ORIGINAL ARTICLE

Early airway infection, inflammation, and lung function in cystic fibrosis

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Children with cystic fibrosis (CF) have structurally normal lungs at birth,¹ but lower airway infection and inflammation may be present from the first weeks of life.^{2–4} Little is known about how these changes within the airways affect lung function.

Studies of lung function in infants with CF have frequently shown abnormalities from early infancy. However, limited subject numbers and differences in subject selection or measures of lung function make meaningful comparisons difficult.⁵ Several studies show that infants with CF have normal thoracic gas volume, specific compliance, and conductance at birth, but by the first year of life some have evidence of hyperinflation, with reduced compliance and conductance.^{6–9} In particular, hyperinflation and airway obstruction may be found in young children with respiratory symptoms at the time of testing.^{8,10} Nevertheless, when using the more sensitive technique of raised volume rapid thoracoabdominal compression, reduced forced expiratory volumes have also been detected in asymptomatic infants.¹¹ While it might be expected that airway infection plays a key role in the relation between lung function and respiratory symptoms, this has not been shown. Indeed, one recent study found lung function in CF infants was not influenced by a history of clinically recognised lower respiratory illness.¹²

The present study examined the relation between airway infection and inflammation, respiratory symptoms, and lung function in infants and young children with CF using bronchial lavage (BL) and the raised volume rapid thoracoabdominal compression technique. Subjects were recruited from a population based birth cohort identified by newborn CF screening and had at most mildly symptomatic lung disease.

METHODS

Participants

The state of Victoria, Australia, has a newborn screening programme for CF, with diagnosis confirmed by gene mutation

Aims: To determine the relation between lower airway infection and inflammation, respiratory symptoms, and lung function in infants and young children with cystic fibrosis (CF).

Methods: A prospective study of children with CF aged younger than 3 years, diagnosed by a newborn screening programme. All were clinically stable and had testing as outpatients. Subjects underwent bronchial lavage (BL) and lung function testing by the raised volume rapid thoracoabdominal compression technique under general anaesthesia. BL fluid was cultured and analysed for neutrophil count, interleukin 8, and neutrophil elastase. Lung function was assessed by forced expiratory volume in 0.5, 0.75, and 1 second.

Results: Thirty six children with CF were tested on 54 occasions. Lower airway infection shown by BL was associated with a 10% reduction in FEV_{0.5} compared with subjects without infection. No relation was identified between airway inflammation and lung function. Daily moist cough within the week before testing was reported on 20/54 occasions, but in only seven (35%) was infection detected. Independent of either infection status or airway inflammation, those with daily cough had lower lung function than those without respiratory symptoms at the time of BL (mean adjusted FEV_{0.5} 195 ml and 236 ml respectively).

Conclusions: In young children with CF, both respiratory symptoms and airway infection have independent, additive effects on lung function, unrelated to airway inflammation. Further studies are needed to understand the mechanisms of airway obstruction in these young patients.

analysis and sweat chloride ≥ 60 mmol/l. The Victorian CF Clinic manages all newly diagnosed infants at one of two affiliated hospitals. From January 1997 until December 1999, the parents of newborn infants and children aged younger than 3 years were approached as outpatients for consent to participate in the study. Children with tachypnoea, respiratory distress, or abnormal chest auscultatory findings at the time of testing were excluded, as were those whose clinical care was compromised by extreme social difficulties. Parents of all participants gave informed consent and the ethics committees of the Royal Children's Hospital and Monash Medical Centre approved the study.

Testing was performed on an elective basis shortly after diagnosis and, in older children, as close as possible to the ages of 12, 24, or 36 months. At presentation for testing, parents were asked about respiratory symptoms in their child. For the purposes of the study, symptomatic children were those with a daily moist cough in the week prior to testing. Oral antibiotics given for this cough were also recorded. No child had received inhaled or systemic steroids, or ibuprofen.

Anthropomorphic measurements were compared with population normal ranges and converted to a standard deviation score, where each individual's weight and height are expressed in units of the standard deviation of the population's normal range for that measurement.^{13,14}

Lung function testing

Lung function testing and bronchoscopy were performed under general anaesthesia, induced with sevoflurane gas or

Abbreviations: BL, bronchial lavage; CBA, chocolate bacitracin agar; CF, cystic fibrosis; CFU, colony forming unit; FEV, forced expiratory volume; GEE, generalised estimating equation; IL, interleukin

intravenous propofol, and maintained with intravenous propofol. Propofol has been shown in older children to have no effect on respiratory system resistance or compliance.¹⁵ Opioids and benzodiazepines were avoided because of their potential bronchodilating effects.

Lung function testing was performed using the raised volume rapid thoracoabdominal compression technique.^{11–18} Briefly, lung volume was raised above the tidal range to an inflation pressure of 20 cm H₂O. Three raised volume breaths were delivered prior to thoracoabdominal compression by an inflatable jacket at end inspiration. The jacket inflation pressure was progressively increased in 5–10 cm H₂O increments until a transmitted compression pressure of 20 cm H₂O was measured at the airway opening during a 0.15 second airway occlusion. This produces a total standardised driving pressure for expiration of 40 cm H₂O. The procedure was repeated until at least three technically satisfactory recordings had been made (no evidence of leak at the mask, adequate transmission pressure, and inflation and expiration uninterupted by a sigh or glottic closure).¹⁹

Flow was measured using an infant pneumotachograph (Hans Rudolph series 3719, calibrated for 0–100 l/min) and forced expiratory volumes (FEV_{0.5}, FEV_{0.75}, and FEV₁) were calculated by the LABDAT-ANADAT 5.2 data acquisition and analysis software package (Montreal, Canada). Despite setting of the delivered inflation pressure at 20 cm H₂O, slight variability in the recorded pressure at the mask at end inspiration occurs.¹⁶ For this reason, forced expiratory volumes were standardised to an exact inflation pressure of 20 cm H₂O using linear regression of forced expiratory volume versus inflation pressure for each individual, to allow for comparison of forced expiratory volumes between infants at the same inflation pressure.^{11–16}

Bronchial lavage

Flexible bronchoscopy was performed immediately after lung function testing.⁴ As described previously,²⁰ a single volume BL of 1 ml/kg of non-bacteriostatic normal saline was performed in the right middle lobe and repeated in the lingula. The lavage fluid from each site was pooled and transported on ice to the laboratory for immediate processing.

