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# *Mycoplasma pneumoniae* infection

## A follow-up study of 50 children with respiratory illness

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SUMMARY Fifty children with a previous history of *Mycoplasma pneumoniae* respiratory tract infection were assessed clinically, and pulmonary function tests carried out after an interval ranging from 1½ to 9½ years (median 2½). 23 suffered from recurrent wheezy bronchitis or asthma, and in 5 the index illness appeared to precipitate the wheezing tendency. All were symptom-free when respiratory function tests were performed. Simple tests of ventilatory function (PEFR, FEV, and FVC) were within normal limits. Increased bronchial reactivity after exercise (a fall in PEFR >15% resting value) was demonstrated only in children known to have asthma. Maximum expiratory flow rates in air at 50% of vital capacity ($\dot{V}$ max$_{50}$) were within the normal range in all patients with the exception of two. The response in flow rate at 50% of vital capacity after inhalation of an 80% helium and 20% oxygen mixture ($\triangle\dot{V}$ max$_{50}$) was reduced ($P<0{\cdot}001$) in asymptomatic patients with a history of *M. pneumoniae* respiratory infection, when compared with normal data from 48 healthy schoolchildren without a background of significant respiratory illnesses. These findings indicate impairment of small airways function, even in totally symptom-free children in the study group.

The clinical manifestations of *Mycoplasma pneumoniae* infection in children have been extensively reviewed (Baernstein *et al.*, 1965; Glezen *et al.*, 1967; Fernald *et al.*, 1975; Stevens *et al.*, 1978; Mok *et al.*, 1979). The clinical course of infections caused by this organism is usually self-limiting whether or not the child has had an effective antibiotic. Studies of pulmonary function after *M. pneumoniae* infection in adults show functional abnormalities both in the acute stage (Dierckx and Gillard, 1976) and after clinical and radiological recovery (Berven, 1962). In children with respiratory symptoms studies have been confined to the acute phase of illness (Kjellman, 1976), and we have been unable to find information on pulmonary function status after clinical and radiological recovery. We report here our findings in 50 children with proved *M. pneumoniae* infection studied 1½ to 9½ years (median 2½) after their index respiratory illnesses.

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### Patients and methods

**Patients.** The names of all children admitted to the Royal Hospital for Sick Children in Edinburgh with *M. pneumoniae* infection during the period from January 1968 to December 1975 were obtained from the records of the Regional Virus Laboratory in Edinburgh. The case records of 103 children were then traced and analysed. 87 with respiratory illnesses were chosen for further follow-up study. Letters were sent to their parents requesting co-operation. Of 57 replies received, 5 declined and 2 did not attend for study. We did not attempt to trace the remaining 30 patients.

Fifty children (20 girls and 30 boys) aged 0·4 to 11·3 years (median 4) at the time of the index illness were studied after an interval of 1½ to 9½ years (median 2½). Chest *x*-rays obtained during the acute phase of illness showed pneumonic consolidation in 19 (16 involving one lobe and 3 more than one lobe), patchy infiltration in 19 (unilateral in 8 and bilateral in 11), and hyperinflation in 2. In the 10 remaining patients with normal chest *x*-rays, cough was the main presenting symptom.

**Plan of investigation.** A clinical questionnaire on each child was completed by one of us (J.Y.Q.M.). Any history of a previous respiratory illness (acute bronchiolitis, whooping cough, pneumonia, measles or chickenpox with chest involvement, or tuberculosis) and/or ongoing symptoms (cough, wheeze, breathlessness, or sputum production) before or after the index illness was noted. Each child was then examined and respiratory function tests carried out in those old enough to co-operate.

With the patient standing, peak expiratory flow rate (PEFR) was measured using the Wright's peak flow meter (Wright and McKerrow, 1959). The best of 3 attempts was accepted. Forced expiratory volume in one second ($FEV_1$) and forced vital capacity (FVC) were measured using the Vitalograph spirometer, and the $FEV_1/FVC$ ratio calculated.

