Paediatric origins of adult lung disease • 7

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Cystic fibrosis

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Cystic fibrosis (CF) remains an incurable life limiting condition which is the most common inherited lethal condition in most Western countries. Advances in the care of this condition, particularly advances in respiratory management, have seen the focus of this review become a reality. In the 1940s adult consequences of CF were minimal as most patients died during infancy and early childhood. Today, the life expectancy of patients with CF has advanced well into adult life and has prompted the development of specific adult CF care centres in many major hospitals as well as publications addressing adult issues relating to this disease.[1] Future projections suggest that, within the next decade, most patients with CF in many countries will, in fact, be adults rather than children. While debate continues between proponents of newborn screening for CF and those against it, the drive of CF care for the paediatric age group is aimed at providing the patient with a high quality life for as long as possible. The underlying element to achieving this is minimisation of lung disease. While nutritional factors—together with endocrinological factors, psychological factors, and sexual factors—are vitally important in providing a good quality of life to the patient with CF, the basic determinant of longevity and quality of life in most CF patients is the degree of lung disease and its rate of progression with increasing age.

Screening

Newborn screening for cystic fibrosis has been adopted in some centres as a way of identifying asymptomatic patients and initiating early treatment with the aim of minimising long term changes. Proponents of this method would suggest that this means a much more aggressive approach to management of lung disease in the early years as opposed to patients born in unscreened populations where clinical evidence of respiratory disease is a frequent cause of presentation. The natural extension of this claim would be that early aggressive and often preventive treatment of lung disease will slow the deterioration of lung function in the long term. Waters and colleagues have studied long term lung function in a group of infants born during a period of population based newborn screening and have shown that those with CF born during this period have better lung function and improved growth parameters compared with children with CF born in the same population in the period before the introduction of screening.[2] We have recently examined similar data from our clinic but have excluded those patients in the non-screened group who presented before the average age of diagnosis of the screened CF infants.[3] We reasoned that those infants would not have benefited from the existence of population based newborn screening as their clinical symptoms led to their diagnosis earlier than would have occurred on the basis of screening. When these early diagnosis infants with CF were excluded from the unscreened group, we found no difference in lung function or nutritional parameters at the age of 9 years between the unscreened (n=29) and the screened (n=31) groups. Further work is required to identify whether population based newborn screening will result in better lung function in later life. While the answer to this question is still unclear when considered on the basis of population based screening, there is no question that limitation of lung disease, particularly in infancy and early childhood, is the major factor in determining the adult consequences of CF lung disease.

Bacterial colonisation

CF lung disease is clinically characterised by the production of thick tenacious mucus with an increased propensity for chronic colonisation with bacterial organisms. At birth and before the onset of lower airway infection there is no destructive inflammatory process present.[4] One of the first steps used to prevent lower airway bacterial colonisation is the early detection of, and aggressive early treatment of, any lower airway colonisation. In a situation similar to that of population based screening, some centres prefer to treat all patients with prophylactic antibiotics in an attempt to prevent, or at least delay, early colonisation of the airway with *Staphylococcus aureus*. While anti-staphylococcal antibiotic prophylaxis has been shown to reduce the amount of cough symptoms as well as the number of antibiotic courses and hospital admissions in the first few years of life, there is also some evidence that it may be associated with earlier acquisition of *Pseudomonas aeruginosa*.[5–7]

An alternative approach to assessment and treatment of early bacterial colonisation of the lower airways in infants with CF is the aggressive use of bronchial lavage as a means of obtaining direct evidence of lower airway colo-

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nisation. While this technique may permit early detection and aggressive treatment of any *S aureus* colonisation, it does not directly achieve what is aimed for with *S aureus* prophylaxis—that is, the delay or prevention of *S aureus* colonisation. While *S aureus* colonisation may certainly produce symptoms when present in the lower airways of infants with CF, it is colonisation with *P aeruginosa* that is associated with a significant increase in airway inflammation and lung injury. Long term prognosis is impaired in infants whose airways are infected with this organism when compared with airways intermittently colonised by *S aureus*. Hudson and colleagues showed that, in infants aged under 2 years whose oropharyngeal flora included *P aeruginosa*, there was a decrease in clinical score at the age of 5 years and decreased pulmonary function at 7 years of age.[8] In those infants colonised with both *S aureus* and *P aeruginosa* the same results were found; however, this group had a 10 year survival estimate of 57% compared with 92–100% for infants not colonised or colonised with *P aeruginosa* alone. Kerem and colleagues studied 895 patients with CF and found that infants colonised with *P aeruginosa* in the first year of life had similar 10 year survival estimates to those who became colonised at 1–7 years of age and also after 7 years. Early colonisation was, however, associated with a significant reduction in lung function at 7 years of age and this reduction continued through into adult life.[9]