Laboratory methods

As previously reported,^{4–20} BL fluid was plated onto selective and non-selective media (horse blood, MacConkey, mannitol salt, chocolate bacitracin agar (CBA), cetrimide, and *Burkholderia cepacia* selective agar) for the counting and identification of respiratory pathogens by standard quantitative and qualitative microbiological methodologies respectively. Viral culture and immunofluorescence for a panel of respiratory viruses (influenza A and B, parainfluenza 1, 2, and 3, respiratory syncytial virus, and adenovirus) were also performed on BL fluid. Infection was defined by $\geq 10^5$ colony forming units (CFU) of bacterial respiratory pathogens per ml of BL fluid²⁰ or if respiratory viruses were detected. Airway inflammation was measured by total and differential cell counts, enzyme linked immunosorbent assay (ELISA) for interleukin 8 (IL-8), and chromogenic assay for free neutrophil elastase concentrations.⁴

Statistical methods

Between group comparisons of all variables were performed using regression models fitted by the method of generalised estimating equations (GEE) to allow for repeated measures on some subjects.²¹ A linear regression model was used for continuous outcomes (after log transformation where necessary), and a logistic regression model for dichotomous outcomes. These analyses provide natural generalisations of the standard approaches based on *t* test and χ^2 to correlated data. This modelling approach was used to produce estimates

of mean forced expiratory volumes by group, adjusted for height by analysis of covariance. Further adjustment for weight or gender did not affect results and was therefore not included. GEE was also used to examine the association between lung function and inflammatory markers. Raw values of IL-8 and free neutrophil elastase concentration exhibited positively skewed distributions, and logarithmic transformation was therefore performed prior to analysis by GEE. All analyses were performed using the Stata statistical software package.²²

The intrasubject variability of the lung function measurements was calculated by one way analysis of variance following logarithmic transformation of the raw data recorded during technically acceptable manoeuvres.²³ This produced an estimate of intrasubject variability for FEV_{0.5} of 5.1%.

RESULTS

Participants

Of 43 eligible children with CF attending the Royal Children's Hospital CF clinic, 30 (70%) took part in the study, including 78% of those diagnosed following newborn screening. Six (14%) families were not approached because of either illness sufficiently severe to preclude elective general anaesthesia (*n* = 4) or extreme social difficulty (*n* = 2). The remaining seven families (16%) declined to be involved. Eleven additional children were recruited to the study: four who were born in 1995, two following transfer from other states, and five from the affiliated CF centre within the city. Of the 41 subjects recruited, five (12%) were subsequently excluded because of technically unsatisfactory lung function tests. Lung function testing and BL were performed on the remaining 36 subjects (21 females) on 54 occasions (14 were tested twice at different ages and two were tested on three occasions). Table 1 presents clinical characteristics.

Lung function in the whole group

No significant difference in lung function was found based on gender, homozygosity for the $\Delta F508$ deletion, method of diagnosis, exposure to tobacco smoke in the home, or a family history of asthma. Ten children were tested aged 6 months or younger, and the lung function adjusted for height for these infants was not significantly different from the group as a whole (*p* = 0.76). Maternal smoking during pregnancy was associated with a mean FEV_{0.5} 16% lower than in those who were not exposed (*p* = 0.08).

Relation between infection, inflammation, and lung function

Lower airway infection was detected by BL on 15/54 (28%) testing occasions in 13/36 (33%) subjects. Infection by a single pathogen was diagnosed on 11 occasions: *Staphylococcus aureus* in three, *Hemophilus influenzae* in four, *Moraxella catarrhalis* in

Table 1 Characteristics of 36 subjects with CF

Females, number (%)	21 (58%)
CF genotype	
Homozygous $\Delta F508$	16 (44%)
Heterozygous $\Delta F508$	20 (56%)
Method of diagnosis	
Newborn screening	29 (81%)
Meconium ileus	4 (11%)
Other gastrointestinal symptoms	2 (6%)
Respiratory symptoms	1 (3%)
History of maternal smoking during pregnancy	7 (19%)
Postnatal exposure to tobacco smoke in the home	12 (33%)
Family history of asthma (at least one parent)	11 (31%)

Table 2 Clinical characteristics, bronchial lavage, and lung function results from 36 CF subjects on 54 occasions, by infection group

	Infection (n=15)	No infection (n=39)	p value*
Mean (SD) age (months)	22.8 (6.7)	15.9 (10.9)	0.02
Age range (months)	12–36	1–37	
Weight Z score, mean (SD)	−0.6 (1.1)	−0.2 (1.1)	0.12
Height Z score, mean (SD)	−0.3 (1.3)	−0.3 (1.1)	0.74
Daily cough in the week of testing, no. (%)	7 (47%)	13 (33%)	0.32
Taking oral antibiotics, no. (%)	6 (40%)	12 (31%)	0.74
Lung function†			
FEV _{0.5} (ml) (n=54)	203 (178 to 228)	228 (209 to 246)	0.06
FEV _{0.75} (ml) (n=52)	240 (209 to 272)	266 (245 to 288)	0.12
FEV ₁ (ml) (n=49)	272 (233 to 311)	286 (261 to 311)	0.50
BL studies‡			
% neutrophils	59 (47 to 70)	28 (21 to 35)	<0.001
IL-8 (pg/ml)	641 (305 to 1350)	253 (158 to 406)	0.03
Free neutrophil elastase (µg/ml)	8.3 (5.3 to 13.1)	5.6 (4.0 to 7.9)	0.09

*By GEE method to allow for repeated measures.