Maximum expiratory flow volume (MEFV) curves were obtained breathing air followed by an 80% He/20% $O_2$ mixture. Each child was seated and breathed quietly through a mouthpiece and an attached Lloyd valve. The subject exhaled to residual volume and then performed 3 vital capacities (VC), first breathing air and then the $He/O_2$ mixture. During the 3rd VC manoeuvre, the child expired forcibly and completely into a 'bag and box' arrangement. Displaced air passed through a flow meter (Mercury Electronics, Scotland Ltd, Glasgow). A linear relationship between flow and output voltage was achieved electronically (Tau Electronics Ltd, Edinburgh). Linearity was checked each week and remained remarkably constant. Volume was obtained from the linearised flow signal using an integrator (Tau Electronics Ltd, Edinburgh). The pneumotachygraph was calibrated for air flow using a rotameter (GEC-Elliott, Process Instruments Ltd, Croydon). A volume calibration was carried out before each study using a 1-litre (BTPS) syringe. An identical volume signal was obtained for flow rates up to 500 l/min. MEFV curves were obtained by displaying flow against volume on the x-y co-ordinates of a storage oscilloscope (Tektronix Inc., Beaverton, Oregon). An electronic time marker indicated $FEV_1$. The curves were then photographed and analysed. Previous studies on normal children (H. Simpson, 1977, unpublished observations) had shown that observed differences between curves were independent of the order in which gases were inspired. Curves were compared when the vital capacity breathing He and $O_2$ was within 5% of that obtained in air. The variables measured were $FEV_1$, FVC, maximum expiratory flow rates at 50% of VC ($\dot{V}\,max_{50}$) and 25% of VC ($\dot{V}\,max_{25}$) for both the air and $He/O_2$ curves. The change in flow rate after inhalation of the $He/O_2$ mixture was measured at both 50 and 25% of VC ($\triangle\,\dot{V}\,max_{50}$ and $\triangle\,\dot{V}\,max_{25}$ respectively).

Patients with a resting PEFR >70% of predicted for height were exercised on a treadmill (Quinton Instruments, Seattle, Washington) for 6 minutes at a speed of 5 km/h at a gradient of 20%. The heart rate was measured after exercise and in each case was at least 160/min. PEFR was measured before exercise, then immediately and at 2, 5, 10, 15, and 30 minutes after cessation of exercise. The percentage fall in PEFR from the resting value was then calculated (fall in PEFR/resting PEFR) × 100.

## Results

**Clinical.** An analysis of case records and clinical questionnaires showed a history of bronchiolitis,

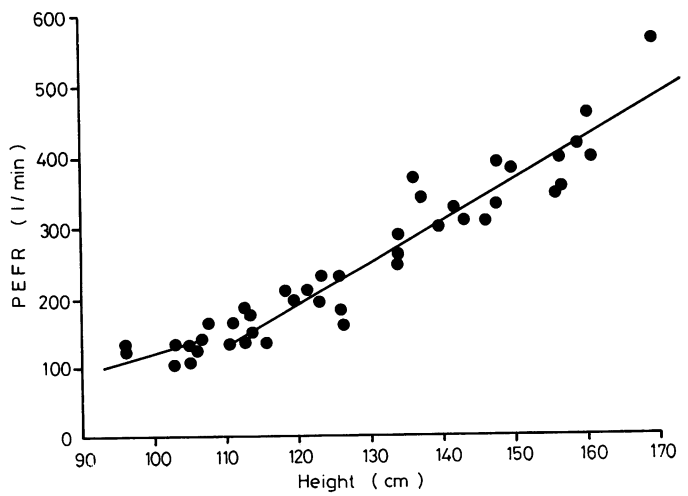



Fig. 1 *Peak expiratory flow rate in 43 children with previous* M. pneumoniae *respiratory infection.*

pneumonia, whooping cough, measles, or chickenpox with chest involvement antedating the mycoplasma illness in 17 children. After recovery, 8 remained symptom-free. Nine had recurrent wheeziness, 8 of them since infancy. 33 children had no specific antecedent illnesses. 19 were symptom-free and 14 had a wheezing tendency which predated the index illness. Six children developed persistent cough or wheeze for the first time after the mycoplasma illness. Five of these (all with recurrent wheeze) had a strong personal or family history of atopic disorders (eczema, food allergy, allergic rhinitis).