Henry and colleagues showed that colonisation with mucoid strains of *P aeruginosa* was associated with an increased level of morbidity and mortality.[10] They compared the survival of 50 children who had mucoid *P aeruginosa* isolated from their sputum cultures with that of 19 children whose sputum showed non-mucoid *P aeruginosa* and 12 children who had no *P aeruginosa* isolated from their sputum. Over an 8 year follow up period 42% of mucoid positive *P aeruginosa* patients died compared with 11% of those with non-mucoid *P aeruginosa* and 8% of those with no *P aeruginosa* colonisation.

Nixon and colleagues have recently shown that, in a group of 56 infants diagnosed with CF on newborn screening, 43% were colonised with *P aeruginosa* by the age of 7 years. This group had higher hospital admission rates and lower National Institutes of Health scores at 7 years than culture negative children. Four infants from this group died before 6 years of age, all of whom had mucoid *P aeruginosa* cultured from the lower airway prior to death.

While these studies all confirm that early colonisation with *P aeruginosa*, with or without *S aureus*, in the paediatric setting has significant implications for CF lung disease in adults, there is evidence that aggressive treatment of early *P aeruginosa* colonisation is associated with a transient clearing of this organism from the airway.[11] Hoiby differentiates between intermittent colonisation and chronic infection with *P aeruginosa* and describes intermittent colonisation as preceding chronic infection by an average of 12 months. The change from intermittent to chronic infection is associated with a rise in specific anti-pseudomonal antibodies. Hoiby has further shown that aggressive treatment of *P aeruginosa* during intermittent colonisation can achieve clearing of the organism from the airways. He compared 48 patients treated with aggressive anti-pseudomonal therapy with 42 historic controls and found that only 16% of the treated patients developed chronic infection with *P aeruginosa* over a period of 3.5 years compared with 72% of the controls. For this reason continuous surveillance for the first sign of airway colonisation, either by regular bronchial lavage or examination of upper airway washings, is now increasingly employed.[12]

A third organism which directly influences adult consequences of paediatric CF lung disease is *Burkholderia cepacia*. Recognised as a CF pathogen initially as an organism which produced aggressive lung disease and usually death within a short period, later work identified two alternative clinical courses.[13 14] While some patients exhibited a slower but still progressive decline in pulmonary function culminating in death, a third group of patients colonised with *B cepacia*, many of whom were children, were shown to carry the organism for extended periods of time without apparently any adverse outcome.[1] Recent work has shown that the differences in clinical severity of lung disease seen following colonisation with *B cepacia* result from different genotypes of the organism.[15]

While 40–80% of adult patients will be colonised with *P aeruginosa*, Hoiby has also shown that regular aggressive treatment with anti-pseudomonal agents in *P aeruginosa* positive patients is associated with an improvement in lung function over a period of 12 months.[16]

Given the drive to prevent or delay the onset of lower airway colonisation with *P aeruginosa*, preventive public health measures have been shown to be important in limiting the spread of the organism between patients. Historically, camps for children with CF were considered a good way of empowering young children with this condition to help manage their lives. However, recognition that cross infection occurs between *P aeruginosa* positive negative patients, as well as between *B cepacia* positive and negative patients, has now led to most major CF organisations recommending that such camps should not be held. Furthermore, in the hospital setting many clinics are now using strategies to limit the possible cross infection between patients in areas such as physiotherapy, wards, and outpatient clinics. A much harder challenge is to set suggested guidelines for limiting cross infection in the community such as at CF group meetings, travelling together in cars, and working in closed spaces. Some CF organisations have drawn up guidelines in an attempt to address this issue.[16] In addition to the early recognition of the first isolation of *P aeruginosa* from the lower airway, limitation of the progressive nature of CF lung disease has been shown to be achieved by regular aggressive therapy of anti-pseudomonal chest infections.[17]

