Pulmonary function in infants with cystic fibrosis: the effect of antibiotic treatment

Caroline S Beardsmore, John R Thompson, Anne Williams, E Kieran McArdle, Geraldine A Gregory, Lawrence T Weaver, Hamish Simpson

Abstract

Since 1982 all infants born within the East Anglian Regional Health Authority have been screened for cystic fibrosis. Between April 1985 and April 1992 infants identified in this way have been entered into a randomised prospective controlled trial of antibiotic prophylaxis. Approximately half the infants received continuous oral flucloxacillin and the remainder received antibiotics when clinically indicated. Infants underwent tests of respiratory function at 3–4 months and at 1 year of age. Measurements of thoracic gas volume and airway conductance were made with an infant whole body plethysmograph, and maximum expiratory flow by the 'squeeze' technique. A total of 73 tests was performed of 42 infants. To facilitate comparisons, measurements were expressed as scores. The mean values of the scores for the two groups of infants fell within normal limits. There was no difference between the treatment groups at either age. A reduction in airways conductance was observed between the two tests.

(*Arch Dis Child* 1994; **71**: 133–137)

Pulmonary disease continues to be a major cause of morbidity in infants and children with cystic fibrosis and it has long been recognised that changes in lung function can be detected even when there is no clinical evidence of respiratory disease.[1] The processes contributing to lung damage have been widely studied and have been the subject of an extensive review.[2] Although our understanding of pulmonary pathophysiology in cystic fibrosis has expanded, the study of function remains important as little is known about the interactions of growth, infections, and treatment with the disease processes.

The advent of neonatal screening for cystic fibrosis provides an opportunity for early therapeutic interventions, with the aim of modifying the natural course of the disease. This is of particular relevance in infancy and early childhood when the growth and development of the lung are rapid and any damage might therefore be expected to be detrimental. In a summary of reports of the early respiratory course in infants diagnosed conventionally and by newborn screening,[3] it was clear that many screened infants had substantial respiratory symptoms and the challenge is now to introduce effective treatment as soon as the diagnosis is confirmed.

Between April 1985 and April 1992 infants born within the East Anglian Regional Health Authority who were found to have cystic fibrosis on neonatal screening were enrolled into a randomised prospective controlled trial of antibiotic prophylaxis. About half of the infants received continuous flucloxacillin and the remainder received antibiotics when clinically indicated. Information about anthropometric, dietary, clinical, and microbiological progress of the first 42 infants to reach the age of 2 years has been published.[4]

This paper describes pulmonary function in this screened population and represents the largest study of lung mechanics in infants with cystic fibrosis to date. The aims of the study were: (a) to ascertain if there were any differences in lung function between those infants treated with continuous antibiotics and those treated episodically; (b) to describe the pattern of lung function in infants in the early stages of disease at a time when many were asymptomatic; and (c) to provide baseline measurements on a large group of infants as the first stage to long term follow up of pulmonary function.

Subjects and methods

SUBJECTS

All infants born within the East Anglian Regional Health Authority since 1982 have been screened for cystic fibrosis by blood immunoreactive trypsin assay on heel prick blood samples obtained at 6–9 days of age for the Guthrie test.[5] In those with increased blood immunoreactive trypsin the test is repeated and, if still positive, diagnosis is confirmed by sweat testing. After confirmation of diagnosis and with parental agreement, infants born between April 1985 and April 1992 were enrolled into a prospective trial of antibiotic treatment and were randomly assigned to one of two treatment groups. One group (group E) received episodic antibiotics as clinically indicated and the other (group P) received continuous prophylactic oral flucloxacillin 250 mg daily in divided doses. All infants received chest physiotherapy from the time of diagnosis, and pancreatic enzyme, vitamin, and mineral supplements as clinically indicated.[4]

The trial was designed to examine many aspects of the growth and clinical progress of the children, including rate of infection, number and duration of hospital admissions, pancreatic function, radiology, and metabolic function. Clinical information was collected at regular routine clinic visits, at the time of hospital admissions, and by the nurse

Department of Child Health, University of Leicester, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX
C S Beardsmore
A Williams
E K McArdle
H Simpson

Department of Ophthalmology
J R Thompson

Department of Paediatrics, Peterborough District Hospital
G A Gregory

MRC Dunn Nutrition Unit, Cambridge
L T Weaver

Correspondence to:
Dr Beardsmore.