†Mean FEV₁ (ml) adjusted by regression analysis (GEE) for height, with 95% CI.

‡Arithmetic (neutrophil %) and geometric (IL-8 and free neutrophil elastase) means and 95% CI.

one, *Pseudomonas aeruginosa* in two, and parainfluenza virus type 3 in one. Mixed infection was diagnosed on the remaining four occasions: *P aeruginosa* and *H influenzae* in one, and *H influenzae* and *M catarrhalis* in three.

Table 2 presents clinical characteristics, BL, and lung function results according to infection status. Children with lower airway infection were older, but the frequency of infection was not associated with gender, CF genotype, cigarette smoke exposure, or a parental history of asthma. Lower airway infection was associated with a reduction in forced expiratory volumes of approximately 10%. This difference only approached statistical significance for FEV_{0.5} ($p = 0.06$), but a difference of 10% is considered a clinically important difference and is twice the intrasubject variability. Small numbers precluded examination of lung function results according to infecting pathogen, however the lowest lung function was seen in a 20 month old child with *P aeruginosa* infection. Although BL inflammatory indices were increased among infected subjects, no direct relation was observed with lung function ($p \geq 0.1$).

Respiratory symptoms and lung function

A moist cough over the previous week was reported at the time of testing on 20/54 (37%) occasions from 18/36 (50%) subjects. All children were otherwise well, and no subject had wheeze

reported or detected on examination. Table 3 shows characteristics of children by symptom group. Infection was identified in a minority of BL specimens obtained from symptomatic children (7/20, 35%). Conversely, only 7/15 (47%) infections shown by BL were associated with symptoms, including all three subjects with *P aeruginosa* infection.

Respiratory symptoms were associated with significantly reduced lung function ($p \leq 0.001$).

The mean difference in FEV_{0.5} between the symptomatic and asymptomatic groups was nearly twice the magnitude of the infection related difference. No association was observed between gender, CF genotype, exposure to tobacco smoke, or parental history of asthma and the presence of respiratory symptoms ($p > 0.1$). Markers of inflammation were not increased in the children with respiratory symptoms ($p > 0.5$).

The majority of subjects with respiratory symptoms were receiving antibiotics (70%), but the results were not significantly affected by adjustment for antibiotic use in the regression analysis. Of the 13 children with daily cough in the absence of infection, nine (69%) were receiving oral antibiotics at the time of testing compared with 18/54 (33%) testing occasions in the CF group as a whole. However, only 2/13

Table 3 Clinical characteristics, bronchial lavage, and lung function results from 36 CF subjects on 54 occasions, by symptom group

	Symptomatic (n=20)	Asymptomatic (n=34)	p value*
Mean (SD) age (months)	20.7 (10.6)	15.7 (9.7)	0.07
Age range (months)	3–37	1–36	
Weight Z score, mean (SD)	−0.5 (0.9)	−0.2 (1.2)	0.16
Height Z score, mean (SD)	−0.6 (1.1)	−0.1 (1.2)	0.001
Oral antibiotics, no. (%)	14 (70%)	4 (12%)	<0.001
Infected, no. (%)	7 (35%)	8 (24%)	0.40
Lung function†			
FEV _{0.5} (ml) (n=54)	195 (174 to 215)	236 (218 to 254)	<0.001
FEV _{0.75} (ml) (n=52)	229 (203 to 255)	277 (255 to 298)	0.001
FEV ₁ (ml) (n=49)	244 (216 to 273)	307 (282 to 331)	<0.001
BL studies‡			
% neutrophils	39 (28 to 51)	36 (26 to 46)	0.54
IL-8 (pg/ml)	375 (192 to 736)	293 (172 to 499)	0.55
Free neutrophil elastase (µg/ml)	6.2 (4.2 to 9.3)	6.4 (4.5 to 9.1)	0.92

*By GEE method to allow for repeated measures.

†Mean FEV₁ (ml) adjusted by regression analysis (GEE) for height, with 95% CI.

‡Arithmetic (neutrophil %) and geometric (IL-8 and free neutrophil elastase) means and 95% CI.

Figure 1 (A) Neutrophil percentages in bronchial lavage fluid, by symptom and infection group. AU, asymptomatic/uninfected ($n = 22$); AI, asymptomatic/infected ($n = 8$); SU, symptomatic/uninfected ($n = 13$); SI, symptomatic/infected ($n = 6$). Open circles represent individual values; closed circles are geometric means following adjustment for repeated measures, with 95% CI. (B) Lung function by symptom and infection group. Open circles represent individual values for each subject; closed circles represent the mean FEV_{0.5} adjusted by analysis of variance for height for each group, with 95% CI. AU, $n = 26$; AI, $n = 8$; SU, $n = 13$; SI, $n = 6$.

(15%) had any respiratory pathogens detected by culture (10^2 CFU/mL *S aureus* and 10^3 CFU/mL *P aeruginosa* respectively). This finding, and the observation that inflammatory indices were not different between symptom groups, suggests that resolving or partially treated infection does not fully explain the lower lung function seen in children with respiratory symptoms.

When the linear regression (GEE) method was used to examine the joint effect of infection and the presence of cough, the evidence for an association of infection with FEV_{0.5} was somewhat increased ($p = 0.02$ compared with unadjusted p value of 0.06), although the magnitude of the estimated differences (infected versus uninfected, and symptomatic versus asymptomatic) was unchanged. There was no evidence for an interaction effect, such as a greater difference between symptomatic and asymptomatic among those infected, although numbers were small for assessing this. Figure 1 shows neutrophil percentages for BL cell counts and FEV_{0.5} results in a subgroup analysis including both symptoms and infection.

