ACUTE LOWER RESPIRATORY TRACT INFECTION IN INFANCY

A SEVEN YEAR FOLLOW-UP STUDY

by

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NOTE OF PREVIOUS PUBLICATION

A preliminary report of this study has been published previously:

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SUMMARY

Seven years after hospitalisation for acute lower respiratory tract infection in infancy, 200 children and their case-controls were assessed for respiratory status and epidemiological characteristics. The index group comprised 100 cases where respiratory syncytial virus had been responsible for the index illness (RSV+) and 100 cases in whom this organism had not been found (RSV-).

No differences were noted between index and control children with respect to birth weight and gestational age, although breast feeding was more frequently observed in control children. Index children reported more respiratory symptoms and asthma as well as other indices of respiratory illhealth. Although index children appeared to be a socially disadvantaged group, parental respiratory symptoms and smoking habits were comparable in both groups of children. The atopic background was similar in index and control populations. At follow-up, index children were shorter than controls, although their weights were comparable. Tests of respiratory function were diminished in index children, who also had evidence of bronchial hyperreactivity.

RSV+ and RSV- index children showed similar clinical characteristics and atopic background. No significant differences were found in the age at which the index illness

occurred, or in the proportion who were breast-fed. The results of tests of respiratory function and exercise test were comparable in RSV+ and RSV- children.

Children who had suffered bronchitis, bronchiolitis or pneumonia had similar clinical characteristics compared to their controls, with the exception that fewer children who had bronchiolitis were breast-fed, and children who suffered pneumonia were of lower birth weight. All three sub-groups of index children reported more respiratory symptoms and ill health than their controls. Social and family factors were less favourable when compared to control children. The atopic background was similar between the three disease categories, and also between index and control children. Tests of respiratory function were significantly reduced only in children who had bronchiolitis, although the trend in the bronchitis and pneumonia children was also towards poorer function. A one-way analysis of variance between disease categories on the differences between case and control for each respiratory function measurement showed that differences within a disease category was geater than the differences between disease categories.

Following the index illness, children were reported to cough, wheeze or remain asymptomatic. Those with symptoms were almost identical in terms of clinical, social and family characteristics, as well as atopic background; but differed

from their controls. Tests of respiratory function were diminished in both groups of symptomatic children, with evidence of bronchial hyper-reactivity. The asymptomatic index children did not differ from the symptomatic children with respect to social factors, suggesting that these contribute little to the occurrence of respiratory symptoms. Asymptomatic children were of similar height to their controls. Respiratory function was also comparable although there was a slight trend to hyper-reactive airways.

Children whose index illness was attributed solely to acute infections (RSV+, non-atopic) reported similar occurrences of respiratory symptoms to their controls. Respiratory function was also comparable. When there was a background history of atopy, children reported more respiratory symptoms and had significantly lower tests of respiratory function as well as evidence of bronchial hyperreactivity when compared with controls. The results suggest that atopy is a determinant of poor respiratory function, but they may have also been influenced by the discrepancy in numbers. Bronchial reactivity was present in excess in atopic and non-atopic index cases, despite being significant only in the atopic children.

Index children with bronchial reactivity showed similar clinical, atopic, social and family characteristics to those without evidence of hyperreactive airways, but

these two groups differed clinically and in social and family background from control children. Those with bronchial reactivity wheezed more, and there was a greater percentage of asthmatics. Respiratory function was significantly diminished compared to controls. There was no excess of atopic disorders in the index children with hyperreactive airways.

Children without evidence of hyperreactive airways also reported more respiratory symptoms, but bronchitis rather than asthma was diagnosed in these children. Except for a lower PEFR, all other tests of respiratory function were similar between index and control children.

Ventilatory dysfunction paralleled bronchial reactivity. It is not clear which is of primary importance, or if there is any relationship between the two. Acute respiratory infection may have caused both these abnormalities, or they could have predated the event, rendering children more susceptible to infection.

INTRODUCTION

Acute lower respiratory tract infections in children are common, and account for about 10% of medical admissions to hospital. A large proportion of these affect the very young child, when the illness can be severe and sometimes life-threatening. The majority of children with acute lower respiratory infections recover, with resolution of radiological changes. Because it is difficult to measure ventilatory function in infants and young children, functional recovery cannot be easily demonstrated. Recent studies show that in the immediate convalescent period, lung function abnormalities are common in children with bronchiolitis (Stokes et al., 1981). The illness can be protracted, when symptoms can interfere with feeding and result in failure to thrive (Hodges et al., 1982). These workers also demonstrated hyperinflation and airways obstruction when lung function was assessed in the children up to a year later.

It is a general impression amongst paediatricians that chesty children lose their symptoms as they grow older. The age pattern of prevalence of respiratory symptoms suggests that symptoms are at their lowest in older children. Such observations imply that no excess risk exists for the development of chronic lung disease as children grow older. Paediatricians are unable to observe their patients' past

adolescence, while adult chest physicians see patients who already have moderately severe disease and are uncertain about childhood respiratory illness. A clinical approach is therefore unhelpful in tracing the natural history of childhood respiratory infections.

Epidemiological studies provide evidence that links childhood and adult respiratory disease (Holland et al., 1969; Bland et al., 1974; Holland et al., 1978; Colley et al., 1973; Kiernan et al., 1976; Burrows et al., 1977; Woolcock et al., 1977). Such studies do not document accurate clinical or aetiological information about early childhood respiratory illnesses. However, several other factors which influence either the occurrence or outcome of respiratory illness are highlighted. These include family factors such as parental smoking, parental respiratory symptoms, family size or the place of the child in the family. Social and environmental factors of importance are the social class, type of housing, air pollution and the fuel used for heating. Very often, it is difficult to separate the effects of all these, but the study of young children eliminates certain environmental factors such as occupational exposure and active smoking.

Clinical studies have concentrated mainly on the subsequent respiratory symptoms following bronchiolitis, the commonest lower respiratory tract infection in infancy.

The prevalence of recurrent wheezing after acute bronchiolitis has been reported to vary from 6% to 50% (Eisen and Bacal, 1963; Wittig et al., 1959; Hyde and Saed, 1966; Zweiman et al., 1971) because the aetiological agent and clinical illness have not been carefully defined.

The respiratory syncytial virus is the commonest pathogen in acute lower respiratory infection in infants and young children (Gardner, 1973; Clarke et al., 1978). Where this agent was identified as the cause of bronchiolitis, reports on subsequent wheeze varied between 42% and 56% (Rooney and Williams, 1971; Sims et al., 1978; Pullan and Hey, 1982). Other respiratory symptoms such as cough were also reported more frequently in children who had suffered from bronchiolitis. In children who remained symptom-free, abnormalities in respiratory function have also been demonstrated (Kattan et al., 1977).

It is not clear how viral infections produce chronic airway changes, or what part atopy plays in the development of acute respiratory infections or in the pathogenesis of chronic lung disease. Frick et al. (1979) suggested that virus infections may sensitise susceptible infants and lead to subsequent cough and wheeze. More recent studies (Welliver et al., 1981) on nasopharyngeal secretions in infants after RSV infection suggest that production of IgE and the subsequent release of chemical mediators may contribute to the pathogenesis of wheezing during the acute

illness and may also explain the subsequent tendency to recurrent wheeze. Atopic children appear to respond to a respiratory virus infection by wheezing (Cogswell et al., 1982; Laing et al., 1982). It may be that a lower respiratory infection in infancy is a marker of the child with a tendency to develop bronchial atopy. However, there are difficulties in distinguishing an infant presenting with acute infectious bronchiolitis from one suffering his first asthmatic attack. The distinction is made more difficult by the fact that viral respiratory infections can precipitate asthmatic attacks. Inclusion of asthmatic children may then lead to the high incidence of wheeze subsequently reported.

Despite the abundant literature on bronchiolitis and subsequent wheeze, there are differences in estimates of prevalence of wheeze. Varying criteria for the selection of patients, paucity of controls and differing periods of follow-up probably account for some of the differences in outcome. Moreover, virological findings during the index illness are rarely documented and information usually scarce on the family, social and atopic background of the children studied.

In Edinburgh, a good virology service has been established since 1971, therefore precise aetiological information is available. There is well-documented data on children admitted to hospital with respiratory illnesses.

Atmospheric pollution is low, thereby minimising any influence this might have on respiratory illnesses. A case-control study was conducted to assess the respiratory status and epidemiological characteristics of children seven years after hospitalisation for acute lower respiratory tract infections in infancy. The index group was selected to include 100 cases with proved respiratory syncytial virus infection and 100 cases in whom this organism was not identified.

The aims of the study were to determine:

a) the occurrence and severity of subsequent respiratory symptoms (eg cough and wheeze)

b) the prevalence of established respiratory disorder (eg asthma and bronchitis)

c) the persistence of abnormalities of lung function, especially in symptom-free patients

d) epidemiological factors of probable importance in influencing respiratory symptoms

e) the distribution of atopic disorders in the children and their first-degree relatives.

In addition, it was hoped to define a cohort of children with abnormalities of lung function for longitudinal study into adult life, to establish whether there is progression to obstructive airway disease.

The material in this thesis is presented in five sections. The first section contains a review of the literature regarding the present state of knowledge, and is divided into four chapters. This is followed by the design of the study and laboratory methods, outlined in four chapters in Section II. Results are presented in Section III, with the discussion and conclusions in the last two sections.

LIST OF ABBREVIATIONS

RSV	Respiratory syncytial virus
R_T	Total respiratory resistance
PEFR	Peak expiratory flow rate
$FEV_{1.0}$	Forced expiratory volume in 1 second
$FEV_{0.75}$	Forced expiratory volume in 0.75 second
$FEF_{25-75\%}$	Forced expiratory flow during the middle half of the expired volume
MMEFR	Maximal mid-expiratory flow rate
$He-O_2$	80% helium and 20% oxygen mixture
FVC	Forced vital capacity
$\dot{V}_{50}$	Maximal flow at 50% of the vital capacity
$\dot{V}_{25}$	Maximal flow at 25% of the vital capacity
$\Delta \dot{V}_{50}$	Change in flow at 50% vital capacity after breathing $He-O_2$
$\Delta \dot{V}_{25}$	Change in flow at 25% vital capacity after breathing $He-O_2$
MEFV	Maximal expiratory flow volume
BTPS	Body temperature and pressure, saturated
FRC/TLC	Ratio of functional residual capacity to total lung capacity
RV/TLC	Ratio of residual volume to total lung capacity
PO_2	Partial pressure of oxygen
$\dot{V}$isoV	Volume of iso-flow
$\dot{V}_{60\%}$TLC	Flow at 60% total lung capacity
$\dot{V}$maxFRC	Flow at functional residual capacity
TGV	Thoracic gas volume
Raw	Airway resistance

IPPV	Intermittent positive pressure ventilation
CPAP	Continuous positive airway pressure
$AaPO_2$	Alveolar-arterial difference in oxygen saturation
IRDS	Idiopathic respiratory distress syndrome
$MEF_{50\%}$	Maximal expiratory flow after 50% of the vital capacity has been expired ($=\dot{V}_{50}$)
$MEF_{75\%}$	Maximal expiratory flow after 75% of the vital capacity has been expired ($=\dot{V}_{25}$)
$MEF_{25-75\%}$	Forced mid-expiratory flow ($=FEF_{25-75\%}$ or MMEFR)
IgG	Immunoglobulin G
IgA	Immunoglobulin A
IgE	Immunoglobulin E

SECTION I

Chapter 1

SOCIAL AND ENVIRONMENTAL FACTORS IN RESPIRATORY DISEASE

Epidemiological studies of the origins of chronic bronchitis in adults have identified several important environmental factors which act singly or in combination. In adults the dominant effects of smoking and occupation on the prevalence of respiratory symptoms make it difficult to assess the relative contributions of other factors. Increasing mobility of the population, changes in occupation and varying exposure to atmospheric pollution increase the complexity of this problem. It is easier to study young children. The effects of active smoking and occupation are less evident and the recording of events in parents and siblings permit an assessment of certain familial factors which may be relevant to the development of respiratory disease.

Air Pollution, Social and Family Factors

Colley and Holland (1967) studied the effects of air pollution and social and family factors on respiratory disease in over two thousand families from two areas in a north-west London suburb. All infants born within a two-year period were selected and reviewed annually for five years. An attack of bronchitis or pneumonia in a sibling, especially during the first year of life of the index infant, was the most important determinant of respiratory illness in young children. Respiratory illness increased with the number of siblings, and the age of the eldest sibling - respiratory illness being greatest when there were siblings of school age. Parents' respiratory

symptoms and smoking habits had a lesser effect (reported separately by Leeder et al., 1976). Tests of respiratory function soon after birth in a sample of index cases were comparable in infants who suffered chest illnesses and those who did not during the subsequent five years (Colley et al., 1976). However, at the age of one year crying PEFR was significantly lower in infants who had suffered from bronchitis or pneumonia in the first year of life.

In a later study of six- to ten-year old primary school children in areas representative of a wide range of urban and rural environments in England and Wales, Colley and Reid (1970) found a pronounced social class gradient in the frequency of chronic cough and recurrent upper respiratory tract infections. Children with chronic cough were more likely to have suffered bronchitis or pneumonia. Air pollution did not influence the prevalence of upper respiratory tract infections, but was a significant factor in lower respiratory illnesses in children from social classes IV & V.