Accepted 18 April 1994

Table 1 Details of infants

Characteristic	*Group E (n=22)*	*Group P (n=20)*
Boys/girls	11/11	12/8
Mean (SD) (range) birth weight (g)	3240 (420) (2440–4030)	3250 (470) (2560–4200)
Mean (SD) (range) gestational age (weeks)	39·3 (1·6) (34–41)	39·7 (1·4) (37–42)
No with meconium ileus	6	2
No of infants (test 1)	18	19
Mean (SD) age at test 1 (weeks)	17·8 (6·45)	14·9 (4·80)
Mean (SD) length at test 1 (cm)	60·8 (3·69)	59·8 (4·17)
No of infant (test 2)	17	18
Mean (SD) age at test 2 (weeks)	48·1 (4·3)	51·1 (4·6)
Mean (SD) length at test 2 (cm)	73·0 (3·4)	74·1 (2·8)

coordinator on domiciliary visits. This paper concentrates only on measures of respiratory function. Forty two infants underwent respiratory function tests, 20 of whom received flucloxacillin and 22 episodic antibiotics. Table 1 summarises the clinical details.

We aimed to study each infant twice, once shortly after confirmation of diagnosis and again at approximately 1 year of age. For a variety of family, medical, and social reasons six infants (two from group P and four from group E) did not have an early test. Five infants did not have a late test (one from group P and four from group E).

RESPIRATORY FUNCTION TESTS

On arrival in the laboratory the infant was weighed, given chloral hydrate (100 mg/kg body weight), and allowed to settle. A routine questionnaire was completed and the tests were explained in detail to the parents, who were encouraged to be present during testing. Once the infant was asleep, measurements of maximum flow at functional residual capacity ($\dot{V}_{max}FRC$) were made using the 'squeeze' technique.[6] In brief, the infant was snugly wrapped in an inflatable plastic jacket extending from shoulders to thighs, with his or her arms at his or her sides. A facemask and pneumotachograph were placed around the nose and mouth and made airtight with sterile putty. The flow signal from the pneumotachograph was integrated electronically to allow a display of flow volume loops on an oscilloscope. The jacket was connected by a three way tap to a pressure reservoir, and at the end of tidal inspiration the tap was opened, leading to rapid inflation of the jacket. The pressure thereby applied to the infant's chest and abdomen produced a partial maximum expiratory flow volume manoeuvre. The recorded signals of flow, volume, and jacket pressure were stored on a personal computer for later analysis. Approximately 12 measurements of $\dot{V}_{max}FRC$ were made on each occasion while varying the pressure within the jacket from 25 to 55 cm H_2O.

After measurements of $\dot{V}_{max}FRC$ the jacket was loosened around the infant and measurements of thoracic gas volume (TGV) and airways resistance (Raw) were made. The infant continued to sleep lying within the whole body plethysmograph, breathing through a facemask and pneumotachograph. This was connected to a pair of pneumatically operated valves so that the operator could switch the infant from breathing room air within the plethysmograph to heated, humidified air from a rebreathing bag (essential for measurements of Raw), or by closing the two valves the airway could be occluded for a brief period during the measurement of TGV.[7] The signals of respiratory flow and volume, together with pressure signals from the plethysmograph and facemask, were recorded on computer and analysed some time after completion of the tests. On completion of the measurements the infant was lifted from the plethysmograph, his or her length was measured, and the infant was allowed home.

ANALYSIS OF RESULTS

Values of $\dot{V}_{max}FRC$, TGV, and Raw were calculated by computer after completion of the tests. In the early part of the study an Apple IIe computer was used with programs supplied by the department of paediatrics, Royal Postgraduate Medical School, Hammersmith Hospital, or developed in-house. Later measurements were made with a Compaq 286 computer using RASP programs (Physio Logic Ltd). $\dot{V}_{max}FRC$ was taken as the flow rate achieved during the forced expiration, at a volume equivalent to the resting end expiratory level. The final value used was the highest value obtained from a technically satisfactory manoeuvre.[8]

Wherever possible measurements of TGV were the mean values taken from at least five separate periods of airway occlusion calculated according to standardised techniques.[7] Measurements of Raw were taken over the initial two thirds of inspiratory flow, and in most instances were the mean of at least 10 breaths taken from two or three separate, technically satisfactory recordings of Raw. The reciprocal of Raw, airway conductance (Gaw), was used for statistical analysis. Specific conductance (sGaw) was calculated for each infant by dividing Gaw by TGV.