DISCUSSION

This study examines the relation between lung function and lower airway infection in a CF population aged younger than

3 years who were diagnosed principally by newborn screening and where BL identified infection. At the time of testing the children were clinically stable with at most mildly symptomatic lung disease. The study confirms earlier reports of lower lung function in some infants with CF,^{11 12 24 25} in particular, those with respiratory symptoms.^{26 27} It extends those findings by showing that airway infection and inflammation do not fully explain the reduced lung function previously described in infants and young children with respiratory symptoms. Lower respiratory infection and respiratory symptoms had an independent and additive adverse effect on lung function, which was not related to the degree of airway inflammation.

Another recently published study from Australia also used BL to examine the relation between lower airway infection and lung function.²⁸ Tests were performed in 22 infants and young children with CF and an association between abnormal lung function (reduced respiratory system compliance and air trapping) and bacterial load was detected. However, unlike our study, there was also a correlation between reduced lung function and airway inflammation. Unfortunately, the relation between respiratory symptoms and lung function was not examined. These contradictions in results might be explained by differences in study subjects. Overall, the children in that study were slightly older and sicker (73% had chronic respiratory symptoms and 27% had *P aeruginosa* infection), with evidence of greater airway inflammation, than subjects in the current study. This suggests more advanced lung disease was present. It is possible that chronic infection and established inflammation masked other effects on lung function. In contrast, our younger study population with minimal CF lung disease allowed a greater opportunity to identify other potential influences on lung function.

Several explanations are possible for the reduced lung function seen in the symptomatic group in this study. In accordance with advice given to parents in our clinic, most children with moist cough had started oral antibiotics before bronchoscopy. This raises the possibility of partially treated or resolving infection in the symptomatic, but uninfected children. However, only two subjects in this group had detectable pathogens on BL, and inflammatory markers were no different between symptomatic and asymptomatic participants. Moreover, findings were unaltered by adjustment for antibiotic use. Previous studies in our clinic population have indicated that oral antibiotics do not appear to alter BL culture results,²⁰ and while there may be an unequal distribution of bacterial numbers within CF lungs, airway inflammatory changes are more likely to be generalised.²⁹ Thus, partially treated infection is an unlikely explanation for the differences in lung function observed between the symptomatic and asymptomatic groups.

Airway inflammation may persist for a variable period following clearance of infection in CF,^{3 4} and may lead to cough and reduced lung function. No relation was apparent however, between markers of airway inflammation and lung function in this study, and markers of inflammation were not increased in symptomatic children. Gastro-oesophageal reflux is common in children with CF.³⁰ No child in this study had clinical evidence of significant aspiration of gastric contents, but the possibility of reflux with microaspiration was not specifically examined. This condition might be expected to lead to both cough and reduced lung function accompanied by airway inflammation. The latter, however, was not increased in symptomatic children.

Factors other than airway infection and inflammation may contribute to small airways obstruction in infancy, such as impaired prenatal lung growth, reactive airways disease, increased airway wall thickness, and mucus plugging. In this study, no subjects were born preterm or had another respiratory disorder. Exposure to tobacco smoke in utero was associated with evidence of small airways obstruction, as it is in healthy infants.^{31 32} However, smoke exposure in utero or at

home was not associated with increased cough and therefore cannot explain the reduced lung function in the symptomatic group. Familial atopic disease is also associated with lower lung function in infancy.³²⁻³⁴ No subjects were wheezy at the time of testing, but reactive airways disease cannot be excluded. However, children with asthmatic parents had neither lower lung function nor an increase in reported cough, making reactive airways disease an unlikely explanation for the study's findings.

Bronchial wall thickening is one of the most frequent early findings on computed tomography of the lungs in children with CF,⁵ and may be expected to lead to airway obstruction detectable by lung function testing. While there were no differences between inflammatory markers in the BL fluid from children with or without respiratory symptoms, persisting abnormalities of the airway wall may still have been present in symptomatic subjects. Reduced lung function in symptomatic young children may then more accurately reflect established bronchial wall pathology than intraluminal inflammation. Alternatively, previous airway infection can also lead to persistent abnormalities in the quantity or quality of airway mucus,^{35,36} contributing to airway obstruction. Others have described increased highly sulphated mucin within airway secretions of adults with CF,³⁷ its possible role in impaired mucociliary clearance,³⁸ and association with bacterial burden and disease severity.^{35,39} Treatment with antibiotics and mucolytic therapy,²⁷ or bronchodilators and chest physiotherapy,⁴⁰ has been shown to improve lung function in infants with CF, suggesting that enhancing clearance of secretions may have a role in treatment of symptomatic infants and young children without airway infection.

Because of the invasive nature of the testing involved in this study, tests were only performed on an annual basis, precluding more detailed longitudinal tracking of changes in airway infection and inflammation, and in lung function. Therapeutic interventions were not standardised, but if anything, the symptomatic children had received more aggressive therapy, and despite this they had lower lung function.

In summary, lower respiratory infection and the presence of a moist daily cough in young children with mild CF lung disease are independently associated with a reduction in lung function that is not explained by airway inflammation. While respiratory infections still influence the prognosis of children with CF,⁴¹ this finding suggests that other factors that may contribute to cough, such as increased airway mucus or submucosal inflammation, should be considered. Further investigations into the underlying causes of cough and reduced lung function are essential for the development of new therapies to improve airway obstruction in young children with CF. Long term follow up of infants with respiratory symptoms in the absence of lower airway infection will help determine subsequent correlates of early cough and reduced lung function and their influence on the course of CF lung disease.