Yarnell and St Leger (1977), examined the influence of housing conditions by comparing the occurrence of respiratory illnesses in children from traditional valley houses with that in children from modern council estates in South Wales. Upper respiratory tract infections were

more common in children from the modern council estates, the children from valley houses being relatively free of such illnesses. $FEV_{0.75}$ and FVC performed in a random sample were lower in children from council houses. These differences could be explained on the basis of differences in the types of heating in these houses. Estate houses were centrally heated, whereas traditional valley houses had coal fires.

The type of dwelling, area of residence and level of atmospheric pollution tend to be closely inter-related. However, there are now several reports on the effects of pollution per se. Toyama (1964) showed that acute exposure to pollutants in the air affected respiratory function in children, with improvement when the level of pollution dropped. Stebbings and Fogleman (1979) presented similar findings in non-asthmatic white school children exposed acutely during a period of air pollution in Pittsburgh. FVC was reduced in 10-15% of children; with an increase of 20% on average following the episode (as judged from trends in the regression curves for FVC).

Wahdan (1963) compared children from an industrial town (Sheffield) with those living in a rural environment (Vale of Glamorgan) and found that upper respiratory tract infection, recurrent or persistent cough and attacks of bronchitis or pneumonia were more common in children from

the polluted industrial area. PEFR and $FEV_{1.0}$ were significantly lower in these children. When the family structure was examined, "overcrowding" (defined as more than two persons per room) was associated with an increase in chest illnesses, especially if there was a bronchitic person in the family. A pre-school child in the home resulted in more frequent colds and sore throats.

The effect of prolonged exposure to varying degrees of air pollution was assessed by Douglas and Waller (1966) in a group of 15-year old children with documented information on respiratory illnesses and exposure to air pollution from birth. Only families who remained at the same address or had moved to areas of comparable pollution were included. Social class distribution was similar in areas with differing levels of pollution, but lower respiratory infections were more frequent and more severe in children from the more polluted areas. Respiratory function was not assessed in this study.

Lunn et al. (1967) studied primary schoolchildren from four areas in Sheffield with contrasting pollution levels. Children from the most polluted areas had more respiratory illnesses and significantly lower values for $FEV_{0.75}$ and FVC. Impairment of respiratory function was greatest in children with previous lower respiratory tract infections. When the cohort was re-examined four years

later after clean air measures had been introduced, no differences were noted in the distribution of respiratory illnesses in children from these areas (Lunn et al., 1970). This suggests that the clean air measures were effective even although only 68% of the original sample were available for study.

Other studies in Europe and North America reached similar conclusions on the effects of air pollution on the respiratory tract. Zapletal et al. (1973) assessed respiratory function in school children from a heavily polluted industrial city in Czechoslovakia. $FEV_{1.0}$ and FVC were within the predicted normal ranges for height and sex. However, more sensitive tests of respiratory function carried out in children with $FEV_{1.0}$ values near the lower end of the normal range showed a significant reduction in MMEFR, especially at low lung volumes. Static lung volumes and elastic properties of the lung were within normal limits. It was concluded that air pollutants caused changes in airway function revealed only by sensitive tests of ventilatory function. The findings for the group were compared with those in children from an area of lower pollution (Zapletal et al., 1977). The groups were similar in respect of housing, socio-economic status, dietary habits and family smoking practices. No differences were noted in the reporting of upper respiratory problems, but the prevalence of pneumonia was twice as great in children

from the more polluted area. Likewise abnormalities of lung function (reduction in $\dot{V}_{25}$) were more common. During the subsequent two years the increase in the number of children with abnormal $\dot{V}_{25}$ in the polluted area was double that of controls from non-polluted areas.

Sharratt and Cerny (1979) set out to examine the pulmonary function in children from two North American cities of contrasting pollution. The groups selected were comparable in age, height, weight and socio-economic status. Respiratory illnesses were more frequent in children from the heavily polluted area but their parents and siblings also suffered more chest illnesses. Despite its careful design, this study illustrates some of the difficulties of separating the effects of atmospheric pollution from potentially significant intra-family variables.

In a preliminary report of a study designed to explore the inter-relationship between exposure to air pollution, acute respiratory illnesses in childhood, smoking and the development of respiratory symptoms, Irvine et al. (1977) found a higher incidence of respiratory illnesses among 18-year olds living in a relatively clean area compared to those living in London. A history of a respiratory illness in childhood and current smoking increased the likelihood of respiratory symptoms and a decrease in $FEV_{1.0}$ irrespective of the area of residence.

Smoking

Norman-Taylor and Dickinson (1972) were first to recognise the effects of "passive smoking" in a study of over one thousand infant school children and their families. Thirty-three point five per cent of non-smoking families had children with respiratory symptoms, compared with 44.5% of heavy smoking families. The prevalence of cough in six- to fourteen-year olds (Colley, 1974) was directly related to parents' smoking habits and phlegm production. This was true within a given social class and in families of similar size.

In a study of hospital admissions, Harlap and Davies (1974) reported an increased morbidity in infants from homes where mothers smoked. Bronchitis and pneumonia were significantly more common (as were injuries and poisonings) in such infants. The increase in hospital admissions for chest illnesses in such children was most marked in the winter months, possibly because the infants spent more time indoors with greater likelihood of exposure to cigarette smoke. The vulnerability of the infant to the effects of inhaled cigarette smoke was further demonstrated in a longitudinal study of over two thousand infants who were assessed annually for five years (Colley et al., 1974). A sample of the parents' replies to postal questionnaires were compared with information from general practitioner records and showed broad agreement between the parents'

and family doctors' accounts of illnesses. In the first year of life, the prevalence of bronchitis and pneumonia was highest when both parents smoked and lowest when they were non-smokers. In subsequent years there was no clear association between parents' smoking habits and chest illnesses in the children. However, throughout the first five years of life, the occurrence of pneumonia or bronchitis was influenced by parents' respiratory symptoms independent of their smoking habits. The higher incidence of lower respiratory illnesses in children whose parents smoked could not be accounted for by social class, family size or weight of the infants. Schilling et al. (1977) reported a study of white families from three towns in the USA which, at first sight, appeared to contradict these findings. These investigators were unable to demonstrate any relationship between respiratory symptoms in children and those of their parents. Moreover, they found that parental smoking had no effect on the frequency and severity of respiratory symptoms or on lung function. A simple explanation for this apparent discrepancy might be the age at which the children were studied. All were over seven, and probably less likely to be exposed to their parents' cigarette smoke or chest symptoms to the same extent as infants or younger children.

Another American study (Lebowitz and Burrows, 1976) also failed to establish any significance of social status,

family size or specific age of children in relation to the effect of parental smoking on children's respiratory symptoms. No differences were noted in the respiratory symptoms of children whether the father alone, the mother alone, or both smoked. However, "children" in this study were those subjects under the age of 15 years, and there was no further breakdown of the age groups of the children. The study did confirm that respiratory symptoms in children were directly influenced by those in adults.

More recently, Fergusson et al. (1980) followed a cohort of infants from the age of one and found that when both parents smoked the risk of medical attendance for lower respiratory illness was more than doubled. Maternal but not paternal smoking was closely related to this increase.

The effects of active smoking in respiratory illness in childhood has been studied by Bland et al. (1978) in first year secondary school children. Smoking was more common in boys than girls and increased in both sexes if parents smoked. Morning cough occurred more frequently in children who smoked and increased in severity with the number of cigarettes smoked. The development of respiratory symptoms was related to the smoking habits of both children and their parents. Tager et al. (1979) assessed respiratory function in a random sample of five- to nine-

year old children in whom personal and parental smoking habits were known. $FEF_{25-75\%}$ values were highest in children who had never smoked and came from non-smoking families. Whenever children smoked, lung function diminished whether or not their parents were smokers. Likewise lung function was diminished in non-smoking children whose parents smoked even although respiratory illnesses were not reported more commonly in this group.

Apart from its effect on the respiratory status of children, parental smoking at home has also been demonstrated to affect the growth of their children (Rona et al., 1981). Using data from the National Study of Health and Growth, these workers found a strong inverse association between children's heights and the number of smokers at home, which was not accounted for by maternal smoking during pregnancy or by respiratory symptoms impairing growth.

S E C T I O N I

Chapter 2

CHILDHOOD RESPIRATORY ILLNESS AND SUBSEQUENT PROBLEMS

Holland et al. (1969) investigated the effects of environmental and personal factors on ventilatory function in ~11,000 schoolchildren at ages 5, 11 and 14 from four different areas in Kent. Parents were asked about the child's respiratory symptoms and illnesses since birth, with particular regard to pneumonia, bronchitis and asthma. Peak expiratory flow rate was lowest in children from the area of worst pollution and in children with past histories of respiratory illnesses. Social class and family size exerted less influence on respiratory function. Bland et al. (1974) reviewed about 40% of these children at age 11. Those with a history of respiratory diseases had more respiratory symptoms and a lower PEFR. However, the inclusion of asthmatics in their study might be adduced to explain lower PEFR recorded. A smaller proportion (12%) of the original sample were examined on three occasions (at ages 5, 11 and 14 - Holland et al., 1978). Although the numbers in the final study were too few to be representative of the initial sample, children with bronchitis in the first five years of life were more prone to bronchitis at the age of 11, and to more severe colds, wheeze, cough and phlegm at 11 and 14. Woolcock et al. (1977) emphasised the contribution of early childhood bronchitis to impairment of respiratory function as children grow older. In a random sample of Sydney schoolchildren, they found that bronchitis as well as asthma in infancy resulted in lower lung function ($\dot{V}_{50}$) confirmed during the

three consecutive annual check-ups. Lung function was further affected when schoolchildren started to smoke.

In a follow-up study to assess the effects of social and environmental factors, Leeder et al. (1976) found that children with a history of bronchitis or pneumonia had lower PEFR's than those who had escaped such illnesses. This effect was most significant when the respiratory illnesses occurred before the age of two. Recurrent illness had a greater influence than single episodes of respiratory ill-health. Parental social class, respiratory symptoms and smoking habits had no effect on PEFR.

The long term consequences of respiratory illness acquired in childhood are underlined by the findings of Colley et al. (1973) in a cohort of infants born in the last week of March 1946 and followed up to the age of 20. In the first two years of this longitudinal study Health Visitors interviewed parents when the children were aged two and documented episodes of respiratory disease occurring before that age. At the age of 20, subjects who smoked or had an early childhood chest illness had more chronic winter cough than others. Social class of the father and air pollution had only minor effects.

Kiernan et al. (1976) studied 54% of this cohort five years later. As the subjects aged, current smoking habits

as well as a childhood chest illness continued to be the major factor in influencing the prevalence of chronic cough. A reduction in respiratory symptoms was reported in those who had stopped smoking between the ages of 20 and 25 but the effects of childhood respiratory illnesses were still clearly seen.

Similar findings have been reported by Burrows et al. (1977) in a study of a random sample of white, non-Mexican, American adults over the age of twenty. Respiratory illness before the age of sixteen and current smoking habits were the subjects of enquiry by means of self-administered questionnaires to 2626 adults. MEFV curves were then obtained and analysed. A higher prevalence of cough and sputum were seen in subjects who reported "childhood respiratory trouble", quite independent of their smoking history. A more rapid decline in ventilatory function was observed in smokers with "childhood respiratory trouble" than in smokers without previous illness. Among non-smokers, those who reported childhood respiratory illnesses showed an excessive decline of ventilatory function with age. It might be argued that many asthmatic children had been included among subjects reporting paediatric respiratory illness, as these were younger and had positive skin tests more frequently than those without childhood respiratory illnesses. However, these differences were still apparent when the numbers were adjusted to exclude subjects with

probable asthma. Ventilatory function was slightly impaired in those reporting upper respiratory illnesses or isolated chest infections. No further details were given on ventilatory function in subjects with previous catarrh, bronchitis, bronchiectasis or "recurrent chest illness". Thus the exact nature of the childhood respiratory illnesses contributing to an increased risk of respiratory disease in adult life cannot be deduced. The study was subject to recall of childhood events, and might therefore be biased to some extent. It could be that adults with current respiratory problems preferentially recall childhood illnesses. Despite this reservation the results of this investigation support the notion of a positive association between childhood and adult respiratory illnesses.

S E C T I O N I

Chapter 3a

SPECIFIC AGENTS IMPLICATED IN CHILDHOOD RESPIRATORY ILLNESS

It is not clear which agents responsible for respiratory infections in childhood are most likely to cause lung damage predisposing to chronic airway disease in adults. Several follow-up studies have been reported in which the specific aetiological agent was known. Kjellman (1968) found that in the acute phase of Mycoplasma pneumoniae chest infections, there was evidence of reduced ventilation (^{133}Xe radio spirometry) and lowered vital capacity. Following apparent clinical recovery one and three months later, the maximal voluntary ventilation was normal whilst ventilation was still impaired in one child, with evidence of air trapping (↑FRC/TLC) in a further four. The follow-up interval may have been too short to document full functional recovery. Mok et al. (1979) studied fifty children hospitalised for Mycoplasma pneumoniae "respiratory illnesses" one to ten years (median three) later. Simple tests of ventilatory function (PEFR, $FEV_{1.0}$ and FVC) were within normal limits. However, there was evidence of residual dysfunction as shown by an impaired response to breathing $He/0_2$, when compared to a normal healthy group of controls.