Physiotherapy

While antibiotic therapy is accepted as the backbone of treatment for pseudomonal colonisation in CF, the underlying abnormality in mucociliary clearance produced by pseudomonal infection of the airway has been addressed by the institution of regular chest physiotherapy, both in acute deteriorations in lung function and also in the maintenance of long term stability of lung function. Most trials of physiotherapy techniques have investigated the effects of differing types of treatment on short term improvements in lung function or other parameters of lung disease such as sputum production.[18 19] At least two trials have examined the benefits of various physiotherapy techniques on long term lung function and thus can be considered in a discussion of adult consequences of paediatric lung disease as institution of such treatment in childhood may limit adult lung diseases in CF. In 1988 Reisman and colleagues compared the effect of a combination of conventional physiotherapy (postural drainage and chest percussion) and the forced expiratory technique (FET) with the effects of FET alone over a three year period in a group of patients with CF.[20] A significantly greater decline in lung function (as assessed by FEF_{25-75}) was seen in patients using FET alone than in those who also performed conventional chest physiotherapy. They concluded that the long term course of pulmonary function is adversely affected when conventional physiotherapy is not used. While this finding justified the continued use of the time consuming conventional postural drainage and chest percussion technique, further advances in chest physiotherapy have included the introduction of devices such as the flutter valve and positive expiratory pressure (PEP) mask which allow application of positive end expiratory pressure during physiotherapy.[21] In a recent study McIlwaine and colleagues compared the long term effect of PEP mask physiotherapy with conventional postural drainage and percussion therapy in a group of 40 patients with CF over a 12 month period and found a significantly greater improvement in lung function, assessed by measurements of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced expiratory flow (FEF_{25-75}), in the patients who used PEP mask physiotherapy compared with those who used conventional postural drainage and percussion therapy. This finding, taken in association with the earlier findings of Reisman, indicate that physiotherapy has a major influence in limiting the adult consequences of CF. The study by McIlwaine *et al* illustrates the importance of assessing newer techniques against proven established older techniques before such techniques are widely incorporated into recommended therapeutic regimes.

One area of chest physiotherapy that has recently received considerable attention, and has direct implications for the adult consequences of lung disease in CF, is the relationship between chest physiotherapy, gastro-oesophageal reflux, and lung disease in young infants with CF. Button *et al*[22] examined six adolescent patients with CF who had significant lung disease requiring frequent admission to hospital and who were symptomatic of reflux during postural drainage physiotherapy. When their physiotherapy was changed to PEP therapy all patients reported a reduction in symptoms of reflux but, in addition, there was a significant improvement in lung function in these patients over the first 6 months of the PEP therapy. This improvement was sustained for a further 18 months and was associated with a reduction in the number of hospital inpatient days per year.[22] In infants with CF, however, the presence of gastro-oesophageal reflux during head down physiotherapy remains controversial.[23]

Tobramycin

Ramsey and colleagues have recently shown that intermittent regular administration of high dose (300 mg bd) nebulised tobramycin to 520 patients with CF of mean age 21 years was associated with improved lung function, decreased density of *P aeruginosa* in the sputum, and decreased risk of admission to hospital over a 24 week study period.[24] However, no significant benefit was found in patients aged 6–12 years, so the role of high dose tobramycin as a therapeutic tool for paediatric patients in limiting the adult consequences of their lung disease remains uncertain. As a significant improvement in lung function was evident in patients aged 13–17 years, there may be a role for tobramycin in influencing the adult consequences of paediatric lung disease.