Each measurement for each infant ($\dot{V}_{max}FRC$, TGV, Gaw, and sGaw) was then expressed as a score to facilitate analysis. A predicted value for each measurement could be made for each infant on the basis of body length, and the score was the number of standard errors of prediction by which the measured value differed from the prediction.[9] The predicted values were based on normal, healthy infants. Thus when the score was close to zero the measured value was close to that predicted on the basis of length. Scores between -2 and $+2$ would be considered to fall within normal limits, whereas more extreme scores would indicate that the measured value differed significantly from the predicted value.

STATISTICAL METHODS

The primary comparison of the treatment groups and the analysis of other factors that might affect lung function are based on a multivariate test that uses all four treatment scales simultaneously. Where this test was significant we investigated the four component

Table 2 Number of missing values and mean scores on each scale at each visit for the two treatment groups. Differences in means and 95% confidence intervals (CI)

	Episodic treatment (n=22)		*Continuous treatment (n=20)*		
	No missing	*Mean*	*No missing*	*Mean*	*Difference in means (95% CI)*
First visit					
TGV	5	0·98	4	0·05	0·93 (−0·09 to 1·95)
Gaw	8	0·00	6	1·16	−0·16 (−3·17 to 0·85)
sGaw	8	−1·07	6	0·24	−1·31 (−3·32 to 0·70)
$\dot{V}_{max}$FRC	4	−0·75	2	−0·69	−0·06 (−0·68 to 0·56)
Second visit					
TGV	4	0·09	2	−0·22	0·31 (−1·06 to 1·68)
Gaw	5	−1·13	4	−1·79	0·66 (−1·71 to 3·03)
sGaw	5	−4·97	4	−1·94	−3·03 (−10·32 to 3·03)
$\dot{V}_{max}$FRC	4	−0·85	1	−0·61	−0·24 (−1·33 to 0·85)

scores using univariate tests. In most statistical packages multivariate tests require complete sets of data on all individuals. As we had missing data on many of our children we adopted an approach based on the EM algorithm[10] that enables us to use all of the data that were collected.[11] The resulting multivariate comparisons were made using a likelihood ratio test. The main aim of the study was to compare treatment groups, but as a secondary analysis we investigated the effects of upper respiratory tract infection (URTI), genotype, meconium ileus, and parental smoking on pulmonary function.

Results

Results are available from 42 infants, of whom 20 received continuous flucloxacillin after the confirmation of the diagnosis of cystic fibrosis. The remainder received episodic antibiotics as clinically indicated. The two groups did not differ significantly on the basis of birth weight, gestational age, or sex distribution.

Where possible, each infant was studied twice within the first year of life, once at about 16 weeks and again at about 50 weeks, although some children missed one of the visits (table 1). For technical reasons no reliable plethysmographic data were obtained on three occasions and on an additional four occasions measurements of airway resistance proved unsatisfactory. Of the possible 42×2×4=336 measurements, 59 (18%) are missing and 21 children had a complete set of all eight measurements.

Table 2 shows the average scores for each of the eight measurements for each group, together with the 95% confidence intervals for the differences in the means. Individual scores and changes between visits are shown (figs 1 and 2). None of the measurements shows a significant difference between the treatment groups. A single multivariate test for any difference between treatment groups based on the eight measurements was non-significant (p=0·6).

We used the same multivariate approach to examine the effect of other factors measured on these children. In the following analyses the two treatment groups have been combined and tests of interaction between the effects and antibiotic treatment were all non-significant.

EFFECT OF VISIT

The profile of scores on the four scales of measurement is significantly different at the second visit compared with the first (p=0·009). The largest differences are in Gaw and sGaw and the scores indicate a worsening between the two visits. An attempt to relate the changes between visits to the age or length of the infants showed that adding either variable would produce only a small improvement in the fit of the model.

EFFECT OF URTI

A current URTI did not relate significantly to the profile of scores (p=0·31). If the definition is expanded to include all children with a current or recent URTI, however, the effect is of borderline significance (p=0·07), with the largest effect being a decrease of 1·25 in the Gaw score, which is just significant if tested alone (p=0·05).

