient
- Treatment must be initiated at an early stage to reduce the risk of fatality.

With laboratories returning to this kind of routine screening, isolation of *C diphtheriae* and *C ulcerans* from asymptomatic carriers will be increased thereby minimising the potential for missed or delayed diagnosis. It will also allow for the collection of consistent epidemiological data on the presence of the organism in the population.

The PHLS has recently issued a standard method for the investigation of throat swabs as part of the 50 specimen SOPs to be issued to the PHLS during the next 18 months.³ These SOPs may also prove useful to microbiology laboratories other than the PHLS.

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- 1 Begg N, Balraj V. Diphtheria: are we ready for it? *Arch Dis Child* 1995;73:568-72.
- 2 Public Health Laboratory Service. *PHLS clinical microbiology standard operating procedure for the investigation of throat swabs*. B.SOP9; Issue 1. London: PHLS, 1996.
- 3 Djemal K, Matthews S, Bevan V. Standardisation of clinical bacteriology methods. *PHLS Microbiology Digest* 1996;13 (1):39-40.

Non-steroidal anti-inflammatory drugs may predispose to invasive group A streptococcal infections

EDITOR.—The suggestion that ibuprofen should be considered as an alternative to paracetamol for the treatment of fever in young children¹ warrants caution. There have been numerous reports suggesting an association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the progression to severe invasive group A streptococcal infections, including necrotising fasciitis.²⁻⁶ NSAIDs may also mask important clinical features that may help in the early recognition of invasive group A streptococcal disease.

Prompt diagnosis and treatment of group A streptococcal infection has become increasingly important as there has been a worldwide resurgence in invasive group A streptococcal disease since the mid-1980s with the emergence of strains of increased virulence.⁵

Recently, it has been proposed that the underlying biochemical basis for the possible link between the use of NSAIDs and invasive group A streptococcal infection is the ability of NSAIDs to inhibit neutrophil function and enhance cytokine (particularly tumour necrosis factor) production.⁶ In addition, by masking cardinal signs of inflammation, such as myalgia, arthralgia, erythema and localised swelling, these agents may delay the recognition of invasive group A streptococcal infection until signs of shock and multiorgan failure are apparent. This hypothesis may also apply to staphylococcal toxic shock syndrome.

Varicella is an important predisposing factor for both invasive group A streptococcal and staphylococcal infection in immunocompetent children.⁷ NSAIDs may be particularly dangerous in this condition: their use has been associated with the progression to necrotising fasciitis and toxic shock syndrome.⁴

Antipyretics play an important part in the management of febrile young children with non-specific signs in whom the diagnosis is unclear. However, the possibility that NSAIDs may facilitate the invasion of group A streptococci should limit the use of these agents in patients with varicella or in those in whom the cause of fever is not known.

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- 1 McIntyre J, Hull D. Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. *Arch Dis Child* 1996;74:164-7.
- 2 Rimailho A, Riou B, Richard C, Auzep P. Fulminant necrotizing fasciitis and nonsteroidal anti-inflammatory drugs. *J Infect Dis* 1987;155: 143-6.
- 3 Smith RJ, Berk SL. Necrotizing fasciitis and nonsteroidal anti-inflammatory drugs. *South Med J* 1991;84:785-7.
- 4 Brogan TV, Nizet V, Waldhausen JH, Rubens CE, Clarke WR. Group A streptococcal necrotizing fasciitis complicating primary varicella: a series of fourteen patients. *Pediatr Infect Dis J* 1995;14:588-94.
- 5 Curtis N. Invasive group A streptococcal infections. *Current Opinion in Infectious Diseases* 1996; 9:191-202.
- 6 Stevens DL. Could nonsteroidal antiinflammatory drugs (NSAIDs) enhance the progression of bacterial infections to toxic shock syndrome? *Clin Infect Dis* 1995;21:977-80.
- 7 Pollard AJ, Isaacs A, Lyall EGH, et al. Life threatening bacterial infection associated with varicella. *BMJ* 1996;313:283-5.

HIV related Kaposi's sarcoma

EDITOR.—McCarthy *et al* report a Zambian mother and her son with HIV related Kaposi's sarcoma and suggest the possibility of vertical transmission of a Kaposi's sarcoma agent.¹ They comment on the rarity of Kaposi's sarcoma in the United States and Europe and in their abstract say that it is 'extremely rare in children'.

In Kampala Kaposi's sarcoma is not rare. In a study of children presenting with lymphadenopathy to the paediatric wards of Mulago Hospital, Kampala, between September 1992 and April 1993, 15 cases were diagnosed. The sex ratio was M:F 10:3. Since 1993 about two to three cases are being diagnosed each month. Apart from lymphadenopathy, which can be differentiated from tuberculosis only by histology, other clinical features include pigmented nodular skin lesions, hepatosplenomegaly, pleural effusion, and oral mucosal lesions. We do not have facilities for bronchoscopy, lung puncture, or intestinal biopsy to detect internal lesions. As mothers are not routinely examined in cases of childhood Kaposi's sarcoma we do not know how many might have it. However, it would not be surprising, considering the not uncommon occurrence of Kaposi's sarcoma in women, that both mother and child might have it if they originate from areas of high HIV prevalence such as Uganda or Zambia.

Nevertheless, a transmissible Kaposi's sarcoma agent (whether vertically transmitted or not) is a possibility, and we are also looking for an association with a herpes-like virus.

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- 1 McCarthy GA, Kampmann B, Novelli V, Miller RF, Mercey DE, Gibb D. Vertical transmission of Kaposi's sarcoma. *Arch Dis Child* 1996;74:455-7.

BOOK REVIEWS

Symptoms of Disease in Childhood. By T J David. (Pp 258; £15.95 paperback.) Blackwell Science, 1995. ISBN 0-632-03635-4.

Updating *Common Symptoms of Disease in Children* by R S Illingworth, this book follows a symptomatic as opposed to a system approach. For each of the 185 symptom (sign) headings a list of causes is followed by a text, giving a brief account of the conditions listed.

In an attempt to be thorough, many of the lists are lengthy and daunting not only to the medical student but also to the experienced paediatrician. Some attempt has been made to subdivide the causes but further subdivision would have supported the problem solv-