Anti-inflammatory therapy

While the aggressive and regular assessment and treatment of bacterial colonisation of the lower airways is the benchmark for limitation of progressive CF lung disease, increasing interest is being shown in the adjunctive use of anti-inflammatory agents. Earlier trials using corticosteroids were unsuccessful because of the increased incidence of side effects in the steroid treated groups of patients.[25] More recently, work has focused on less toxic oral agents such as ibuprofen and inhaled agents with anti-inflammatory actions such as inhaled steroids. Konstan *et al*[26] showed, in a small group of patients treated with high doses of ibuprofen over 4 years, that there was less deterioration in lung function in the ibuprofen treated group (n=27) than in a placebo treated group (n=30). The ibuprofen treated group had a significantly lower reduction in FEV_1 than the placebo treated group (1.48% *v* 3.57% per year); however, the rate of decline in the control group in this study is significantly higher than that recorded in other larger studies. In a 4 year study of oral steroids in children with CF the placebo treated group had an annual rate of decline in FEV_1 of only 1.5%.[25] Recent data on 2100 patients released from the European Epidemiologic Registry of Cystic Fibrosis showed an annual rate of decline in FEV_1 of 1.1% for the group as a whole. It remains to be confirmed whether long term treatment with high doses of ibuprofen produces a clinical difference in reducing the rate

of decline in FEV_1 as opposed to a statistical difference. A wide range of other anti-inflammatory agents has been postulated as possibly being effective in influencing the long term progression of lung disease in CF. At least three trials of inhaled steroids have been reported but none has produced convincing long term benefits.[27–29] In addition, other inflammatory agents under review include pentoxifylline, fish oil, tyloxapol, antiproteases (including secretory leukoprotease inhibitor, α_1-antiprotease inhibitor, cell penetrant monocyclic β lactam inhibitor, and monocyte/neutrophil elastase inhibitor), and antioxidants such as glutathione and β-carotene.[30] Whether any of these agents will influence the adult consequences of paediatric CF lung disease is yet to determined.

Recognition of the group of compounds called inbiotics such as tegrins has led to current trials of agents such as protegrin, a polypetide of porcine origin which has been shown to have antibacterial properties. Successful use of these agents in the paediatric setting may limit the adult consequences of CF lung disease. In addition, successful identification of agents which can promote the function of the CFTR molecule or alter the airway environment (such as amiloride) may, in the long term, be able significantly to influence the adult consequences of paediatric CF lung disease by limiting the rate of progression of this condition.

Pulmozyme or recombinant DNase has been shown to produce an improvement in lung function in some patients with CF and is now widely used in many countries to help patients expectorate thick mucus. A large multinational placebo controlled study (the Pulmozyme Early Intervention Trial) is currently being conducted which aims to investigate whether regular administration of Pulmozyme in children with mild lung disease (starting FEV_1 >80% predicted) will limit the deterioration in FEV_1 over the 2 year period of the study.

Gene therapy

The ultimate way to limit the adult consequences of CF is to correct the underlying biochemical effect in the respiratory system soon after birth. While trials of gene therapy in CF have been occurring for over 5 years, there are still fundamental problems with the therapy both in terms of safety (viral vector gene therapy) and efficiency (liposomal gene therapy). At present trials of gene therapy for CF are being conducted in the adult population; however, gene therapy introduced early in life after the diagnosis of CF has been made would have the potential to produce a major alteration in the spectrum of CF lung disease in the adult. Despite the intense desire of many parents whose children have CF for this therapy to be available and effective in the near future, the reality is that it is still many years away from being a regular and effective therapy.[31]

Nutritional factors

Early studies of the relationship between malnutrition and lung disease in children with CF found a direct relationship between the two parameters and an equal relationship between both factors and survival rates. What was unclear, however, was whether this was a direct causal relationship and, further, whether improving the nutritional aspects would improve pulmonary disease. In a comparative study between the Boston and Toronto CF clinics in the early 1980s a significantly different median age of survival between the two clinics was evident with Toronto, a clinic which placed a heavy emphasis on nutritional therapy, being associated with a much better survival rate. Interestingly, despite the difference in survival rates between the two clinics, the level of pulmonary function was the same. With the recognition of the CF gene in the late 1980s, attention was drawn to whether there were genotype-phenotype correlations which could predict the severity of lung disease. While pancreatic sufficient patients are known to have better pulmonary function at any given age and longer survival than those with pancreatic insufficiency, it is as yet unclear whether this milder lung disease is secondary to a milder CF genetic lesion or whether it is directly associated with better nutrition (pancreatic sufficient patients having normal levels of fat soluble vitamins and normal fatty acid composition of membrane lipids[32]). While this discussion suggests that nutrition may be an influencing factor in limiting the adult consequences of paediatric CF lung disease, it does highlight a larger area of influence—namely, the variation in the clinical course of CF lung disease associated with different CF genotypes.