EFFECT OF GENOTYPE

Information on genotype was available for 40 of the 42 infants. Twenty seven were homozygous for the delta F508 deletion and 13 were heterozygous. The proportion of homozygotic infants did not vary significantly between the two treatment groups. Combining the two treatment groups and comparing homozygotic

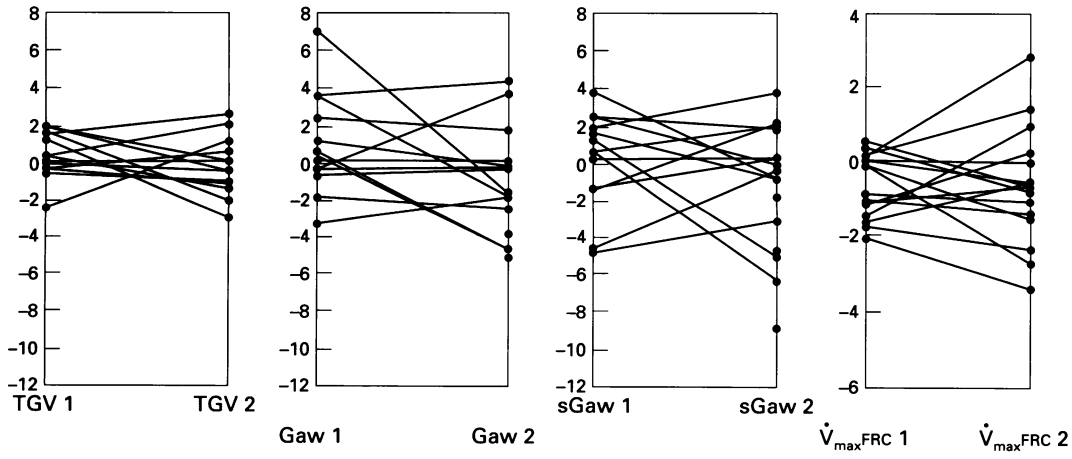

Figure 1 Changes in the pattern of pulmonary function scores: infants treated with continuous antibiotics.

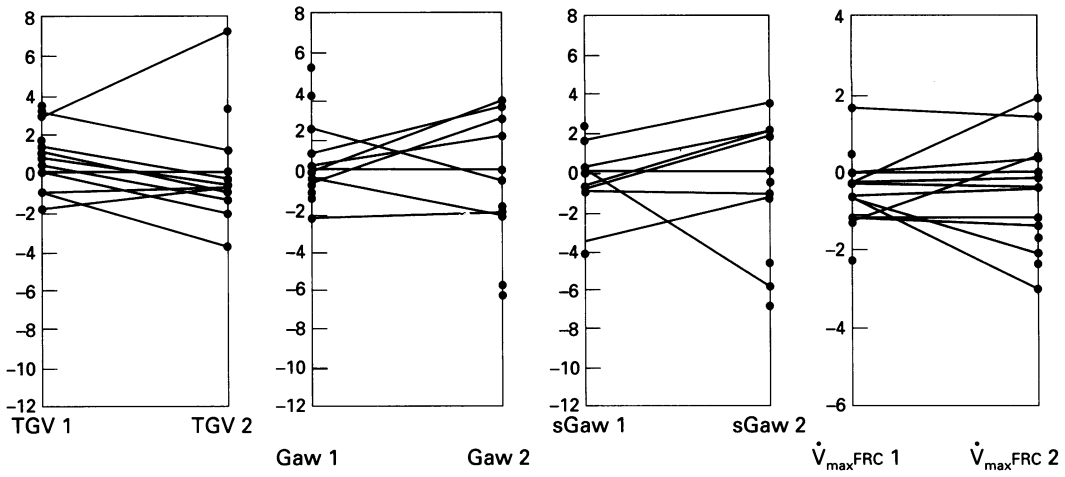

Figure 2 Changes in the pattern of pulmonary function scores: infants treated with episodic antibiotics.

infants with those who were heterozygotic, however, showed a borderline significant difference in the multivariate test (p=0·08). The homozygotic infants had slightly higher TGV and Gaw scores.

EFFECT OF MECONIUM ILEUS

Eight of the infants were born with meconium ileus. These children had a significantly different profile of scores (p=0·02), typified by lower Gaw scores and higher TGV scores.

EFFECT OF PARENTAL SMOKING

Twelve infants lived in homes where at least one adult smoked. This did not have a significant effect on the profile of scores, however (p=0·52).