Adeno viruses usually cause mild respiratory illnesses in children, although severe and fatal pneumonias have been reported (Chany et al., 1968; Becroft, 1971). Long-term consequences have been recognised in survivors. Gold et al. (1969) described chronic pulmonary disease (bronchiectasis, interstitial fibrosis and hyperluscent lung) in 53% of

children following adenoviral chest illnesses. Adenovirus types 1, 3 and 4, were implicated and subjects examined at intervals varying from one month to five years following the index illness. Adenovirus type 21 was shown to be a cause of serious pulmonary sequelae by Lang et al. (1969) in their review of children one month to three and a half years following the index illness. Sixty-five per cent of the children had chronic respiratory symptoms and radiological evidence of bronchiectasis or other lung changes. Both studies were of indigenous populations with problems of poor housing and malnutrition, which could have contributed to the unfavourable outcome. A Finnish study (Similä et al., 1971) comparing children with pneumonia caused by adenovirus type 7 with a group of children with pneumonia caused by other agents found the clinical course of adenoviral type 7 pneumonia to be especially severe. A postal enquiry to parents of both groups after an interval of two and a half years revealed that those with adenoviral pneumonia were treated more often in hospital for chest infections. Nine of 43 children attended for review. All had previous adenoviral pneumonia, and four showed residual abnormalities on chest X-ray. In a later study (~ 10.5 years after the index illness) of 22 subjects with previous adenoviral infections, twelve showed residual changes on chest X-ray (Lanning et al., 1980).

In many countries pertussis is a major cause of respiratory morbidity in young children. There have been surprisingly few follow-up studies. Lees (1950) studied 150 consecutive cases of pertussis admitted to hospital to determine the incidence of atelectasis and bronchiectasis following the illness. Many (43%) had radiological evidence of atelectasis during the acute illness. All were followed up until they were symptom free or had a normal chest X-ray - this invariably occurred within a year. Similar encouraging results were reported by Fawcitt and Parry (1957) in their review of children hospitalised for pertussis or measles. During the acute illness, there were more abnormalities on the chest X-ray of children with measles, with children over the age of one showing more abnormalities. The follow-up interval ranged from one to six years, where it was found that only 87 of the original 1894 children had residual radiological changes. Respiratory symptoms were associated in 34 children who had X-ray changes.

Jernelius (1964) assessed a group of children seven to ten years after pertussis with pulmonary complications. None had further pneumonia, but 25% admitted to recurrent cough for up to three years following the acute illness. Chest X-rays were normal. Spirometry ($FEV_{1.0}$ and FVC) and nitrogen washout studies were normal, but static lung volumes were slightly lower than predicted. White et al. (1964) conducted a case-control study to assess the pulmonary and neurological outcome in infants who had had pertussis.

After nine years there was no evidence of chronic pulmonary disease in patients or controls.

Primary staphylococcal pneumonia carries a high mortality rate in infancy and until recently the long-term prognosis for survivors was uncertain. Binder et al. (1961) reported recurrent pneumonia in 21 of 92 patients recalled for study and 17 had residual radiological abnormalities. The criteria for diagnosis of staphylococcal pneumonia and the interval between index illness and re-examination were not clearly stated, which limits the usefulness of the study.

Huxtable (1964) contacted all 22 survivors of staphylococcal pneumonia about four years later. They had thrived satisfactorily and none admitted to chronic cough or diminished exercise tolerance. Two had further attacks of pneumonia and in three, minor radiological residua were present.

Ceruti et al. (1971) studied 36 children two to four years after staphylococcal pneumonia. One child had recurrent respiratory symptoms. Thirteen had minor changes on chest X-ray and one was shown to have bronchiectasis. Arterial blood gas tensions were normal at rest and on exertion in 25 children investigated. Spirometry, in a third of their patients, showed no abnormalities.

S E C T I O N I

Chapter 3b

RESPIRATORY SYNCYTIAL VIRUS INFECTIONS AND BRONCHIOLITIS

Respiratory syncytial virus (RSV) is the most important respiratory pathogen in infancy and accounts for more than 50% of lower respiratory tract infections in this age group. Bronchiolitis is the commonest lower respiratory illness caused by this virus and although most infants appear to recover uneventfully, there is growing suspicion that the immediate and long term outlook is not entirely benign.

Follow-up studies of bronchiolitis give conflicting results. In part this may be due to the fact that the aetiological agent has not been specified or is unknown or that asthmatic subjects have been included from the outset.

There have been few follow-up studies of children with proven RSV infections. Rooney and Williams (1971) reviewed sixty-two of 100 children admitted to hospital with RSV bronchiolitis in the first 18 months of life, two to seven years later. Fifty-six per cent had wheezed recurrently and 43% admitted to wheeze on more than five occasions. There was a strong family history of atopic disorders in these children - 72% gave a positive family history of atopy, compared with 18% of the non-wheezing group. No information was given on whether children had wheezed before the index episode, making it difficult to draw conclusions on the temporal relationship between infections and recurrent wheeziness.

Sims et al. (1978) reviewed 35 children eight years after RSV proven bronchiolitis in infancy and compared the findings with controls matched for age, sex and social class but with no previous hospital admissions for respiratory illnesses in infancy. Although half of the index group had wheezed subsequently, the wheezy tendency was not severe and had largely resolved by the age of eight. Only one of the control children had wheezed. The bronchiolitis group had lower resting PEFR's and greater bronchial lability than controls following a non-standardised exercise test. The prevalence of atopic features in children and their first degree relatives was similar in the two groups. However, the families of children with bronchiolitis were larger and parents smoked more in the first year of the child's life. It was therefore concluded that environmental factors were more important than respiratory tract infection in determining the outcome.

In a more recent study of 130 children who had suffered RSV lower respiratory tract infections in infancy, Pullan and Hey (1982) showed that although the index children did not have an excess of atopy when compared with 111 control children, more wheeze (42% index children; 19% controls), cough (9% index, 2% controls) and upper respiratory infections (22% index, 4.5% controls) were reported. Bronchial lability, demonstrated by histamine challenge or

exercise testing, was three times as common in the index children. Pulmonary function was also significantly reduced - ↓PEFR, ↓FVC, ↓$FEV_{1.0}$, ↓$FEV_{1.0}$/FVC%, ↓$MEF_{50\%}$, ↓$MEF_{75\%}$ and ↓$MEF_{25-75\%}$. As in the previous study, index children had more siblings and their parents tended to smoke more, especially mothers during the children's first year of life (68% mothers of index children compared with 46% mothers of control children). Again, it could be argued that environmental factors were contributing to the findings.

"Bronchiolitis" and Sequelae - Aetiological Agents Unspecified

Most studies of the subsequent course of infants with "bronchiolitis" have concentrated on the prevalence of "recurrent wheeze" or "asthma" and the relation to personal and family atopic background. The results are somewhat conflicting. Case selection is inevitably difficult in view of the confused terminology applied to infants and young children with wheeziness. The diagnosis "bronchiolitis", "wheezy bronchitis", and "asthmatoid bronchitis" are made on a clinical rather than a pathological basis so that a distinction between "bronchitis" and "bronchiolitis" is not clear-cut. It is seldom possible to diagnose "asthma" with confidence under the age of eighteen months. However, on reviewing histories of older children with asthma, it is often possible to say that symptoms started in the first year of life.

Boesen (1953) was first to attempt to establish whether "asthmatoid bronchitis" was a forerunner of asthma. One hundred and sixty-two children previously admitted to hospital with that diagnosis were divided into different age groups. It was found that those aged less than a year at the time of the index illness had a 6% occurrence of asthma, compared with 25% in those between one and three years and 43% in children over 3. It is probable that the term "asthmatoid bronchitis" covered a wide range of respiratory illnesses. Children under one year old may have had "bronchiolitis" while those over three years were probably asthmatics. This might explain the differences in outcome in these groups. Moreover, the children whose wheeze was precipitated by respiratory infections had a lower incidence of subsequent asthma (0.6%) compared with others with "pure asthmatoid bronchitis" (20%).

Wittig et al. (1959) reported an incidence of 51% of allergic disorders (asthma, nasal allergy, eczema) in 100 children in whom "bronchiolitis" had been diagnosed clinically. Although 76% were less than a year old during the index illness, some were aged up to four years. The follow-up period ranged from one to seven years. Poor case selection and a widely varying follow-up period makes it difficult to draw conclusions from this study. Ściślicki et al. (1978) studied children diagnosed as having "obstructive bronchitis" in the first two years of life.

No further information was given on the illnesses covered by this term. Children with this diagnosis reported a high frequency of recurrent lower respiratory diseases. The occurrence of obstructive bronchitis even in the presence of allergic symptoms in the child was insufficient to predict subsequent asthma. In assessing respiratory function in these children, greater prognostic value was attached to bronchial hyper-activity.

To determine whether the wheeze which occurred in children during and following respiratory tract illnesses was associated with an allergic diathesis, Freeman and Todd (1962) contacted 230 of 357 (64%) such patients twenty months later. Included were ambulant and hospitalised patients with upper and lower respiratory tract infections. Para-influenza virus types 1 and 3, RSV, and adenoviruses types 1-5 and 7 were the main viral pathogens. Fifty per cent of the children who wheezed with the index illness had a history of allergic disorders compared with 17% of the non-wheezers. Thirty-nine per cent of children aged less than 18 months had associated allergy compared with 73% older than 18 months. This supported the view that the younger the child at the index illness the less likelihood of subsequent wheeze. The inclusion of older children increased the chance of including asthmatics.

These studies depended on parental information for the diagnosis of "allergic disorders". Eisen and Bacal (1963) studied the frequency of physician-confirmed asthma or rhinitis in 63 children who had suffered a single attack of bronchiolitis in infancy. All were under two when the diagnosis was made with follow-up four to fourteen years later. Fifty-one per cent remained symptom free, and 25% had established asthma (as diagnosed by the family doctor). A smaller proportion (21%) wheezed with respiratory infections. Of the children with asthma, 62% had a positive family history of "allergy" - asthma or seasonal rhinitis.

Hyde and Saed (1966) investigated the allergic background of 100 children under two who had been hospitalised for bronchiolitis. The children were seen later at intervals ranging from six to twenty months. Thirty-one per cent had wheeze, most of whom (81%) had evidence of atopic disorders on physical examination. Almost half of the group had wheezed prior to the index illness. They concluded that in many patients bronchiolitis and asthma were one and the same condition clinically, and suggested that differentiation lay in virological methods. However, the spectrum of viruses included RSV, adenovirus, parainfluenza and influenza viruses which can either cause bronchiolitis or precipitate wheeze in asthmatic children.

Simon and Jordan (1967) conducted a clinical and aetiological study of 122 children under the age of five who wheezed in association with respiratory infection. Two groups were identified - first-time wheezers and recurrent wheezers. First-time wheezers were further classified as RSV positive or RSV negative. Clinical and laboratory similarities between the RSV negative first-time wheezers and the recurrent wheezers suggested that the two conditions were probably related. It was concluded that RSV negative children had a predisposition to asthma, while RSV positive bronchiolitis was an infectious disease seen primarily in infants under six months of age, occurring in epidemics and having a good outcome.

This finding was supported by Foucard et al. (1971) and Polmar et al. (1972). The former workers correlated IgE levels with virology and atopic manifestation in children who wheezed. Although positive virus serology (to RSV, parainfluenza, influenza, adeno and ECHO viruses) was as common among children with high IgE levels, children who wheezed for the first time with RSV infections all had normal IgE levels Eosinophilia was more common in children with high IgE levels.

Polmar et al. studied two groups of children - 16 with "epidemic bronchiolitis" and 17 with "sporadic bronchiolitis" in an attempt to elucidate the apparent heterogeneity in the

diagnosis of bronchiolitis. IgE levels were measured and compared with control values from children with atopic disease. Thirty-five per cent of the children with "sporadic bronchiolitis" had serum IgE levels above the 95th centile for their age, while only 6% of those with "epidemic bronchiolitis" were abnormally high. They found no correlation between family or personal history of atopy and raised IgE levels. It was suggested that the measurement of serum IgE might help to identify bronchiolitic children destined to develop asthma or other allergic disorders.

In a prospective study of infants with bronchiolitis (Zweiman et al., 1966; Zweiman et al., 1971) reviewed annually for five years, 40-50% were noted to wheeze recurrently. They had a higher incidence of other allergies; as well as stronger family histories of allergy than non-wheezers. Recurrent wheezers had eosinophilia in nasal secretions and peripheral blood. Skin test responses to common allergens were more common in wheezy children and increased in frequency over the five year period. Although an episode of wheeze indistinguishable from bronchiolitis may be the first manifestation of asthma, a strong family or personal history of allergy should alert the clinician to the increased likelihood of recurrent wheeze.

The evidence presented suggest that RSV bronchiolitis, especially in the absence of personal or family history of atopy, carries a good prognosis. However, Kattan et al. (1977) have shown that lung function abnormalities may persist following apparent clinical recovery. Respiratory function tests were performed ten years after the diagnosis of bronchiolitis in 23 children who had remained symptom free and had no previous history of asthma. Despite the absence of a history of asthma and failure to demonstrate exercise-induced bronchospasm, most subjects were shown to have evidence of hyperinflation (↑RV/TLC), hypoxaemia (↓PO_2) and/or small airway dysfunction (↓$\dot{V}$ iso V and ↓$\dot{V}$ 60% TLC). Over 30% of the children had all three abnormalities, suggesting that residual parenchymal or airway lesions existed despite clinical recovery. More sensitive tests revealed abnormality of small airways rather than the lung parenchyma (Kattan et al., 1978).