On examination 4 children were <10th centile for height and weight and 17 had mild to moderate degree of chest deformity. All patients were symptom-free and had no clinical signs of airways obstruction when respiratory function tests were performed.

**Respiratory function tests.** Fig. 1 gives the results of PEFR in relation to the normal data of Polgar and Promadhat (1971) and Milner and Ingram (1970). PEFR exceeded 70% of the predicted for height in all but one child. The results of $FEV_1$ and FVC were within normal limits, compared with the data of Polgar and Promadhat (1971). The $FEV_1$/FVC ratio expressed as a percentage was 85·1 (±7·8). When patients with wheezy bronchitis or asthma were excluded this ratio was 86·7 (±8·0).

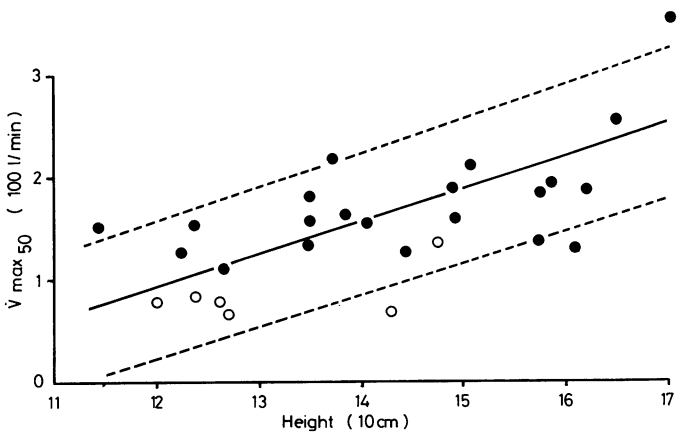
MEFV curves breathing air and then a $He/O_2$ mixture were obtained in 28 children. 18 had been symptom-free both before and after their index illnesses, 4 had occasional mild wheeze, and 6 were known asthmatics. The results were analysed and compared with 'normal' values obtained in 48 schoolchildren of similar heights and age range but without antecedent lower respiratory tract infections or wheezing tendency. No difference was seen with respect to $FEV_1$ and FVC between the study and control groups.

Figs 2 and 3 show that in all but 2 patients, the results obtained for $\dot{V}\,max_{50}$ and $\dot{V}\,max_{25}$ were within or above the normal range for controls. Figs 4 and 5 show the results for $\triangle\,\dot{V}\,max_{50}$ in the control and non-asthmatic patients within the study groups. $\triangle\,\dot{V}\,max_{50}$ varies widely even in normal healthy children but in most cases exceeds 20 l/min. Table 1 gives the mean values ±SD for $\triangle\,\dot{V}\,max_{50}$ and $\triangle\,\dot{V}\,max_{25}$ in our controls and the 22 patients studied who did not have asthma. The $\triangle\,\dot{V}\,max_{50}$ of 12·6 ± 13·7 l/min in our study group differed significantly ($P<0·001$) from 24·4 ± 20·8 l/min in our controls. The 22 patients included 4 in whom chest *x*-rays were normal during their index illnesses. The values for $\triangle\,\dot{V}\,max_{50}$ in these patients were 5, 10, 10, and 25 l/min. When our results were reanalysed, excluding data from these patients, significance remained unaltered. There was no relation between $\triangle\,\dot{V}\,max_{50}$ or $\triangle\,\dot{V}\,max_{25}$ and height in either the control or study group.

Table 1 *Response in flow at 25 and 50% of vital capacity after breathing a mixture of helium and oxygen ($\triangle\,\dot{V}\,max_{25}$ and $\triangle\,\dot{V}\,max_{50}$ respectively)—actual values ± SD for control and study groups (excluding children with asthma)*