Discussion

We have measured pulmonary function in a group of 42 infants with cystic fibrosis diagnosed after neonatal screening. Measurements of lung mechanics showed that although the mean values for pulmonary function scores were within normal limits during the first year of life, some infants showed abnormalities in one or more tests. The spread of values in the two groups exceeded that of the normal population from which the scores were derived[9] for each of the measurements made. There was no difference in lung mechanics between the two groups (P and E) at either age studied, however. These measurements formed only a part of the assessment of the two groups, and interim reports of overall findings have been published elsewhere.[4 12] These showed that at the age of 12 months the groups had similar chest radiographic scores, and no differences in the clinical signs of respiratory infection. Group P had fewer isolates of *Staphylococcus aureus* and coughed less. In addition, group P infants had fewer and shorter hospital admissions than their group E counterparts. Thus although the use of continuous prophylactic antibiotic treatment over the first year of life is not justifiable on the basis of early pulmonary function tests, other findings support this treatment.

Long term follow up of all the children in this study is being undertaken, including pulmonary function testing at the age of 5 or 6 years to determine whether or not differences in lung mechanics emerge in later childhood. Studies with older patients have indicated that continuous antibiotics reduce the number of exacerbations in cystic fibrosis, and that lung function (assessed by spirometry) remains stable in most.[13]

Many of the children in this study had normal measurements, as observed in other groups of infants with cystic fibrosis.[14–16] In unscreened infants pulmonary function may vary according to the mode of presentation.[16] The early respiratory course of infants with cystic fibrosis is important as it represents a significant source of morbidity, and lung damage occurring in the first year may be particularly important given the rapid rate of growth and development at this stage. Although it is gratifying to note that the mean values of pulmonary function scores were within normal limits during the first year, some infants showed considerable changes (figs 1 and 2), and 20 of the 42 infants were admitted to hospital during the first year of life with respiratory disease. The patients in our study were not compared directly with an unscreened group of cystic fibrosis patients, but other studies have indicated improved survival in screened populations,[17] and fewer, shorter, hospital admissions in the early months.[18]

This study found that infants with meconium ileus had worse airway conductance than those without, and in several patients the measurement of conductance was below the normal range. This contrasts with the findings of Tepper *et al* where pulmonary function was normal in infants with meconium ileus unless they were also failing to thrive.[16] The study of Tepper *et al* was based on measurements of FRC and $\dot{V}_{max}$FRC and did not include measurements of conductance; it is therefore not strictly comparable with ours. Meconium ileus is associated with significant mortality and morbidity,[19] but in patients old enough to perform conventional spirometric measurements there was no difference between those born with and without meconium ileus.[20]

The genotype of patients with cystic fibrosis has been found by some workers to be related to pulmonary function, with patients who are homozygous for the delta F508 mutation having poorer lung function than heterozygotes.[21] This finding is not universal,[22] and out study did not find significant differences related to genotype.

We did not find a relation between parental smoking and pulmonary function in this group of 42 infants, even though respiratory illnesses are more common in the first year of life in children from smoking households.[23 24] The study was not designed to investigate the effect of parental smoking (which was recorded only at the time of entry to the trial) and the lack of effect may be the result of small sample size (type II error).

In conclusion, this study has shown that there is no difference in pulmonary function tests over the first year of life in infants with cystic fibrosis who receive continuous or episodic antibiotics. Continuous treatment with oral flucloxacillin, however, is associated with fewer hospital admissions, lower rates of *S aureus* isolation, and less clinical morbidity than episodic antibiotic treatment.[4] Routine treatment for newly diagnosed infants with cystic fibrosis in our areas now includes continuous oral flucloxacillin.

We thank S Johnson, K Nicholson, and P Howat for their help in this study, and S Austin for help with data retrieval. We thank all the children and their parents who participated in the study, and their consultants for their willing cooperation. We thank Emeritus Professor J Davis for his work in establishing the trial of antibiotic treatment. The work was funded in part by the Medical Research Council and the Cystic Fibrosis Research Trust, to whom we express our gratitude.