A prospective study (Beckerman et al., 1978) of seven children who had had bronchiolitis in infancy but who had remained asymptomatic three to six years later, also showed lung function abnormalities (↓$\dot{V}$ max FRC and exercise induced bronchospasm) which occurred independent of an allergic tendency. However, the numbers in this study were small, and only two children performed the exercise test.

In an attempt to elucidate the effects of the disease further, Stokes et al. (1981) followed up a group of 22 infants who were aged between six and twenty-two weeks when they had bronchiolitis. Lung function was assessed during the convalescent period, three to four months later, and again after an interval of twelve to fifteen months. The diagnosis of bronchiolitis was made on clinical grounds, although 11 of the children had RSV isolated during the index illness. The health of the children in the past year was enquired into during the third attendance. It was shown that 35% of the infants had attacks of coughing, 50% wheezed and over 75% of the original group had disturbed lung function ($\uparrow$TGV, $\uparrow$Raw, $\uparrow R_T$). Respiratory symptoms were closely correlated with abnormal lung function, while no connection was established between prevalence of symptoms and atopic background of these children.

Unfortunately, little attention was paid to the sub-group of children who had had RSV proven bronchiolitis and no attempt made to compare their outcome with children who were negative for RSV during the index illness.

The role of bronchial reactivity in causing recurrent wheeze following bronchiolitis was assessed in 48 children about ten years after their index illness (Gurwitz et al., 1981). Fifty-seven per cent of these children were found, on challenge with methacholine, to have hyperreactive

airways. A significant correlation was found between a positive methacholine response and a history of "recurrent bronchiolitis". Positive responders also had impaired pulmonary function ($\downarrow$VC, $\downarrow FEV_{1.0}$, $\downarrow FEF_{25-75\%}$, $\downarrow$ PEFR, $\uparrow$ TLC and $\uparrow$RV/TLC). Fourteen children gave a history of asthma or wheezing, which appeared mild and few were on long-term therapy. There was a strong genetic predisposition to the development of bronchiolitis and airway reactivity, as 33% of first-degree relatives of positive methacholine responders also had a positive response. It was concluded that a previous history of bronchiolitis in children with hyperreactive airways strongly predisposed them to the development of chronic obstructive pulmonary disease in later life.

Sims et al. (1981) postulated that genetic factors accounted for post-bronchiolitic wheezing. About eight years after their RSV proven infection, 32 children and 26 of their paired controls were studied to assess the role of immunodeficiency and atopy in the causation of bronchiolitis and wheezing following it. No differences were found between patients and controls with respect to a positive family history or laboratory indices for atopy (skin tests, eosinophilia, yeast opsonisation defect, C_2 deficiency, IgE antibodies). These findings suggested that atopy occurred independently in these groups of children, and did not predispose to RSV bronchiolitis.

Eighteen (56%) of the patients were reported to wheeze following their index illness. Although the personal and family atopic background of the post-bronchiolitic wheezers and non-wheezers were similar, laboratory tests (although not all reaching statistical significance) did demonstrate more "atopy" in the recurrent wheezers. Exercise induced bronchial lability was highest in the wheezy children, intermediate in the non-wheezy index cases, and lowest in the control children. It would appear, therefore, that although an atopic background did not predispose to bronchiolitis, in these children atopy did play a part in causing wheeze afterwards and that atopic children with an attack of bronchiolitis could well be suffering their first attack of asthma.

S E C T I O N I

Chapter 4

OTHER FACTORS INFLUENCING RESPIRATORY DISEASE

1. Obesity

In a retrospective study of infants under one year old hospitalised for lower respiratory infection, Hutchinson-Smith (1970) found that 30% were more than 20% above expected weight. This led to a prospective study of 200 infants from birth to one year which confirmed an association between lower respiratory infections and obesity. The early introduction of solid feeds (at <9 weeks of age) was associated with more frequent lower respiratory infections and an increased tendency to obesity. A significant increase in chest infections was observed in babies weighing less than 2.5Kg at birth suggesting proneness to infection was also increased by low birth weight. The type of feeding was important - fully breast-fed infants gained weight less rapidly than partially breast-fed or artificially fed infants and were less likely to suffer lower respiratory infection. Other factors shown to influence the prevalence of respiratory illnesses were the presence of siblings in the family and social class. No attempt was made to assess the relative contributions of these variables.

2. Feeding Practices

Several studies have suggested that human milk has a protective effect and helps to reduce the incidence of respiratory infection. In a hospital study of infants with RSV infections and a control group without respiratory illnesses, Downham et al. (1976) found that breast feeding

was significantly less common in the index cases, implying suboptimal protection against RSV infection. To elucidate the mechanism of this possible protection, human colostrum was examined for RSV neutralising activity. The detection of specific IgA and IgG in most specimens examined, led to the postulate that inhalation or regurgitation of milk feeds through the nose aided the deposition of specific IgA throughout the respiratory tract and thereby contributed to the acquisition of local immunity. However, the results might equally have been explained on the basis of social class, as significantly more children with RSV infection came from social classes IV and V. The selection of controls from child-health clinics may have resulted in the inclusion of children in whom the standards of maternal care were higher. However, the finding that the breast feeding is protective is supported by anecdotal evidence (Evans-Jones et al., 1978) of the very low incidence of breast feeding in babies hospitalised for bronchiolitis. Watkins et al. (1979) examined the relationship between the type of feeding and the occurrence of bronchitis and pneumonia in the first year of life in a cohort of babies studied from birth. Breast-fed babies had fewer episodes of bronchitis or pneumonia than those who were bottle-fed. This association held when other social and family factors (family size, birth order, maternal smoking habits) were taken into account. Prospective studies of the effect of exclusive breast feeding on the incidence of infection and

allergy were conducted by Chandra (1979) in three different populations. In a rural Indian community, breast-fed infants were found to have significantly less cough, otitis or pneumonia than artificially fed controls matched for socio-economic status, parental occupation and family size. In an urban population in Canada a group of breast-fed infants were matched with controls in a similar way. Exclusive breast-feeding was associated with a decrease in cough and otitis media. The beneficial effect of breast feeding was further demonstrated in newborn siblings of children known to suffer from atopic disorders. A decrease in the incidence of eczema and recurrent wheezing were observed in breast-fed infants together with a reduction in serum IgE and cow's milk antibodies.

The effectiveness of breast feeding in reducing morbidity was demonstrated by Cunningham (1979) in a study of infants seen regularly during the first year of life. Information was obtained regarding feeding practices, significant illnesses (otitis, lower respiratory illness, vomiting, diarrhoea and any illness treated in hospital but excluding surgery and trauma), father's educational level, maternal age and family size. Protection was greatest in the early months of life and increased with the duration of breast feeding. The effect was independent of the social and environmental factors studied. The prevalence of exclusive breast-feeding has been compared in

community and hospitalised infants under three months of age (Fallot et al., 1980). The "community" cases were selected from patients attending paediatric clinics of a general hospital or private paediatricians. The incidence of breast-feeding was significantly lower in hospitalised patients. Upper respiratory infection, bronchiolitis and pneumonia occurred predominantly in exclusively bottle-fed babies. Those who received breast milk alone had no proven bacterial infections. Breast-feeding was advocated as a means of reducing the number of infants admitted to hospital, thereby minimising disruption of mother-infant bonding during the early months of life.

3. Prematurity

Premature birth, even without neonatal respiratory complications, influences susceptibility to chest infections. Douglas and Mogford (1953) and Drillien (1959) reported a high incidence of respiratory illness in premature infants outwith the newborn period but did not comment on the relation of these illnesses to respiratory problems in the newborn period. Coates et al. (1977) studied the pulmonary function of fourteen children born at about 33 weeks gestation and weighing about 2000 grammes at birth. Seven had had respiratory distress syndrome of the newborn and seven had escaped neonatal lung disease. The respiratory function of each subgroup was then compared with that of seven normal children born at term and without subsequent pulmonary

disease or a family history of allergy. There were no significant differences in lung volumes, MMEFR and $FEV_{0.75}$ between the three groups of children. Flow volume curves were obtained breathing air and then an He/O_2 mixture. Children who were born prematurely had lower expiratory flow rates in air than full-term infants. The volume of iso-flow was highest in the premature group with RDS, intermediate in "normal" premature children and lowest in those born at term. The results implied that impairment of lung function and possibly lung development was greater in premature infants with RDS than in premature infants without this complication.

The Wilson-Mikity syndrome (1960) affects premature infants and is thought to result from delayed and uneven alveolar development. Coates et al. (1978) assessed long-term pulmonary sequelae in five surviving children with this condition, none of whom had been treated by mechanical ventilation, eight to ten years later. Flow-volume curve variables were compared with those of six apparently normal premature children and eight healthy children born at term. The lowest flow rates were observed in survivors of the Wilson-Mikity syndrome, and next in pre-term infants without respiratory distress. Four of the Wilson-Mikity syndrome children had repeated episodes of wheeze, sometimes severe enough to merit hospitalisation. No child in the remaining groups was hospitalised for respiratory problems. The

pre-term infants with Wilson-Mikity syndrome were significantly lighter at birth than those who remained symptom free, which might explain the findings. Information is not available on the possible effect(s) of intra-uterine growth retardation on pulmonary development and function.

4. Idiopathic Respiratory Distress Syndrome and Ventilatory Assistance

The effect of immaturity on lung growth is exaggerated by additional insults in the neonatal period such as may be caused by the idiopathic respiratory distress syndrome (IRDS), high concentration of oxygen and mechanical ventilation (Northway et al., 1967). Survivors of IRDS are particularly susceptible to lower respiratory tract infections. Lewis (1968) reported that about 18% of 63 IRDS survivors were admitted to hospital subsequently for respiratory tract infections. Lung compliance was measured in three children under three months of age and found to be low but PEFR was within the normal predicted range (performed in ten children aged 2½-5 years). Shepard et al. (1968) described bronchiolitis and broncho-pneumonia in about 31% of IRDS survivors. Similar findings were reported by Outerbridge et al. (1972) in a follow-up assessment of 53 survivors who had radiological clearing of the disease prior to discharge from hospital. Eleven had severe lower respiratory infections later necessitating their admission to hospital. Eight of these eleven had persistent changes

on chest X-ray. The period of follow-up was short (26 months) and resolution of chest X-ray abnormalities might have occurred eventually. Johnson et al. (1974) investigated the contribution of mechanical ventilation in the newborn period to chronic cardio-pulmonary disease. After an average interval of 5.7 years an attempt was made to assess the progress of fifty-five children who had received mechanical ventilation in the neonatal period. A diagnosis of broncho pulmonary dysplasia had been made in 16 of the 55 survivors at the time of discharge from the neonatal unit. "Many" of these 16 children (number not stated) had recurrent episodes of respiratory infection in the first two years of life and four developed recurrent wheeze. Abnormalities persisted on chest X-rays in 10, and in five there was equivocal evidence of right ventricular hypertrophy on electrocardiography.

Harrod et al. (1974) studied the effects of IRDS, the application of IPPV and 0_2 therapy on cardio-pulmonary outcome. Twenty-two survivors of IRDS treated with IPPV in the newborn period were examined one to five years later. Only two were reported to have had respiratory infection after the age of one year. However, the persistence of radiological abnormalities in 68% of the children was significantly related to the duration of 0_2 therapy. In children over two years, eight out of 16 had persistent right ventricular hypertrophy, 10 had arterial hypoxaemia and 15

had abnormally high $AaDO_2$ values breathing 100% oxygen. These findings implied that pathological changes in the lungs persisted beyond clinical recovery.

Ahlstrom (1975) studied pulmonary mechanics during the first year of life in 24 infants who survived severe neonatal respiratory disease (RDS, recurrent apnoea and birth asphyxia). Ventilatory assistance had been given in the form of CPAP or IPPV. The infants treated with CPAP alone had a normal respiration rate, tidal volume, minute ventilation, dynamic compliance and pulmonary conductance. IPPV-treated infants had lower than expected values for dynamic compliance and conductance, especially if treatment had been prolonged. However, the infants treated by IPPV were on average three weeks more pre-term than the CPAP group. Pressure-flow loops showed evidence of airway obstruction in most infants, irrespective of the original diagnosis or treatment.

The relative contributions of artificial ventilation, oxygen and CPAP to subsequent lung damage was assessed by serial lung function studies in the first year of life in 18 infants with IRDS at birth (Stocks and Godfrey, 1976). Prior to discharge from the neonatal unit, lung function was normal in most infants. Between 4-11 months of age, artificially ventilated infants had an increase in airways resistance. Normal values were obtained in others who received CPAP and/or oxygen only. The ventilated infants

were of lower birthweight and gestational age and therefore more likely to be affected adversely by prematurity. Despite this, no differences in lung function were noted initially between the two groups prior to discharge from hospital. At follow-up, two of the "ventilated" infants had recurrent wheeziness while no symptoms were reported in the non-ventilated group.

Kamper (1978) reported a good long-term prognosis for children ventilated for IRDS when compared with controls matched for birth weight, gestational age and socio-economic characteristics, 2.6-7.6 years later. The morbidity for lower respiratory illnesses was significantly higher in IRDS survivors and more such children were hospitalised for these illnesses. Abnormalities were present on chest X-ray in 21 of 57 IRDS survivors, compared with nine matched controls. The occurrence of chest illnesses and radiological changes were not related to birth weight, gestation or ventilatory therapy. Respiratory frequency, lung volume, oxygen saturation and acid-base status were similar in both groups. Perhaps more sophisticated tests of respiratory function would have revealed occult abnormalities which these tests were too insensitive to detect.