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REFERENCES

- 1 **Chow CW**, Landau LJ, Taussig LM. Bronchial mucous glands in the newborn with cystic fibrosis. *Eur J Pediatr* 1982;**139**:240-3.
- 2 **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.
- 3 **Khan TZ**, Wagener JS, Bost T, et al. Early pulmonary inflammation in infants with cystic fibrosis. *Am J Respir Crit Care Med* 1995;**151**:1075-82.
- 4 **Armstrong DS**, Grimwood K, Carlin JB, et al. Lower airway inflammation in infants and young children with cystic fibrosis. *Am J Respir Crit Care Med* 1997;**156**:1197-204.
- 5 **Gappa M**, Ranganathan SC, Stocks J. Lung function testing in infants with cystic fibrosis: lessons from the past and future directions. *Pediatr Pulmonol* 2001;**32**:228-45.
- 6 **Beardmore CS**. Lung function from infancy to school age in cystic fibrosis. *Arch Dis Child* 1995;**73**:519-23.
- 7 **Beardmore CS**, Bar-Yishay E, Maayan C, et al. Lung function in infants with cystic fibrosis. *Thorax* 1988;**43**:545-51.
- 8 **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.
- 9 **Tepper RS**, Hiatt P, Eigen H, et al. Total respiratory system compliance in asymptomatic infants with cystic fibrosis. *Am Rev Respir Dis* 1987;**135**:1075-9.
- 10 **Tepper RS**, Hiatt P, Eigen H, et al. Infants with cystic fibrosis: pulmonary function at diagnosis. *Pediatr Pulmonol* 1988;**5**:15-18.
- 11 **Turner DJ**, Lanteri CJ, Lesouef PN, et al. Improved detection of abnormal respiratory function using forced expiration from raised lung volume in infants with cystic fibrosis. *Eur Respir J* 1994;**7**:1995-9.
- 12 **Ranganathan SC**, Dezateux C, Bush A, et al. Airway function in infants newly diagnosed with cystic fibrosis. *Lancet* 2001;**358**:1964-5.
- 13 **World Health Organization**. *Measuring change in nutritional status: guidelines for assessing the impact of supplementary feeding programmes for vulnerable groups*. WHO, 1983.
- 14 **Hamill PV**, Drizd TA, Johnson CL, et al. NCHS growth curves for children birth-18 years. United States. *Vital Health Stat* 11 1977;**165**:i-74.
- 15 **Habre W**, Matsumoto I, Sly PD. Propofol or halothane anaesthesia for children with asthma: effects on respiratory mechanics. *Br J Anaesth* 1996;**77**:739-43.
- 16 **Turner DJ**, Stick SM, Lesouef KL, et al. A new technique to generate and assess forced expiration from raised lung volume in infants. *Am J Respir Crit Care Med* 1995;**151**:1441-50.
- 17 **ATS/ERS Workshop Summary**. The raised volume rapid thoracoabdominal compression technique. *Am J Respir Crit Care Med* 2000;**161**:1760-2.
- 18 **Hayden MJ**, Sly PD, Devadason SG, et al. Influence of driving pressure on raised-volume forced expiration in infants. *Am J Respir Crit Care Med* 1997;**156**:1876-83.
- 19 **Stocks J**, Sly PD, Tepper RS, et al, eds. *Infant respiratory function testing*. Philadelphia: Wiley-Liss Co., 1996.
- 20 **Armstrong DS**, Grimwood K, Carlin JB, et al. Bronchoalveolar lavage or oropharyngeal cultures to identify lower respiratory tract pathogens in infants with cystic fibrosis. *Pediatr Pulmonol* 1996;**21**:267-75.
- 21 **Zeger S**, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;**42**:121-30.
- 22 **Stata Corporation**. *Intercooled Stata 6.0*. 1999. Stata Corporation, College Station, TX 77840, USA.
- 23 **Chinn S**. The assessment of methods of measurement. *Stat Med* 1990;**9**:351-62.
- 24 **Eid NS**. Early asymptomatic pulmonary changes in infants with cystic fibrosis. *Pediatr Pulmonol* 1997;(suppl 16):276-7.
- 25 **Mohon RT**, Wagener JS, Abman SH, et al. Relationship of genotype to early pulmonary function in infants with cystic fibrosis identified through neonatal screening. *J Pediatr* 1993;**122**:550-5.
- 26 **Hiatt P**, Eigen H, Yu P, et al. Bronchodilator responsiveness in infants and young children with cystic fibrosis. *Am Rev Respir Dis* 1988;**137**:119-22.
- 27 **Phelan PD**, Gracey M, Williams HE, et al. Ventilatory function in infants with cystic fibrosis. Physiological assessment of inhalation therapy. *Arch Dis Child* 1969;**44**:393-400.
- 28 **Dakin CJ**, Numa AH, Wang H, et al. Inflammation, infection and pulmonary function in infants and young children with cystic fibrosis. *Am J Respir Crit Care Med* 2002;**165**:904-10.
- 29 **Gutierrez JP**, Grimwood K, Armstrong DS, et al. Interlobar differences in bronchoalveolar lavage fluid from children with cystic fibrosis. *Eur Respir J* 2002;**17**:281-6.
- 30 **Heine RG**, Button BM, Olinsky A, et al. Gastro-oesophageal reflux in infants under 6 months with cystic fibrosis. *Arch Dis Child* 1998;**78**:44-8.
- 31 **Hanrahan JP**, Tager IB, Segal MR, et al. The effect of maternal smoking during pregnancy on early infant lung function. *Am Rev Respir Dis* 1992;**145**:1129-35.
- 32 **Dezateux C**, Stocks J, Dundas I, et al. Impaired airway function and wheezing in infancy. The influence of maternal smoking and a genetic predisposition to asthma. *Am J Respir Crit Care Med* 1999;**159**:403-10.
- 33 **Sheikh S**, Goldsmith LJ, Howell L, et al. Comparison of lung function in infants exposed to maternal smoking and in infants with a family history of asthma. *Chest* 1999;**116**:52-8.