1 Phelan PD, Gracey M, Williams HE, Anderson CM. Ventilatory function in infants with cystic fibrosis. *Arch Dis Child* 1969; **44:** 393–400.
2 Zach MS. Lung disease in cystic fibrosis – an updated concept. *Pediatr Pulmonol* 1990; **8:** 188–202.
3 Accurso FJ, Sokol RJ, Hammond KB, Abman SH. Early respiratory course in infants with cystic fibrosis: relevance to newborn screening. *Pediatr Pulmonol Suppl* 1991; **7:** 42–5.
4 Weaver LT, Green MR, Nicholson K, *et al.* Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period. *Arch Dis Child* 1994; **70:** 84–9.
5 Heeley AF, Heeley ME, King DN, Kuzemko JA, Walsh MP. Screening for cystic fibrosis by dried blood spot trypsin assay. *Arch Dis Child* 1982; **57:** 18–21.
6 Taussig LM, Landau LI, Godfrey S, Arad I. Determinants of forced expiratory flows in newborn infants. *J Appl Physiol* 1982; **53:** 1220–7.
7 Stocks J, Levy NM, Godfrey S. A new apparatus for the accurate measurement of airway resistance in infancy. *J Appl Physiol* 1977; **43:** 155–9.
8 Silverman M, Prendiville A, Green S. Partial expiratory flow-volume curves in infancy: technical aspects. *Bull Eur Physiopathol Respir* 1986; **22:** 257–62.
9 Hampton FJ, Beardsmore CS, Morgan W, Williams A, Taussig L, Thompson JR. A scoring system for lung function tests in infants. *Pediatr Pulmonol* 1992; **14:** 149–55.
10 Dempster AP, Laird NM, Rubin DB. Maximum likelihood estimation from incomplete data via the EM algorithm. *Journal of the Royal Statistical Society B* 1977; **39:** 1–22.
11 Beale EML, Little RJA. Missing values in multivariate analysis. *Journal of the Royal Statistical Society B* 1975; **37:** 129–45.
12 Green MR, Weaver LT, Heeley AF, *et al.* Cystic fibrosis identified by neonatal screening: incidence, genotype, and early natural history. *Arch Dis Child* 1993; **68:** 464–7.
13 Loening-Baucke VA, Mischler E, Myers MG. A placebo-controlled trial of cephalexin therapy in the ambulatory management of patients with cystic fibrosis. *J Pediatr* 1979; **95:** 630–7.
14 Godfrey S, Mearns M, Howlett G. Serial lung function studies in cystic fibrosis in the first five years of life. *Arch Dis Child* 1978; **53:** 83–5.
15 Beardsmore CS, Bar-Yishay E, Maayan C, Yahav Y, Katznelson D, Godfrey S. Lung function in infants with cystic fibrosis. *Thorax* 1988; **43:** 545–51.
16 Tepper RS, Hiatt P, Eigen H, Scott P, Grosfeld J, Cohen M. Infants with cystic fibrosis: pulmonary function at diagnosis. *Pediatr Pulmonol* 1988; **5:** 15–8.
17 Dankart-Roelse JE, te Meerman GJ, Martijn A, ten Kate LP, Knol K. Survival and clinical outcome in patients with cystic fibrosis, with or without neonatal screening. *J Pediatr* 1989; **114:** 362–7.
18 Chatfield S, Owen G, Ryley MC, *et al.* Neonatal screening for cystic fibrosis in Wales and the West Midlands: clinical assessment after five years of screening. *Arch Dis Child* 1991; **66:** 29–33.
19 Wesley AW, Smith PA, Elliott RB. Experience with neonatal screening for cystic fibrosis in New Zealand using measurement of immunoreactive trypsinogen. *Australian Paediatric Journal* 1989; **25:** 151–5.
20 Kerem E, Corey M, Kerem B, Durie P, Tsui L-C, Levison H. Clinical and genetic comparisons of patients with cystic fibrosis, with or without meconium ileus. *J Pediatr* 1989; **114:** 767–73.
21 Johanssen HK, Mir M, Hoiby N, Koch C, Schwartz M. Severity of cystic fibrosis in patients homozygous and heterozygous for delta F 508 mutation. *Lancet* 1991; **337:** 631–4.
22 Al Jader LN, Meredith AL, Ryley HC, *et al.* Severity of chest disease in cystic fibrosis patients in relation to their genotypes. *J Med Genet* 1992; **29:** 883–7.
23 Fergusson DM, Horwood LJ, Shannon FT. Parental smoking and respiratory illness in infancy. *Arch Dis Child* 1980; **55:** 358–61.
24 Pedreira FA, Cuandolo VL, Feroli EJ. Involuntary smoking and incidence of respiratory illness during the first year of life. *Pediatrics* 1985; **75:** 594–7.