A similar good prognosis, at least during the first year of life, was reported more recently (Wong et al., 1982). In a prospective clinical and physiological study, 20 infants

who had received IPPV in the neonatal period were compared with 15 healthy controls, matched for birthweight. Abnormalities of lung function (↑thoracic gas volume, ↓dynamic compliance and ↓flow conductance) were significantly more common during the middle four months of life in the group which had received IPPV. There was also a higher incidence of lower respiratory tract infections in infancy. Towards the end of the first year of life, lung function in the IPPV group returned to normal, except for those with recurrent respiratory infections.

However, the control group were of a higher mean gestational age and probably accounted for the uneventful neonatal period. There were also insufficient infants in the IPPV group with IRDS alone (not requiring IPPV) to allow differentiation between the effects of the disease and the treatment for it. The authors were cautious in predicting a good prognosis on a longer-term basis.

Coates et al. (1982) evaluated the pulmonary sequelae in two groups of children who had IRDS of similar severity, who were not mechanically ventilated but who received different amounts of oxygen during their illness. Ten years later, 23 of 102 survivors were recalled for study. Fourteen had received a low oxygen regime during the neonatal illness while nine were administered high concentrations of oxygen. The two groups were comparable in terms of gestational age,

birth weight and severity of the original illness (judged by blood gas estimations and duration of stay in hospital). None of the children had clinically significant respiratory impairment (term not defined), and all routine tests of lung function (lung volumes, RV/TLC, $FEF_{25-75\%}$) were within the normal range. Both groups had similar abnormalities of large airways ($\dot{V}max_{50}$ and $\dot{V}max_{25}$) when compared to normal premature children. When helium-oxygen curves were analysed, higher volumes of iso-flow were found in children who had received high oxygen concentrations. The authors concluded that high oxygen concentrations in the absence of mechanical ventilation was capable of causing long-term changes in small airways.

5. Congenital Diaphragmatic Hernia

A congenital diaphragmatic hernia may interfere mechanically with the growth of the lung resulting in a varying degree of hypoplasia on the affected side, and reduction in the size and number of airways, alveoli and arteries (Kitagawa et al., 1971). Little information is available on ultimate lung function following surgical correction of such hernias. Chatrath et al. (1971) assessed ventilatory function in 14 children 6-12 years after surgical repair of a congenital diaphragmatic hernia in infancy. Five had "normal looking" lungs at operation. At follow-up, three children had over-inflation of the

affected lung on chest X-ray. FEV_1 and FVC were significantly reduced in these patients but lung volumes (FRC, RV and TLC) were within normal limits.

Wohl et al. (1977) reported persistent vascular abnormalities in a group of patients 6-18 years following repair of congenital diaphragmatic hernia in infancy. Respiratory function tests - spirometry, flow volume curves in air and $He/0_2$, total respiratory resistance, diffusing capacity and ventilation studies using ^{133}Xe were normal in most. However, pulmonary perfusion was reduced on the side of the hernia in nine patients who were investigated. Lung volumes had become normal with continuing growth of the alveoli, but without a corresponding increase in vascular tissue.

6. Tracheo-eosophageal Fistula

Respiratory problems are common following repair of oesophageal atresia and tracheo-oesophageal fistulae. Laks et al. (1972) studied 42 such patients between 15-25 years following primary repair of these abnormalities and found that 33% had long-term respiratory problems (frequent colds, bronchitis and pneumonia). Although this could have resulted from respiratory complications in the post-operative period, cinefluorography demonstrated disordered oesophageal motility in 15 patients studied. This often resulted in retrograde flow of oesophageal contents and aspiration in the lungs.

One hundred of 192 survivors of repaired oesophageal atresia were reviewed by Dudley and Phelan (1976) after intervals ranging from 1-20 years. About half were studied after nine years. Persistent cough, recurrent bronchitis and pneumonia were reported in 78% and many patients had been hospitalised on this account. Respiratory problems were commonest in the first eight years of life, and not obviously related to post-operative respiratory complications. Abnormal oesophageal peristalsis was demonstrated in 42 patients studied. Indirect evidence of milk aspiration was found in seven children based on examination of tracheal aspirates for fat globules.

Milligan and Levison (1979) studied pulmonary function in 24 patients 7-18 years following repair of tracheo-oesophageal fistula. Only one had normal tests of lung function. Obstructive airway disease ($\downarrow$ MMEFR, $\downarrow FEV_1$, $\uparrow$ RV/TLC, $\uparrow \dot{V}isoV$) was seen in 13 and restrictive disease in five ($\downarrow$TLC), but three of the latter had some degree of thoracic deformity which might have accounted for the small lung volumes. After challenge with methacholine, 15 of 23 patients (65%) had positive responses suggesting an increase in bronchial reactivity. The authors postulate that continuing subclinical aspiration caused lung damage and rendered the airways hyperreactive.

7. Hydrocarbon Ingestion

It might be argued that the factors so far discussed have either a congenital basis or were operative because of some genetic susceptibility to respiratory disease. However, a single acquired insult to the lung in childhood can cause long-term sequelae irrespective of host factors. Gurwitz et al. (1978) studied pulmonary function in 17 asymptomatic children 8-14 years after ingestion of hydrocarbons (petroleum distillate, turpentine, coal oil or cleaning fluid). Mild to severe pneumonia had been present initially. At follow-up only one child had chest X-ray abnormalities persisting from the initial illness. However, 14 (82%) had one or more abnormalities of pulmonary function ($\uparrow\dot{V}$isoV, $\uparrow$RV/TLC, $\uparrow$slope of phase III, $\downarrow\dot{V}_{50}$, $\downarrow\dot{V}_{25}$, $\downarrow\dot{V}_{60\%}$ TLC/sec, $\downarrow$FEV and MMEFR) when compared with matched controls. Children who had inhaled petroleum distillate all had residual abnormalities whereas lung function was normal in one third of those patients who had aspirated turpentine. On the other hand, Taussig et al. (1977) studied three patients who had swallowed fuel oil, furniture polish or stove oil, and found no abnormalities in chest X-rays or on pulmonary function testing 7.5, 9.7 and 8.0 years later.

S E C T I O N II

Chapter 1

BACKGROUND AND ORGANISATION OF THE STUDY

A case-control study was planned to assess the respiratory status and epidemiological characteristics of children some seven years after hospitalisation for acute lower respiratory tract infection in infancy. Index cases were selected from infants admitted to the Royal Hospital for Sick Children in Edinburgh with bronchitis, bronchiolitis or pneumonia during the winter periods 1971-72, 1972-73 and 1973-74 and divided into two sub-groups - RSV positive where the respiratory syncytial virus was responsible for the index illness, and RSV negative where no virus was demonstrated or the index illness was caused by another virus. For each child a classmate was chosen from the same school, and matched for sex, age (to within three months) and as far as possible, height. The essential difference was that no control had a respiratory illness in infancy which necessitated admission to hospital.

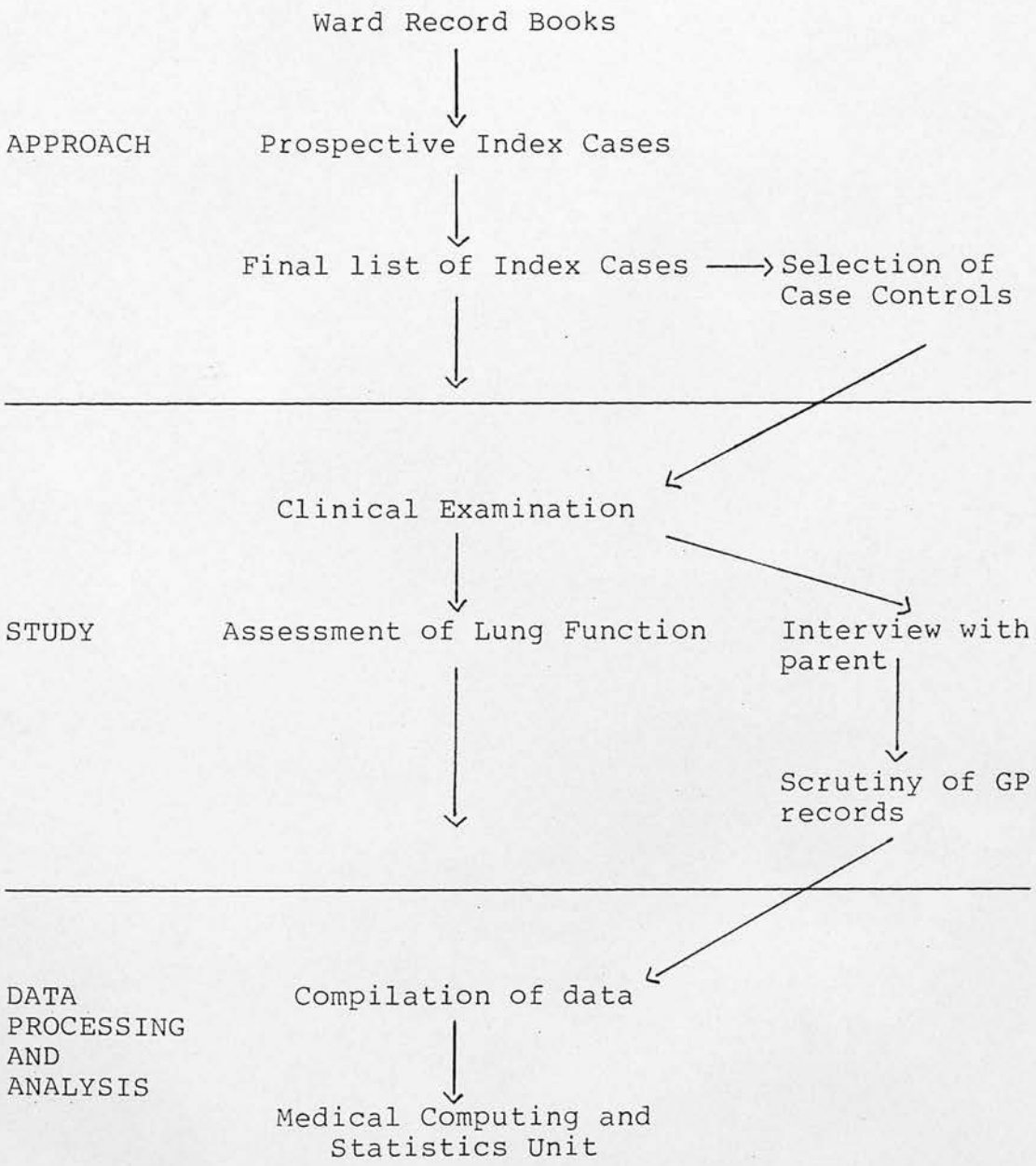
Parents were contacted by letter requesting permission to include their children in the study. The children were then seen at the Respiratory Function Laboratory of the Royal Hospital for Sick Children, Edinburgh. The accompanying parent(s) was interviewed, and the detailed history obtained was recorded on a questionnaire. Each child was examined fully and tests of respiratory function performed. Later, general practitioners were contacted by letter to obtain permission to scrutinise the medical records of these children as an independent source of information. This necessitated visits to many health centres and surgeries.

The data on each subject (clinical, family and social histories, general practitioner information, clinical examination and results of pulmonary function tests) were recorded so as to facilitate subsequent statistical analysis in the Medical Computing and Statistics Unit of the University of Edinburgh. The design of the study is depicted in the flow chart (Figure 1).

Cooperation was assured from the Education Department of Lothian Regional Council so that headteachers could be approached for the names of possible control children. The Lothian Local Medical Committee (General Practice) approved the study and general practitioners cooperated by returning questionnaires or allowed perusal of records of children in their care.

FIGURE 1

Flow Chart of Study



Patient Selection

Children selected for the study had been admitted to the Royal Hospital for Sick Children, Edinburgh, during three consecutive winters , from:

1 November 1971 - 30 April 1972

1 November 1972 - 30 April 1973

1 November 1973 - 30 April 1974

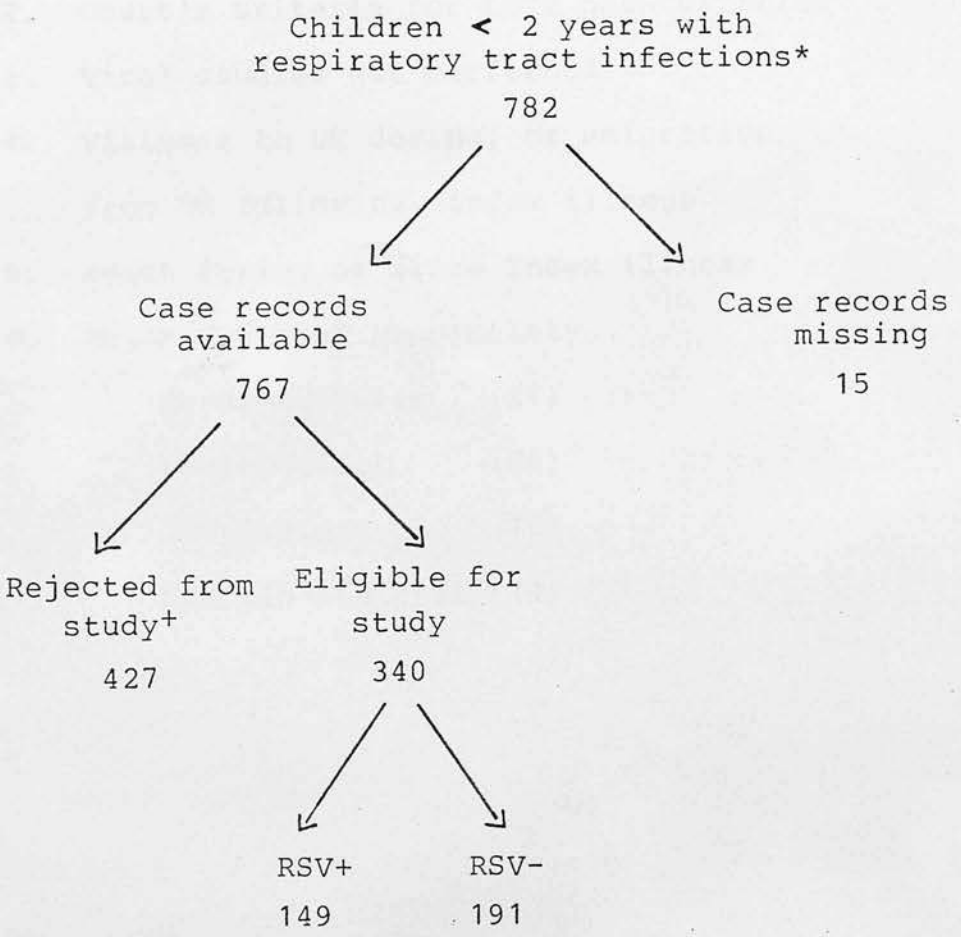
The medical ward records were scrutinised for the names of children under two years of age, admitted during these winter periods with respiratory tract infections. As the ages of children were not always noted with accuracy, it was hoped that by taking two years as the cut-off point, few children would be missed. Seven hundred and eighty-two names were thus obtained (see Figure 2).