- 34 **Stick SM**, Burton PR, Gurrin L, *et al*. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet* 1996;**348**:1060–4.
- 35 **Puchelle E**, Jacquot J, Beck G, *et al*. Rheological and transport properties of airway secretions in cystic fibrosis—relationships with the degree of infection and severity of the disease. *Eur J Clin Invest* 1985;**15**:389–94.
- 36 **Regnis JA**, Robinson M, Bailey DL, *et al*. Mucociliary clearance in patients with cystic fibrosis and in normal subjects. *Am J Respir Crit Care Med* 1994;**150**:66–71.
- 37 **Boat TF**, Cheng P-W, Iyer RN, *et al*. Human respiratory tract secretions. Mucous glycoproteins of nonpurulent tracheobronchial secretions and sputum of patients with bronchitis and cystic fibrosis. *Arch Biochem Biophys* 1976;**177**:95–104.
- 38 **Lethem MI**, James SL, Marriott C. The role of mucous glycoproteins in the rheologic properties of cystic fibrosis sputum. *Am Rev Respir Dis* 1990;**142**:1053–8.
- 39 **Chace KV**, Leahy DS, Martin R, *et al*. Respiratory mucous secretions in patients with cystic fibrosis: relationship between levels of highly sulphated mucin component and severity of the disease. *Clin Chim Acta* 1983;**132**:143–55.
- 40 **Hardy KA**, Wolfson MR, Schidlow DV, *et al*. Mechanics and energetics of breathing in newly diagnosed infants with cystic fibrosis: effect of combined bronchodilator and chest physical therapy. *Pediatr Pulmonol* 1989;**6**:103–8.
- 41 **Nixon GM**, Armstrong DS, Carzino R, *et al*. Clinical outcome after early *Pseudomonas aeruginosa* infection in cystic fibrosis. *J Pediatr* 2001;**138**:699–704.

ARCHIVIST

Cost of delayed childbearing

Many people are choosing to put off having children until relatively late in life. In the USA the proportion of first births with mothers in their thirties more than doubled between 1970 and 1990. Similar statistics have been reported from Canada. Is there a biological cost for this social trend? Data from Canada (Suzanne C Tough and colleagues. *Pediatrics* 2002;**109**:399–403) suggest that there might be.

In the province of Alberta there were 42 930 births in 1990 and 37 710 in 1996. At the same time the number of births to mothers aged 35 years or older increased from 3626 (8.4%) to 4798 (12.7%). The number of low birth weight babies increased by 0.5% for mothers aged under 35 and by 11% for older mothers. Preterm delivery increased by 3.5% among younger mothers and by 14% among older mothers. Older mothers accounted for 78% of the increase in low birth weight and 36% of the increase in preterm delivery. Older mothers were not more likely to have small-for-gestational-age babies. During the study period multiple births increased by 15% (twins and 14% (triplets). Older mothers accounted for 15% of the increase in twins. Only 0.36% of births in 1996 resulted from in vitro fertilisation.

Delayed childbearing may lead to an increase in preterm delivery and low birthweight.

PostScript

LETTERS

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The editors will decide, as before, whether to also publish it in a future paper issue.

Oral clodronate as treatment of osteogenesis imperfecta

The benefits of treatment with intravenous pamidronate in osteogenesis imperfecta (OI) have recently been reported.¹⁻³ These include reduced bone resorption, increased bone density, and improved clinical outcomes as judged by apparently lower fracture rates. We would like to report a single case of OI treated by the orally administered bisphosphonate, clodronate, with good effect.

A boy, whose mother was affected with clinically diagnosed type 1 osteogenesis imperfecta, was referred to our unit aged 13½ with a recent onset of severe back pain that had required hospital admission. He appeared of normal stature with blue sclerae and was able to walk independently. He had sustained four previous limb fractures; lateral radiographs of the thoracic and lumbar spine confirmed three vertebral wedge fractures. He was 158.9 cm tall (10th centile) and weighed 49 kg (25th centile). Lumbar spine bone mineral density scanning by dual x ray absorptiometry (DXA, Hologic QDR-1000, Hologic, Bedford, MA) revealed a BMD of 0.398 g/cm² (Z score -5.22, comparing his value to the average young man). Fasting urinary hydroxyproline/creatinine ratio, an index of bone resorption, was 96.6.

With informed parental consent for "off label" usage, he was commenced on oral sodium clodronate (Bonafos, Leiras Oy, Turku, Finland) at a dose of 400 mg daily. Dietary intake of calcium and vitamin D was above the estimated average requirement and supplementation was not given. Subsequent BMD scanning after one year of therapy showed an improvement of bone density by 7.8% to 0.468 g/cm² with a consequent increase in the BMD Z score to -5.09.

Treatment with clodronate was continued for five years, during which time he did not

sustain any new low trauma fractures. By the end of treatment, his BMD was 0.552 and his Z score had improved from -5.22 at first referral to -4.59. The fasting urinary hydroxyproline:creatinine ratio was decreased by 86% compared to baseline (13.6 v 96.6). Clodronate was discontinued for eight months; during this time his BMD remained stable but the Z score showed a small decline. His height at that stage lay on the 50th centile (176 cm) and his weight on the 10th (58 kg). The BMD remained considerably below the normal value and clodronate was recommenced at a dose of 800 mg daily.