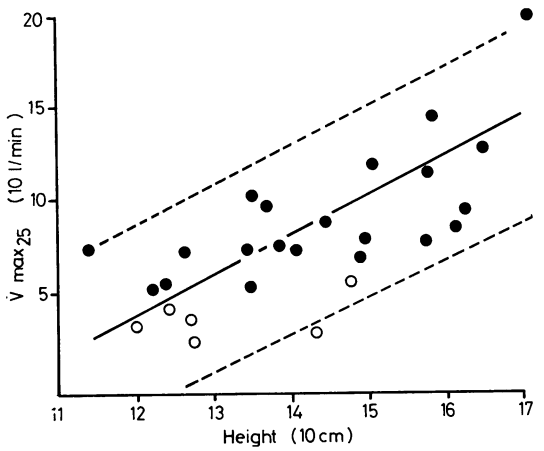
| *Variable* | *Control (Mean ±SD)* | *Mycoplasma (Mean ±SD)* | *Significance* |
|---|---|---|---|
| Height (cm) | 140·6 ± 11·4 | 142·9 ± 17·1 | NS |
| $\triangle\,\dot{V}\,max_{25}$ | 11·5 ± 14·3 | 8·3 ± 14·2 | NS |
| $\triangle\,\dot{V}\,max_{50}$ | 24·4 ± 20·8 | 12·6 ± 13·7 | P<0·001* |

*Wilcoxon test.




(Slope = 3·27 ± 0·22, y intercept = −297·8 ± 31·1, R = 0·73).
● Nonasthmatic patients
○ Asthmatic patients

Fig. 2 *Maximum expiratory flow at 50% of vital capacity ($\dot{V}\,max_{50}$). Lines represent the regression and ± 2 SD for the control group of children.*




(Slope = 1·97 ± 0·15, y intercept = −200·5 ± 22·1, R = 0·67).
● Nonasthmatic patients
○ Asthmatic patients

Fig. 3 *Maximum expiratory flow at 25% of vital capacity ($\dot{V}$ max$_{25}$). Lines represent the regression and ± 2 SD for the control group of children.*

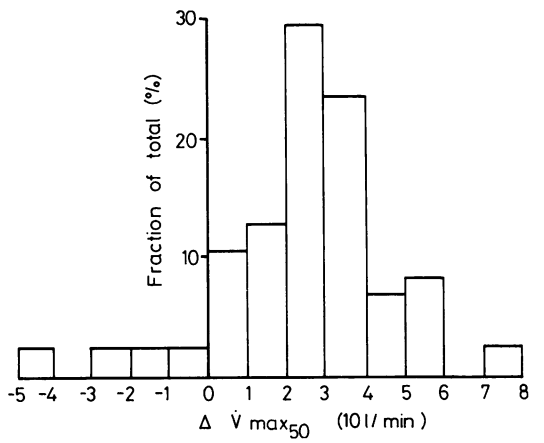



Fig. 4 *Response in flow at 50% of vital capacity after breathing a mixture of helium and oxygen ($\Delta\dot{V}$ max$_{50}$)—control group of children.*

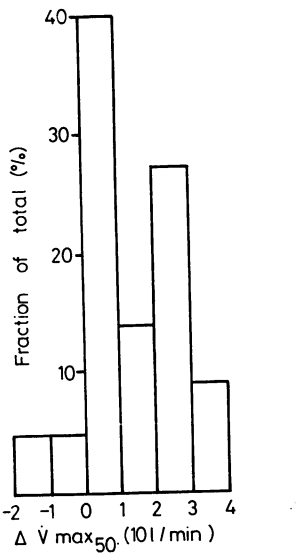



Fig. 5 *Response in flow at 50% of vital capacity after breathing a mixture of helium and oxygen ($\Delta\dot{V}$ max$_{50}$)—study group of children excluding asthmatics.*

Table 2 *Exercise test in 34 children*

| *Ongoing symptoms (%)* | *Fall in PEFR* | | |
|---|---|---|---|
| | *<10* | *10–15* | *>15* |
| None | 16 | 5 | 0 |
| Wheeze/cough | 4 | 1 | 8 |
| Total | 20 | 6 | 8 |

Table 2 summarises the results of the exercise study obtained in 34 patients. Of the remaining 16, 14 were preschool children who could not be persuaded to perform the test, one had a PEFR less than 70% of predicted, and another withdrew from the test after 2 minutes of exercise. 20 children showed a normal response to exercise, namely a fall in PEFR in the postexercise period of <10% of the resting value (Silverman and Anderson, 1972). The 8 children with a fall in PEFR >15% of the pre-exercise value were known asthmatics in whom a wheezing tendency antedated their mycoplasma illnesses. One of the remaining 6 children with a fall in PEFR of between 10 and 15% after exercise had only minor symptoms.