The list of names was given to the Records Officer at the Royal Hospital for Sick Children, Edinburgh, who made case notes available for detailed perusal. Fifteen sets of case records could not be traced. Following scrutiny of the remaining case notes, 427 children were rejected from the study (see criteria for rejection, Table 1).

Virological studies had been performed in 340 children during their index illnesses. Nasal and throat swabs were obtained during the first winter period, and naso-pharyngeal secretions during the subsequent periods. Swabs and

FIGURE 2

Patient Selection



* From scrutiny of ward records

+ See criteria for rejection (Table 1)

TABLE 1

CRITERIA FOR REJECTION OR INELIGIBILITY

1.	Age >1 year at index illness	166
2.	Court's criteria for LRTI not fulfilled	136
3.	Viral studies not performed	36
4.	Visitors to UK during, or emigration from UK following, index illness	11
5.	Death during or since index illness	12
6.	Major "system" abnormality	66
	Cardiovascular (31)	
	Neurological (21)	
	Respiratory (10)	
	Musculo-skeletal (4)	
		427

secretions were obtained within a day of admission to hospital. Respiratory syncytial virus infection was diagnosed on the basis of immunofluorescent or culture techniques. No attempt was made to obtain paired sera in these infants.

The 340 children were divided into two groups:

1) Children < 1 year with LRTI caused by RSV 149
2) Children < 1 year with LRTI where RSV was not isolated 191

The children were then grouped according to the winter period when they were hospitalised. In each winter period, there were RSV+ and RSV- index cases who were matched (to within three months) according to their age at presentation. This allowed approximately equal numbers of RSV+ and RSV- children to be selected from each winter period.

In the first two winters (1971-72 and 1972-73) there were 74 RSV+ children. All these were included in the study. RSV- children were randomly selected by drawing the required number of names in each age group from a hat. Thus 74 names were chosen out of a possible 150 RSV- children.

During the third winter (1973-74) the selection procedure was reversed to include all RSV- children (41) and randomly selecting an equal number of RSV+ children from appropriate age groups (see Table 2).

TABLE 2

PATIENT TRACING

Winter Period	Number Eligible for study		Selection of index cases		Refusals		Gone Away		Number From Eligible Group Augmenting List		Contact Not Necessary		Final Number in Study	
	RSV+	RSV-	RSV+	RSV-	RSV+	RSV-	RSV+	RSV-	RSV+	RSV-	RSV+	RSV-	RSV+	RSV-
1971-72	31	69	31	31	1	5	5	7	-	12	-	26	25	31
1972-73	43	81	43	43	4	3	5	10	-	8	-	35	34	38
1973-74	75	41	41	41	3	0	8	10	11	-	23	-	41	31
	149	191	115	115	8	8	18	27	11	20	23	61	100	100

Patient Tracing

The above procedure had selected 115 RSV+ and 115 RSV- children as possible candidates for study. Letters were sent to parents of each child requesting cooperation (Appendix 1). Where a favourable reply was received from the parents, an appointment was sent for the child to be seen at the Respiratory Function Laboratory of the hospital. If the parents refused permission, then the next child on the list was selected. This applied to the RSV- lists of 1971-72, 1972-73 and the RSV+ list of 1973-74. Where the list was exhaustive (as the 1973-74 RSV- and 1971-72, 1972-73 RSV+ lists), the child was not replaced and the final number made up from the original list. Table 2 shows how the procedure was carried out.

Some families had moved from their original address. The Lothian Regional Council was able to supply new addresses within the Lothian Region. The National Health Service Central Register provided the names of general practitioners and relevant Health Boards of children who had moved outwith Edinburgh. If the family was within reasonable travelling distance of Edinburgh, the Health Boards were requested to provide the addresses of the children. The children's general practitioners were informed of our intention to include the children in the study.

Some parents did not reply to the first letter, although many did so after a second was sent. If no reply was received after two letters were sent, general practitioners were contacted (by telephone) for information about the family. Health Visitors, either from the practice or from the hospital, visited the family and permission was usually granted. Where the parents both worked and could not attend for their appointment, the family was visited and interviewed at home. Transportation arrangements were then made for the child to attend the laboratory for respiratory function tests.

Selection of Control Children

We considered selecting as controls those children who were hospitalised at the same time as the index cases, but who did not have respiratory illnesses. Review of the ward records showed this to be impractical as most admissions during the winter periods were for respiratory illnesses. There were thus too few children from which to select controls.

It was decided to select controls from the same class at school as the index children, but who did not suffer respiratory infections in the first year of life severe enough to warrant hospitalisation. By choosing controls from the same school as the index children, we hoped to minimise or eliminate socio-economic and environmental differences between index and control children.

Parents of each index case gave the name of the school their child attended. Headteachers were contacted (Appendix 2 and 3) and asked to provide the names and addresses of four children in the same class as the index, matched for sex, age (to within three months) and as far as possible, height. The child closest in age to the index was selected, and parental permission sought (Appendix 4 and 5). If permission was refused, or the child had been hospitalised for respiratory illnesses in the first year of life, then the next child was selected.

Children from each winter period were seen separately, index cases followed by their controls.

Protocol at Follow-up (Table 3)

Before the child attended for follow-up, hospital in-patient records were perused, and information on the index illness extracted for the questionnaire. Any other relevant information in the notes, such as the immunisation history, family or social history were also recorded in the questionnaire.

The child and parents were then seen. The parents were interviewed according to the questionnaire and answers coded. The child was examined and tests of respiratory function performed.

TABLE 3

PROTOCOL AT FOLLOW-UP

1. Perusal of hospital in-patient records of index cases and extraction of relevant information concerning the index illness.

2. Interview with parents and completion of questionnaire.

3. Clinical examination of child:

   Height and weight

   Upper respiratory tract

   Chest

   Skin

4. Respiratory function tests:

   a) Total respiratory resistance (R_T)

   b) Peak expiratory flow rate (PEFR)

   c) Spirometry - forced expiratory volume in 1 second (FEV_1)
   - forced expiratory volume in 0.75 sec ($FEV_{0.75}$)
   - forced vital capacity (FVC)
   - forced expiratory flow during the middle half of the expired volume ($FEF_{25-75\%}$)

d) Maximal expiratory flow volume curves in air and in an 80% helium - 20% oxygen (He/O_2) mixture with the following measured:

$FEV_{1.0}$

FVC

Maximal flow at 50% of the vital capacity ($\dot{V}_{50}$)

Maximal flow at 25% of the vital capacity ($\dot{V}_{25}$)

Change in flow at 50% vital capacity after breathing He/O_2 ($\Delta \dot{V}_{50}$)

Change in flow at 25% vital capacity after breathing He/O_2 ($\Delta \dot{V}_{25}$)

e) Exercise study with PEFR measurements before, during and after exercise.

5. Reimbursement of travelling expenses
6. Letters to general practitioners of every child
7. Visits to health centres or surgeries in selected cases
8. Final compilation of data
9. Computer analysis

General Practitioner Records

During the interview with the parent(s), it was asked if the child (index or control) had been prone to respiratory illnesses. The parents' history was accepted, and then the general practitioner of every child was written to. Letters took two forms:

a) Appendix 6 and 7 - Where the parents stated that the child had had no respiratory illnesses of note during his life. The general practitioner was asked to review the child's records, and either confirm or refute the parents' account of the history. If the general practitioner agreed with the parents that the child had been free of respiratory problems, then the records were not perused further. Should the reply from the family doctor state that the child had had respiratory illnesses in the past, thereby disagreeing with the parents' statement, then the notes of that child were scrutinised to clarify the situation.

b) Appendix 8 and 9 - If the parents stated that the child had been subject to respiratory illnesses, the general practitioners were asked to consent to the records being scrutinised. Only two doctors refused to have their patients' case records made available for scrutiny, but were willing to divulge relevant information over the telephone.

Therefore about two thirds of the children's medical records were reviewed at their general practitioner's surgeries or health centres. The receptionists were contacted and a mutually convenient time arranged for the perusal of the records. Information was extracted, and particular attention paid to house-calls or consultations of a respiratory nature. Respiratory illnesses were coded according to Court's criteria into upper, middle and lower respiratory infections and then entered into the questionnaire, according to the number of episodes per each year of the child's life.

S E C T I O N II

Chapter 2

THE QUESTIONNAIRE

Questions were structured so as to obtain information on the index illness (in index children only), the child's past medical history, the occurrence of respiratory symptoms and established respiratory disease in the child and his parents, the socio-economic situation and the atopic background of the child and his first-degree relatives. The questionnaire was divided into eight sections (Appendix 11).

1. The Index Illness

Information on this was obtained from the hospital case records. Each index case was classified as having had bronchitis, bronchiolitis or pneumonia according to Court's criteria (1973), and further divided into RSV+ or RSV-. The height and weight recorded during admission provided some information on the growth and nutritional status at that time. The severity of the index illness was assessed by the necessity to perform blood gas analyses, the administration of antibiotics or the institution of mechanical ventilation. The results of bacteriological studies performed during the illness were also recorded.

2. The Child

Information regarding the child's past and present medical history was provided by the accompanying parent. Enquiry was made of environmental variables which might have affected outcome. These included the birth weight, gestational age, type and duration of infant feeding as

well as immunisation procedures. The nature of coincidental respiratory illnesses in the neonatal period and early childhood was recorded. Questions on respiratory symptoms - cough, wheeze, sputum, breathlessness - were modified from the MRC questionnaire on respiratory symptoms (1976). The parent was also asked about the child's upper respiratory symptoms - rhinitis, "colds", sore throats, hearing difficulties.

Where the child suffered respiratory symptoms, information on the chronicity or severity of the problem was obtained by enquiring into the type of medication used and the frequency of use, time lost from school, and the number of general practitioner consultations in the preceding year.

3. Social Information

Social and environmental factors which influence the occurrence or outcome of respiratory illness include the social class (or socio-economic group), housing conditions, overcrowding, the place of the child in the family, type of heating, pets at home, smoking habits in the house and the day-time care of the child. Only the main type of fuel used for heating the living room was recorded, on the assumption that the child (and family) would spend most time during the day in the living room. While smoking habits in the home were important, it was unrealistic to

expect parents to recall the actual amount smoked during the child's lifetime. The mother's smoking habits were noted separately as it seemed likely that she would have most contact with the child. The total number of smokers at home was noted as a rough estimate of "pollution" - especially in the first year of life.

4. Family factors

The health of the father and mother was assessed, paying particular attention to respiratory symptoms and smoking habits. The average number of cigarettes smoked per day (see footnote for conversions) was recorded. An ex-smoker was one who had smoked as much as one cigarette per day (or one large cigar per week or an ounce of tobacco per month) for as long as a year, and who at the time of the interview had not smoked for six months or more. Whether or not the mother worked was also noted, as well as the age of the child when she started to work.

5. Atopic Background

The occurrence of atopic disorders in first degree relatives as well as the children themselves was noted. First-degree relatives included the parents and siblings (from the same parents) of the child. The atopic disorders asked about were eczema, hayfever, food allergy

Footnote: 1oz tobacco = 28 cigarettes
1 small cigar = 2 cigarettes
1 large cigar = 5 cigarettes

and asthma. These words were not used as they might imply different conditions, but descriptive terms were substituted, eg for "eczema" the phrase used was "skin condition where the skin is rough, chapped and dry, with red, itchy areas that sometimes crack or weep".

Information was obtained on the real father, mother, brothers or sisters, whether alive or dead. The history was sometimes incomplete for children who had been adopted. For each atopic condition, the total number of first-degree relatives with that particular condition was entered.

6. General Practitioner Records

Records were reviewed at the surgeries or health centres when children had respiratory symptoms or disorders, where the parental recall was in doubt, or where there was disagreement between parental and medical (general practitioner) account of respiratory illnesses.