Eight years after initial referral, his bone mineral density had increased by 60.6% to 0.613 g/cm² (Z score -4.16). To compensate for the expected increase in bone size, the bone mineral adjusted density (BMAD) was computed (BMD_{1-1.4}/square root of area_{1-1.4}) and showed an improvement of 24.6% in BMAD over the duration of therapy. Clodronate was discontinued when the patient was aged 22. He had reached a height of 177.4 cm and a weight of 60.8 kg, and the spine BMD Z score was -3.92. He had suffered no atraumatic fractures since commencing oral clodronate.

The rationale in using bisphosphonates for osteogenesis imperfecta is the inhibition of osteoclastic bone resorption leading to increased bone density and a potentially lower risk of fracture. This young man exhibited a good response to therapy with oral clodronate, suffering no adverse reactions. The increase in height of 18 cm over eight years, moving him from the 10th to 50th centile, suggests that his growth was not impaired by therapy.⁴ Many studies have shown that clodronate does not impair mineralisation. We are unable to determine the contribution of remodelling of vertebral fractures to his height gain.

A limitation of this report is that pubertal status was not documented at presentation. However, the increases in lumbar spine density are in excess of the expected average rates in growing children (3-6% per year and 14-16% during puberty).¹ The increase was also observed following adjustment for bone growth by BMAD and Z scores relating the measured BMD to age matched controls. The Z score (-5.22 to -3.92) improvement during therapy was not dissimilar to that reported with pamidronate¹ in younger children.

We agree that there is increasing evidence of a role for bisphosphonate therapy as part of the multidisciplinary management of osteogenesis imperfecta. Oral clodronate in our patient appeared to elicit a similar response to that of cyclical intravenous pamidronate, suggesting that orally administered bisphosphonates may be of value in the management of this disease.

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References

- 1 **Glorieux FH**, Bishop NJ, Plotkin H, *et al*. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med* 1998;**339**:947-52.
- 2 **Åström E**, Söderhäll S. Beneficial effects of long term intravenous bisphosphonate treatment of osteogenesis imperfecta. *Arch Dis Child* 2002;**86**:356-64.
- 3 **Banerjee I**, Shortland GJ, Evans WD, *et al*. Osteogenesis imperfecta and intravenous pamidronate. *Arch Dis Child* 2002;**87**:562.
- 4 **Nagant de Deuxchaisnes C**, Rombouts-Lindemans C, Haux JP, *et al*. Diphosphonates and inhibition of bone mineralisation. *Lancet* 1982;**2**:607-8.

Serum prolactin in coeliac schoolchildren

Literature published suggests that in children with coeliac disease (CD) serum prolactin concentrations are increased, and correlate with the grade of mucosal atrophy. It has been proposed that prolactin is a possible marker of disease activity.¹ Other studies, however, have failed to show this correlation in children with CD.²

We studied prolactin levels in children with CD, and the correlation with the severity of intestinal mucosal atrophy.

We used samples from a serum bank obtained during a mass screening for CD in Sardinian schoolchildren, using both antiendomysial antibodies and antigliadin antibodies as screening tests, as previously described.³ The sample included 20 children with CD on a gluten containing diet (16 girls, 4 boys, mean age 12.9 years, range 11.5-14.4 years) and 40 sex and age matched normal children (32 girls, 8 boys, mean age 13.0 years, range 11.2-14.8 years). All subjects were euthyroid. Prolactin was assayed in duplicate using a commercial immunoradiometric method; results were analysed by analysis of covariance.

Data are expressed as mean (SE). Prolactin levels were 4.62 (2.1) ng/ml in patients with CD and 5.90 (2.6) ng/ml in controls (no statistically significant difference). No correlation was found between prolactin concentrations and the degree of intestinal damage (Marsh criteria).

Our study did not confirm the increased prolactin concentrations in children with CD reported by Reifen and colleagues.⁴ Our population differed somewhat in that there was a higher mean age (12.9 v 11.3 years), a narrower age range (11.5-14.4 v 5-18 years), and a different girl:boy ratio (4:1 v 1:1). Furthermore, our study included three potential coeliacs (subjects with antiendomysium antibodies positivity but normal intestinal biopsy⁴) and 11 asymptomatic coeliac children. The hypothesis that the normal prolactin values observed in our study may be due at least in part to the different clinical characteristics of the population studied is plausible, but its validation requires a specifically designed study.

Acknowledgement

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References

- 1 Reifen R, Buskila D, Maislos M, *et al*. Serum prolactin in coeliac disease: a marker for disease activity. *Arch Dis Child* 1997;77:155-7.
- 2 Theintz GE, Nussle D, Cox J, *et al*. Prolactin and the gut: a controversy. *J Pediatr Gastroenterol Nutr* 1984;3:523-8.
- 3 Catassi C, Fanciulli G, D'Appello AR, *et al*. Antiendomysium versus antigliadin antibodies in screening the general population for coeliac disease. *Scand J Gastroenterol* 2000;35:732-6.
- 4 Ferguson A, Arranz E, O'Mahony S. Clinical and pathological spectrum of coeliac disease—active, silent, latent, potential. *Gut* 1993;34:150-1.

BOOK REVIEWS

A Clinical Guide to Inherited Metabolic Diseases, 2nd edn

Edited by JTR Clarke UK: Cambridge University Press, 2002, £29.95, pp 306. ISBN 0521890764

Dr Clarke's enthusiasm and erudition are evident on every page of this book, which is handily sized, and, wonder of wonders, costs only £30.

Most of the chapters are written with a clinically based approach, and the chapters on basic principles in understanding inherited metabolic disease, neonatal screening, hypoglycaemia, metabolic acidosis, storage diseases, and dysmorphism will be read with a sensation of increasing revelation by just about any paediatrician, and those with a secure background in biochemistry and metabolic disease will pick up many nuggets of wisdom.