## Discussion

Our results show that after clinical and radiological recovery from *M. pneumoniae* respiratory tract infection in children, routine tests of ventilatory function do not show abnormality, although the series included 10 children with wheezy bronchitis and 13 with asthma in remission at the time of study. Kjellman (1976) reported a decrease in $FEV_1$ and FVC in children with *M. pneumoniae* pneumonia during the acute phase of their illness, which returned to normal within a week. However, distribution of ventilation, assessed by $^{133}Xe$ radiospirometry, remained abnormal for a longer period and in one of 9 children persisted several months later.

Mycoplasma chest infection may be associated with wheeze in otherwise normal children, or may precipitate wheeze in those with a wheezing tendency (Berkovich *et al.*, 1970). Our series had a high proportion of children with wheezy bronchitis or asthma, including 5 patients who developed wheeze for the first time after the index illness. It seems likely that they would have developed asthma, for each had a strong background history of atopy.

The importance of exercise studies in showing increased bronchial reactivity and thus an asthmatic tendency has been demonstrated both in normal and asthmatic children (Godfrey, 1974). Our patients who had a fall in PEFR after exercise >15% of the pre-exercise value were known to have asthma and had been shown previously to have reversible airways obstruction. Sims *et al.* (1978) demonstrated bronchial hyper-reactivity in children 8 years after recovery from respiratory syncytial virus bronchiolitis in infancy, but they were careful not to infer a cause and effect relationship, but rather suggested that an environmental factor (low socioeconomic status or parental smoking) was the most likely link between respiratory infection in infancy and subsequent respiratory symptoms. Three of our 34 patients who did the exercise test gave a history of bronchiolitis in infancy from which they had recovered without further symptoms. All showed a normal response to exercise. It seems therefore that abnormal bronchial reactivity in our present series was due to including children with coexistent asthma and was not the result of antecedent bronchiolitis or the index mycoplasma respiratory illness.

It is now apparent that considerable obstruction of peripheral airways of the lung may be present before routine tests of ventilatory function show any abnormality. As a result there has been a search for new tests of lung function which are simple and sensitive (Macklem, 1972). One such test is based on a comparison of MEFV curves with the subject breathing air followed by an 80% He/20% $O_2$ mixture (Dosman *et al.*, 1975). We have shown an impaired response to the inhalation of this mixture at 50% of VC in a group of asymptomatic non-asthmatic children with a history of *M. pneumoniae* chest infection. It might be argued that equilibration with helium was incomplete after 3 VC manoeuvres. However, Dosman *et al.* (1975) demonstrated in symptom-free adults with normal values for routine ventilatory function tests that 3 successive VC manoeuvres were adequate to ensure equilibration with helium. This method gave results comparable with those obtained by Despas *et al.* (1972). We assumed that this was also true in our patients. The response to breathing the He/$O_2$ mixture was also less than in controls at 25% of vital capacity but the difference was not significant (Table 1). Impairment of response is more likely to reflect events in peripheral airways the closer to residual volume that measurements are made. However, the methodological difficulty of measuring low flow rates accurately, especially changes in flow rate, increases greatly in this part of the flow-volume curve. This may explain, at least in part, the wide range of values for $\dot{V}\,max_{25}$ breathing air in both control and index cases, and account for the $\triangle\,\dot{V}\,max_{25}$ being less discriminating an index of small airways dysfunction than $\triangle\,\dot{V}\,max_{50}$ in the present series.

Our control data were obtained from schoolchildren attending a state primary school which served a community with children from differing socioeconomic backgrounds. Our patients were similarly drawn from varied social backgrounds. A social bias in the selection of controls is unlikely, although no attempt was made to match precisely the study and control groups of children on this basis. In our analysis of MEFV curves (Table 1) we excluded children with a background history of asthma. Thus no patient in either group had significant respiratory symptoms. We conclude therefore that impairment of response in flow rate at 50% of VC to the He/$O_2$ mixture was due to preceding *M. pneumoniae* respiratory infection. It is not possible to say whether the impairment of function represents permanent residual lung damage or whether these children are at risk of chronic obstructive airways disease in later life.

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