Each respiratory illness recorded by the general practitioner was coded according to Court (1973). Upper respiratory tract infections (URTI) included "common colds", rhinitis, pharyngitis, tonsillitis or otitis. Croup, laryngitis and tracheitis were coded as middle respiratory tract infections (MRTI), while bronchitis, bronchiolitis, pneumonia, "chest infection" or "respiratory infection" were classified as lower respiratory tract infection

(LRTI). The total number of consultations for URTI, MRTI and LRTI for each year of the child's life was recorded in the questionnaire.

Established respiratory disorders were designated as asthma/wheezy bronchitis (four or more episodes of wheeze in the preceding year necessitating medical attention), recurrent bronchitis (four or more episodes of cough in the preceding year necessitating medical attention), or recurrent upper respiratory tract sepsis (six or more episodes of sore ears or throat requiring medical attention in the preceding year).

7. Clinical Examination

The child's height and weight were recorded in his indoor clothes, to one decimal point. The centile was recorded, rounded off to the centile below. Examination of the ears resulted in a code for the one which was more abnormal. The rest of the upper respiratory tract examined included the nose and throat. The presence of an upper respiratory tract infection excluded the performance of respiratory function tests only if abnormal chest signs co-existed. Such children were asked to return on a later date.

8. Respiratory function tests

The actual values recorded were entered into the questionnaire. The predicted value according to the height was analysed by computer, with the regression equations shown in Appendix 10.

In preparing the questionnaire, helpful advice on many aspects of format and design were obtained from:

Dr Mary Fulton - Community Medicine Specialist
Department of Community Medicine
University of Edinburgh

Professor J.R.T. Colley - The London School of Hygiene and Tropical Medicine
University of London

Professor W.W. Holland - Department of Community Medicine
St Thomas's Hospital Medical School
London

Mr W Lutz - Director
Medical Computing & Statistics Unit
University of London

Further guidance was obtained from the MRC questionnaire on Respiratory Symptoms (1976).

S E C T I O N II

Chapter 3

LABORATORY AND STATISTICAL METHODS

1. Total Respiratory Resistance (R_T)

Total respiratory resistance was measured using the forced oscillation technique (Goldman et al., 1970). The subject wore nose clips and stood during the procedure and breathed normally through a disposable mouthpiece for one or two minutes (Plates 1 & 2). During normal breathing, a 6 cycle/second oscillation at a pre-selected pressure of 2cm water was super-imposed on the subject's respiratory cycle with the operator supporting the subject's cheeks to prevent excessive fluctuations.

Figure 3 shows how R_T was calculated from the recording obtained. The volume trace gave information of the phase of the respiratory cycle and permitted calculation of inspiratory and expiratory resistance. R_T was reported for all children during expiration, and the normal range related to height was obtained from data in normal children (Cogswell 1973).

Flow was calibrated using a rotameter. The deflection resulting from a flow rate of 30 1/min was constant at approximately one centimetre on the recording paper. A water manometer was used to calibrate pressure. The deflections from a water pressure of 2cm were in the range 1.8-2.2cm.

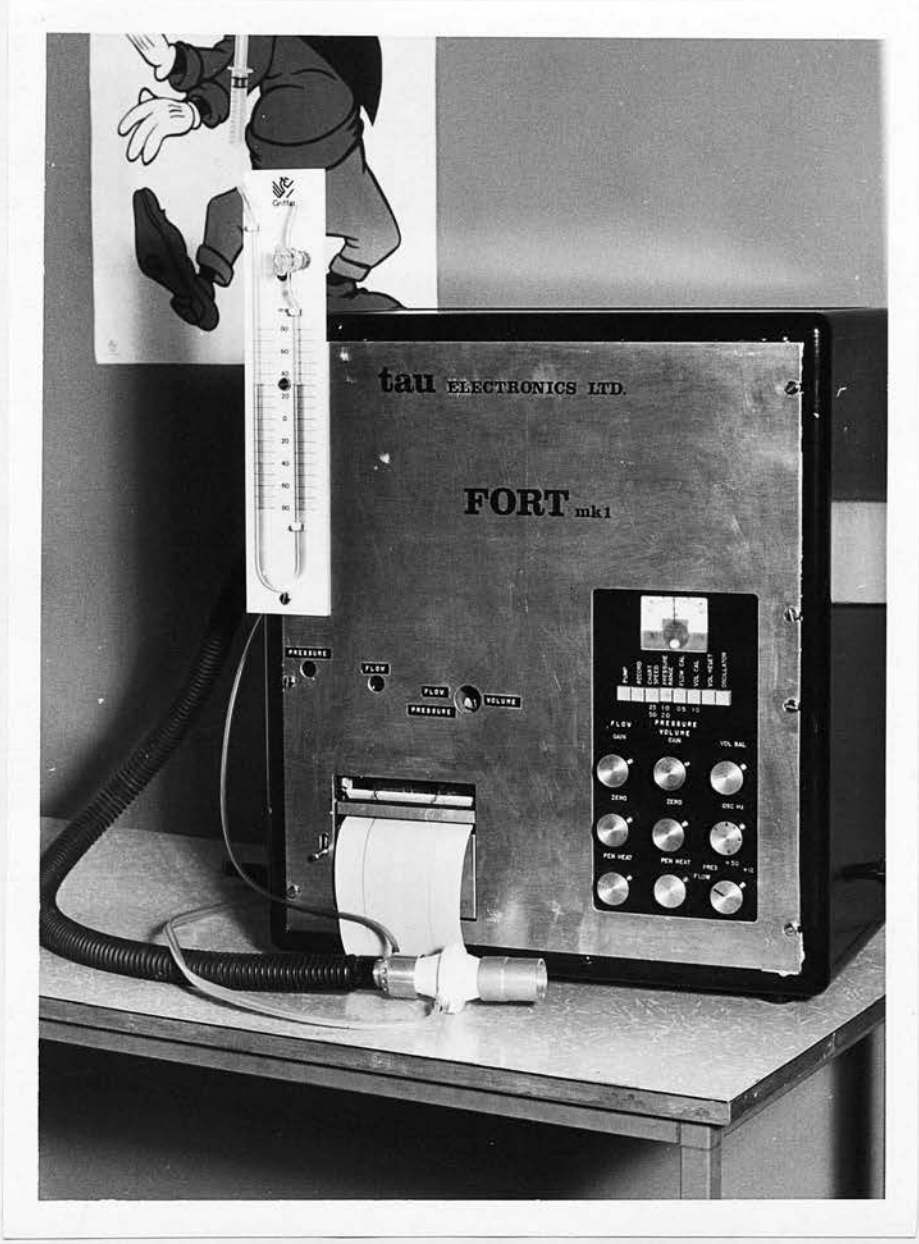


Plate 1

Equipment used for measurement of total respiratory resistance.

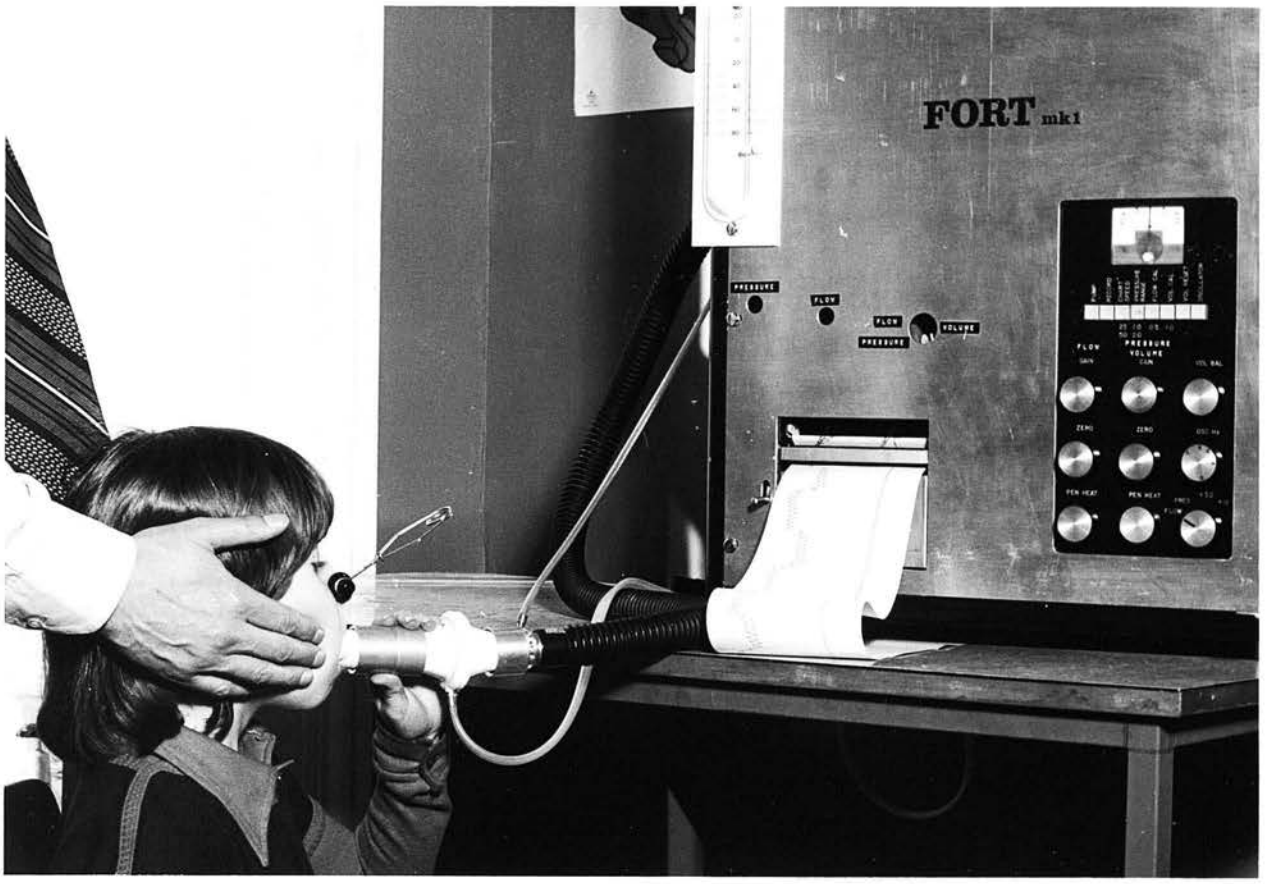


Plate 2

Child having total respiratory resistance measured

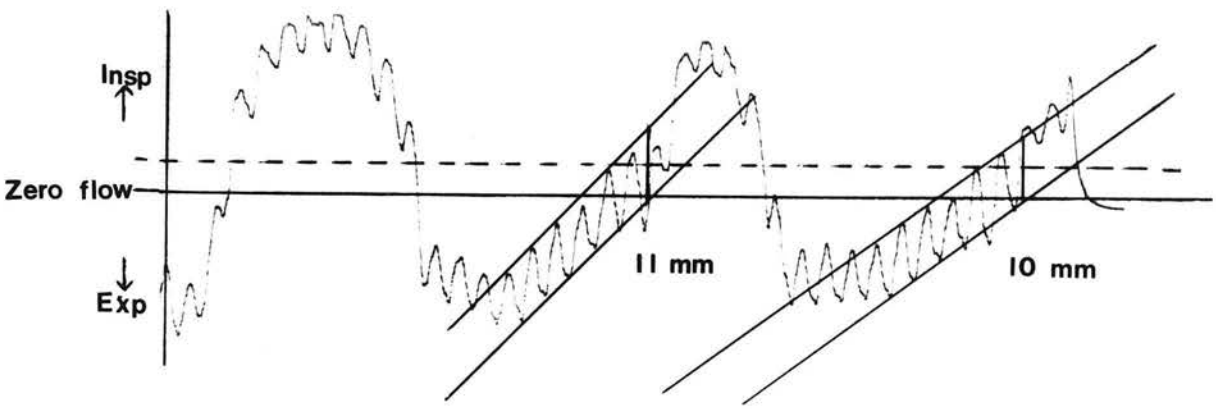


Figure 3

Calculation of total respiratory resistance

Average amplitude = 10.5mm

10mm = Flow rate of 30 l/min or 0.5 l/sec

$\therefore$ 1mm deflection = 0.05 l/sec

$$R_T = \frac{\text{Pressure}}{\text{Flow}} = \frac{2\text{cm } H_2O}{10.5\text{mm} \times 0.05 \text{ l/sec}}$$

= 3.81cm H_2O/l/sec or 0.37 KP/l/sec

2. Peak Expiratory Flow Rate (PEFR)

A Wright's peak flow meter (Wright and McKerrow, 1959) measured PEFR with the subject standing (Plates 3 & 4). Maximal inspiration with the mouth away from the mouthpiece was followed by rapid and complete expiration via the mouthpiece. The best of three attempts was accepted and the result reported as a percentage of the predicted value for height for both males and females (Cotes 1979: Appendix 10). The same peak flow meter was used throughout the study.

3. Spirometry

An electronic spirometer (Spirotron, Drager Ltd) measured forced expiratory volume in 1.0 sec ($FEV_{1.0}$) and forced vital capacity (FVC) (Plates 5 & 6). Results were displayed digitally and recorded graphically. The highest values from three forced expirations were used for recording and measuring data.

The forced expiratory volume in 0.75 sec ($FEV_{0.75}$) and the forced expiratory flow in the middle half of the expired volume ($FEF_{25-75\%}$) were calculated from the spirogram obtained (Figures 4 & 5).