Conclusions

Although this review has focused on therapeutic interventions which may limit the adult consequences of paediatric CF lung disease, it is important to recognise the challenge of long term adherence to prescribed therapy in patients with CF—from the perspective of the patient, the family, and the healthcare personnel. A disappointing result in this present era is to witness the natural course of CF in a child as a result of either misdiagnosis or failure to accept or use conventional therapy. While considerable advances are yet to be made to permit accurate genotype-phenotype correlations, for most genotypes there is no question that, if untreated, the adult consequences of paediatric CF lung disease are generally very poor. For this reason measures aimed at improving and encouraging adherence to therapy are vital tools in minimising these adult consequences.

As mentioned earlier, changes in paediatric treatment for CF have meant that concerns regarding the adult consequences of paediatric CF lung disease have become a reality. While the preceding discussion has concentrated on some of the specific steps that have been identified as minimising the adult consequences of paediatric lung disease, it is implicit that care of patients with CF is best conducted in centres with experience in CF care and the ability to

provide the wide spectrum of expertise necessary for total care—not only medical staff of various disciplines including respiratory physicians, gastroenterologists, endocrinologists, and interventional radiologists but also dietitians, physiotherapists, and psychologists. Early reports suggesting that care of CF patients in tertiary centres provided a better long term prognosis were sometimes criticised.[33 34] However, in a recent study by Mahadeva *et al*, in which the long term outcome of patients treated in a tertiary care centre specialising in CF was compared with that in patients treated in paediatric centres not specialising in CF care, the improved nutritional and pulmonary status of patients treated at a specialist centre is good evidence that regular treatment and assessment in centres specialising in CF care is a further way of minimising the adult consequences of paediatric CF lung disease.[34]