Why then, do I simply not recommend every paediatrician who sometimes deals with metabolic problems—and there must be few of us who do not—to rush out and buy a copy before such a gem either goes out of print or rises in price? My caveat is that this book's clinical approach coupled with its encyclopaedic coverage of some topics means that several chapters leave the non-expert mentally breathless, and this effect is made worse by the absence of the structural formulae of the molecules named; this may be of little moment to those with these formulae at their fingertips, but that excludes rather a lot of us. By contrast the metabolic sections of "Nelson" and "Forfar and Arniel" clearly benefit from their inclusion.

So, for those on a unit dealing with many patients with inborn errors of metabolism, this book is invaluable, but general and

trainee paediatricians who think they can read this book from start to finish and become initiated into the mysteries of metabolic disease are likely to be overwhelmed.

If you can peruse this paperback at your local medical bookshop, do so; you may find it an answer to prayer, and anyway, at just under £30 it won't bankrupt anyone.

R A F Bell

Eating Problems in Children: Information for Parents.

Edited by C Fox, C Joughin. London: Gaskell, 2002, £10.00, pp 621. ISBN 1901242862

How commonly do we encounter the following scenario?

A desperately anxious mother at last convinces her GP that she needs to see a paediatrician because her normally growing toddler is eating nothing. The paediatrician wonders why his time is being wasted, and "reassures" the mother that there is nothing to worry about. Needless to say the anxiety persists with, no doubt, damaging consequences. As a profession, we handle these cases poorly. With 30% of preschool children suffering from mild to moderate eating problems, we need a better way to address these issues.

The Royal College of Psychiatrists has produced this small book for parents that should prove helpful, not only to parents but also to paediatricians and other health professionals. It provides information about the epidemiology of eating problems, and gives a useful classification, categorising eating difficulties into nine types, including persistence of eating inappropriate texture of food for age, food refusal, restrictive eating and selective eating. This allows the parent or professional to come to a more specific "diagnosis", and also a sense of the anticipated course these difficulties are likely to take. In particular, it provides clear pointers for those conditions that are indicative of significant emotional or psychiatric conditions.

Giving clear indications to the parent as to when to worry is helpful, as it is likely to encourage a sense of proportion to the anxiety accompanying the more common eating difficulties. The book goes on to provide specific and sensible advice about the practical management for each of the different types of eating difficulty.

At the end of the day, one is left with the finding that for most parents, not surprisingly, reassurance is what is required. I felt, however, that this book could help us proffer the advice in a more substantive form than we do at present, and can give us an approach that is likely to help diffuse the anxiety which contributes to the perpetuation of stressful mealtimes. I suspect the book will prove to be of most value to health visitors, but selected reading could be of use to the paediatrician too.

This book is therefore of value for a problem that presents so frequently to the general paediatrician, but I must admit to some reservations. It could have been better written, and in particular was rather unnecessarily repetitive. It certainly would have benefitted from paediatric review—I wondered who or what a community practitioner was, and gulped when I saw growth hormone mentioned in the section of treatment for restrictive eating! It was rather more concerning that children with disabilities got an occasional mention,

implying that they merited the same sort of approach. It surely would have been better to emphasise that they require a different sort of understanding and input. But, despite these concerns, the book should prove useful as it provides a systematic approach to the child with eating difficulties, and some clear, sensible practical advice to guide the parent in handling the problem.

M Rudolf

Childhood Headache

Edited by I Abu-Arafah. UK: Cambridge University Press, 2002, £45, pp184. ISBN 1 898 68326 3

Headaches in children are a common problem—70% of school children have headaches at least once a year, with 25% suffering from recurrent headaches. This book is part of the Clinics in Developmental Medicine series, and provides a comprehensive overview of the subject. The book is divided into clear chapters, which makes it easy to dip into. It includes interesting sections on pain perception in children and neonates, as well as a good epidemiology section. Throughout the book there are summary tables of recently published studies. In the later chapters there are case histories, including parental descriptions, which break up the occasionally slightly long winded text. There is an extensive list of references at the end of each chapter.

I found the chapters on migraine enlightening, especially the theories on pathophysiology of migraine. The diagnostic criteria for migraine are easy to read and clear. There is an excellent overview on the psychological treatment of headaches, regardless of diagnostic type. Again, the evidence is summarised in clear tables. There is a practical section on managing abdominal migraine. Causes of headaches are divided into separate chapters for specific and rare causes, which was helpful when I used the text when on call.

The final chapter talks about setting up a headache clinic, including a discussion on diagnostic tests. There is a headache questionnaire for parents, which I would find very helpful. There is also advice on the role of the multidisciplinary team in management.

This book would be a valuable addition to a general paediatric department, both in out-patients and for reference when on call.

A Morjaria

CORRECTIONS

In the article by Nixon *et al* (*Arch Dis Child* 2002;87:306-11), Dr Claire Wainwright should have been included as an author. Dr Wainwright's contribution was the establishment of the methodology and early patient recruitment and testing. Dr Wainwright moved from The Royal Children's Hospital at the end of 1997, and was funded by The Royal

Children's Hospital Foundation, Brisbane and the Cystic Fibrosis Research Inc, Queensland. The authors apologise for the omission.

The authors of the letter "Childhood SARS in Singapore" in the August issue (*Arch Dis Child* 2003;**88**:742) were written incorrectly. The authors names should be P Van Bever, C P P Hia, S C Quek.

In the acknowledgements for the leading article by Duke *et al* (*Arch Dis Child* 2003;**88**:563–5), Dr Diana Silimperi should have been acknowledged as part of the Paediatric Quality Care Group. The authors apologise for the error.

An error occurred in the paper by Riordan M, Rylance G, Berry K in the November issue.

(Poisoning in children 1: General management. *Arch Dis Child* 2002;**87**:393–6). In table 2, pupillary constriction associated with signs of increased sympathetic nervous system activity should read as mild pupillary dilation. Anticholinergic agents are likely to produce a more marked dilation. The authors apologise for the error.

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