1 Yankaskas JR, Knowles MR. *Cystic fibrosis in adults*. Philadelphia: Lippincott-Raven, 1999.
2 Waters DL, Wilcken B, Irwig L, *et al*. Clinical outcomes of newborn screening for cystic fibrosis. *Arch Dis Child* 1999; **80**:F1–7.
3 Robinson PJ, Newman Y, Vyas J. Does neonatal screening influence spirometry at 9 years of age? *Pediatr Pulmonol* 1999;Suppl 19:S337.
4 Armstrong DS, Grimwood K, Carzino R, *et al*. Lower respiratory infection and inflammation in infants with newly diagnosed cystic fibrosis. *BMJ* 1995;**310**:1571–2.
5 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.
6 Wright GLT, Harper J. Fusidic acid and lincomycin therapy in staphylococcal infections in cystic fibrosis. *Lancet* 1970; i:9–14.
7 Harrison CJ, Marks MI, Welch DF, *et al*. A multicentric comparison of related pharmacologic features of cephalexin and dicloxacillin given for two months to young children with cystic fibrosis. *Pediatr Pharmacol* 1985;**5**:7–16.
8 Hudson VL, Wielinski CL, Regelmann WE. Prognostic implications of initial oropharyngeal bacterial flora in patients with cystic fibrosis diagnosed before the age of two years. *J Pediatr* 1993;**122**:854–60.
9 Kerem E, Corey M, Gold R, *et al*. Pulmonary function and clinical course in patients with cystic fibrosis after pulmonary colonisation with *Pseudomonas aeruginosa*. *J Pediatr* 1990;**116**:714–9.
10 Henry RL, Mellis CM, Petrovic L. Mucoid *Pseudomonas aeruginosa* is a marker of poor survival in cystic fibrosis. *Pediatr Pulmonol* 1992;**12**:158–61.
11 Valerius NH, Koch C, Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by early treatment. *Lancet* 1991;**338**:3725–6.
12 Frederiksen B, Koch C, Hoiby N. Antibiotic treatment of initial colonization with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. *Pediatr Pulmonol* 1997;**23**:330–5.
13 Tablan OC, Chorba TL, Schidlow DV, *et al*. *Pseudomonas cepacia* colonisation in patients with cystic fibrosis: risk factors and clinical outcome. *J Pediatr* 1985;**107**:382–7.
14 Lewin LO, Byard PJ, Davis PB. Effect of *Pseudomonas cepacia* colonization on survival and pulmonary function of cystic fibrosis patients. *J Clin Epidemiol* 1990;**43**:125–31.
15 Sun L, Jiang R-Z, Steinbach S, *et al*. The emergence of a highly transmissible lineage of cbl$^+$ *Burkholderia cepacia* causing cystic fibrosis centre epidemics in North America and Britain. *Nature Med* 1995;**1**:661–6.
16 Frederiksen B, Koch C, Hoiby N. Changing epidemiology of *Pseudomonas aeruginosa* infection in Danish cystic fibrosis patients (1974–1995). *Pediatr Pulmonol* 1999;**28**:159–66.
17 Fridkin SK, Weinstein RA. Resistant gram-negative infections, including cystic fibrosis. In: Abrutyn E, Goldman D, Scheckler W, eds. *Saunders Infection Control Reference Service*. New York: WB Saunders, 1998: 662–4.
18 Braggion C, Cappelletti LM, Cornacchia M, *et al*. Short term effects of three chest physiotherapy regimens in patients hospitalized for pulmonary exacerbations of cystic fibrosis: a cross over randomized study. *Pediatr Pulmonol* 1995;**19**:16–22.
19 Desmond KJ, Schwenk WF, Thomas E, *et al*. Immediate and long term effects of chest physiotherapy in patients with cystic fibrosis. *J Pediatr* 1983;**103**:538–42.
20 Reisman J, Rivington-Law B, Corey M, *et al*. Role of conventional physiotherapy in cystic fibrosis. *J Pediatr* 1988;**113**:632–6.
21 McIlwaine M, Wong LT, Peacock D, *et al*. Long-term comparative trial of conventional postural drainage and percussion versus positive expiratory pressure physiotherapy in the treatment of cystic fibrosis. *J Pediatr* 1997;**131**:570–4.
22 Button BM, Heine RG, Catto-Smith AG, *et al*. Postural drainage in cystic fibrosis: is there a link with gastro-oesophageal reflux? *J Pediatr Child Health* 1998;**34**:330–4.
23 Phillips GE, Pike SE, Rosenthal M, *et al*. Holding the baby: head downwards positioning for physiotherapy does not cause gastro-oesophageal reflux. *Eur Respir J* 1998;**12**:954–7.
24 Ramsey BW, Pepe MS, Quan JM, *et al*. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *N Engl J Med* 1999;**340**:23–30.
25 Eigen H, Rosenstein BJ, FitzSimmons S, *et al*. A multicenter study of alternate-day prednisolone therapy in patients with cystic fibrosis. *J Pediatr* 1995;**126**:515–23.
26 Konstan MW, Byard PJ, Hoppel CL, *et al*. Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 1995;**332**:848–54.
27 Nikolaizik WH, Schoni MH. Pilot study to assess the effect of inhaled corticosteroids on lung function in patients with cystic fibrosis. *J Pediatr* 1996;**128**:271–4.
28 Van Haren EHJ, Lamers J-WJ, Festen J, *et al*. The effects of the inhaled corticosteroid budesonide in lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis. *Respir Med* 1995;**89**:209–14.
29 Balfour-Lynn IM, Klein NJ, Dinwiddie R. Randomized controlled trial of inhaled corticosteroids (fluticasone propionate) in cystic fibrosis. *Arch Dis Child* 1997;**77**:124–30.
30 Oerman C, Sockrider MM, Konstan MW. The use of anti-inflammatory medications in cystic fibrosis. *Chest* 1999; **115**:1053–8.
31 Geddes DM, Alton EWFW. The CF gene: 10 years on. *Thorax* 1999;**54**:1052–3.
32 Gaskin K, Gurwitz D, Durie P, *et al*. Improved respiratory prognosis in patients with cystic fibrosis with normal fat absorption. *J Pediatr* 1982;**100**:857–62.
33 Phelan P, Hey E. Cystic fibrosis mortality in England and Wales and in Victoria, Australia. *Arch Dis Child* 1984;**59**: 71–3.
34 Lewis PA. Inferences for health provision from survival data in cystic fibrosis *Arch Dis Child* 1998;**79**:297–9.
35 Mahadeva R, Webb K, Westerbeek RC, *et al*. Clinical outcome in relation to care in centers specializing in cystic fibrosis: cross sectional study. *BMJ* 1998;**316**:1771–5.