Results were expressed in BTPS units and reported as percent predicted values for height and sex (Cotes 1979; Appendix 10).

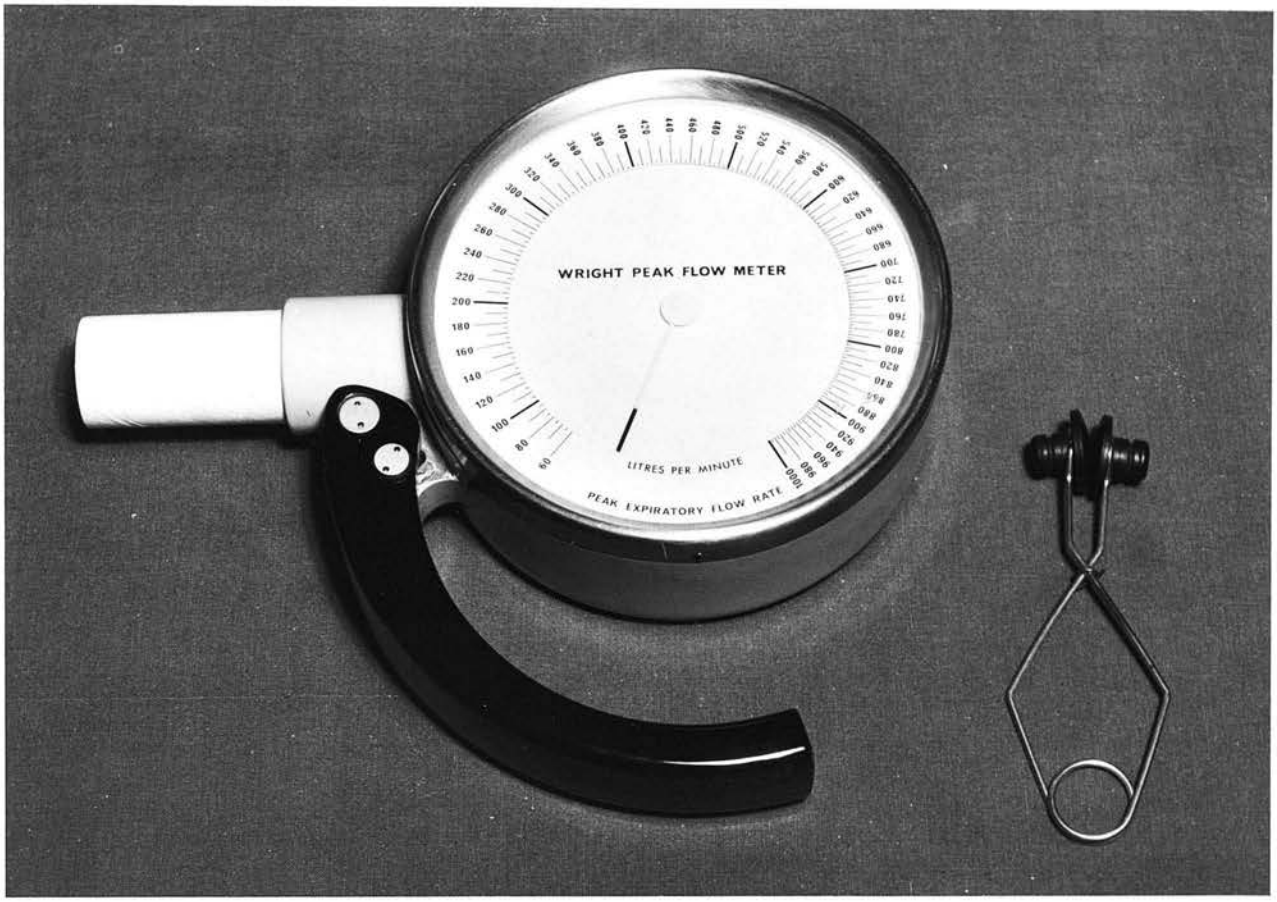


Plate 3

Wright's peak flow meter

Plate 4

Measurement of peak expiratory flow rate

Plate 5

Electronic spirometer and recorder

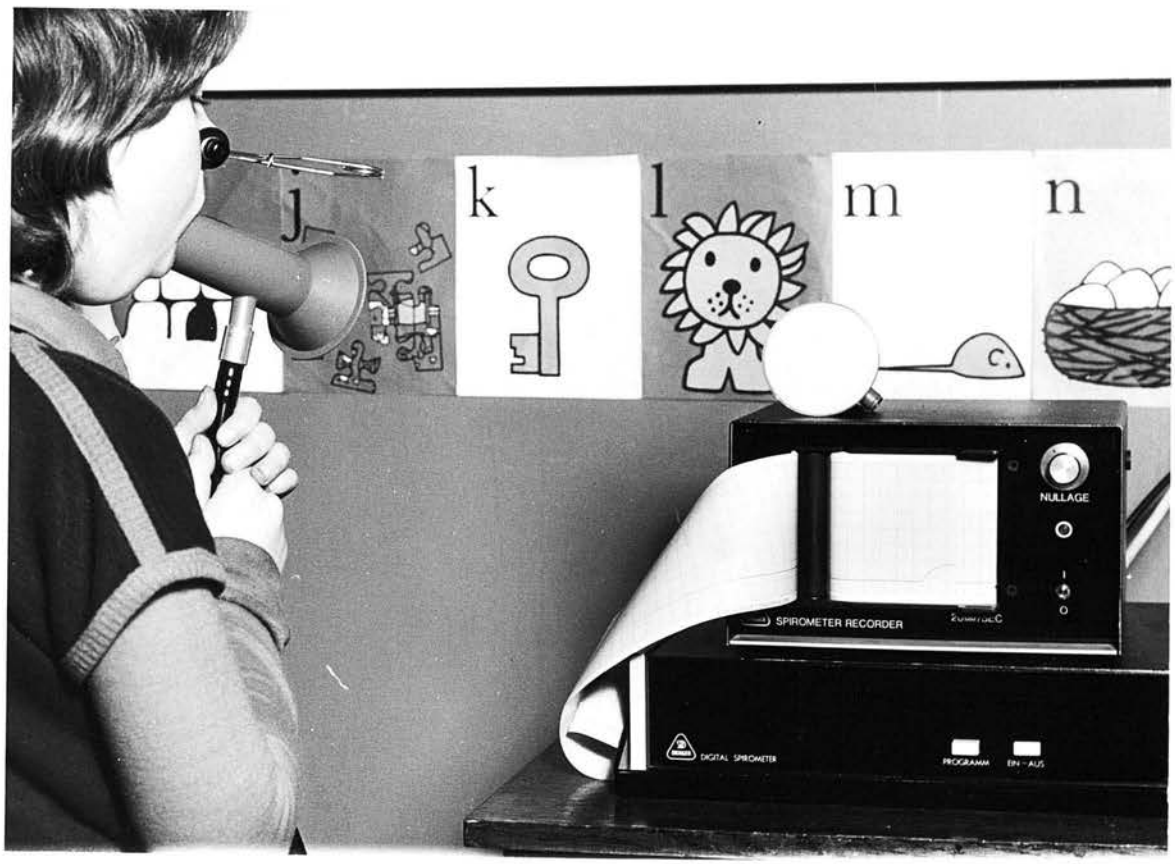


Plate 6

Measurement of $FEV_{1.0}$ and FVC

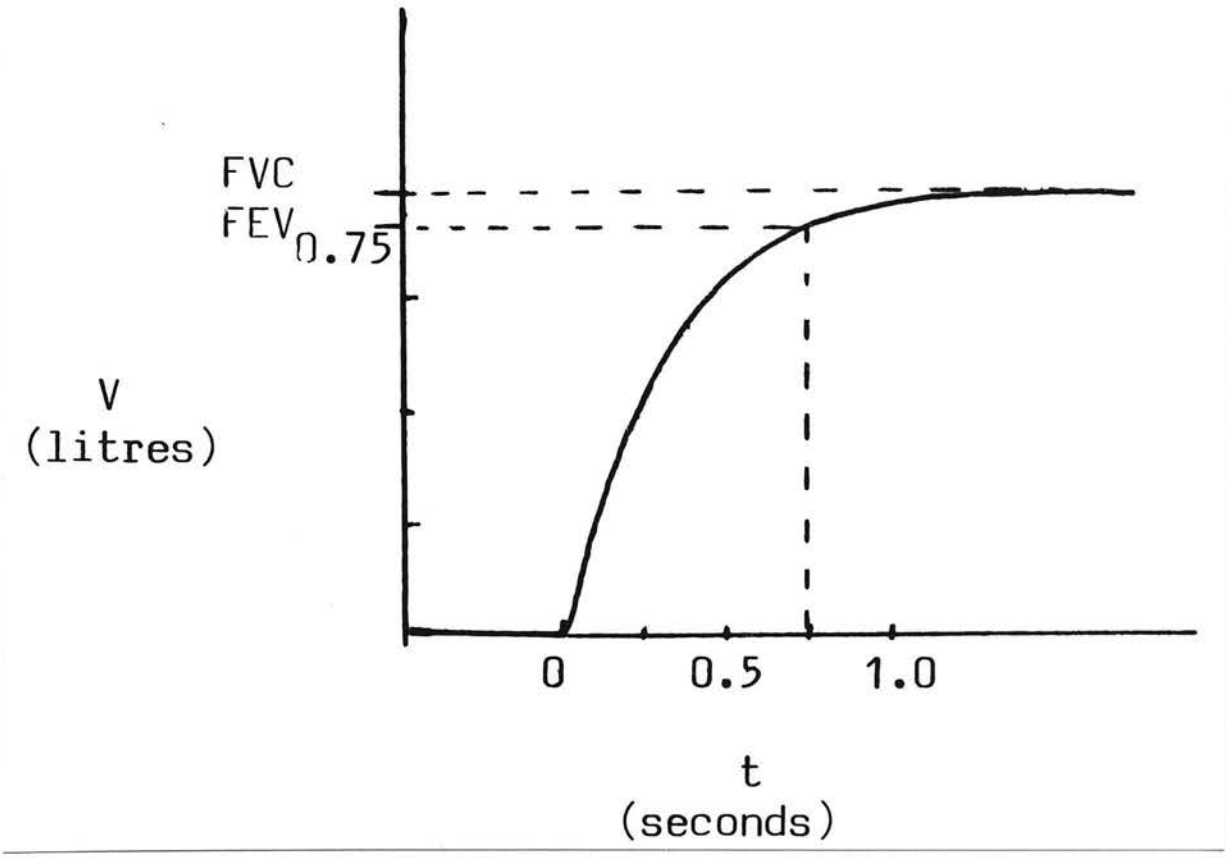


Figure 4

Calculation of $FEV_{0.75}$

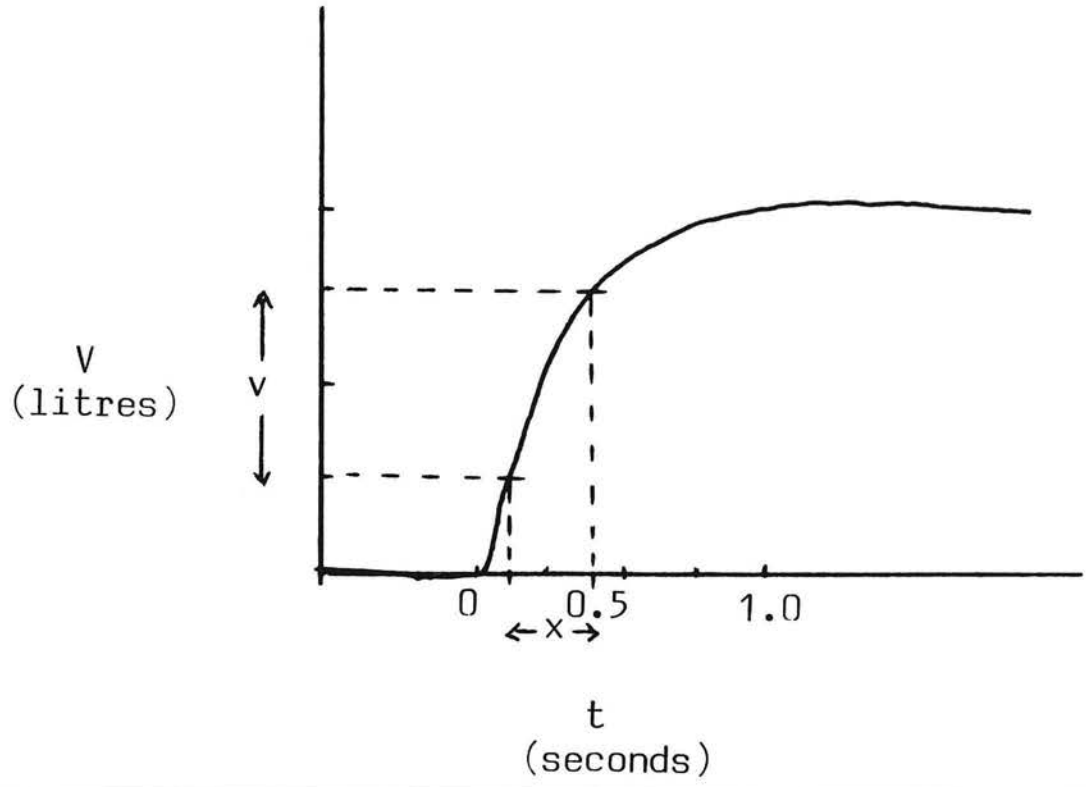


Figure 5

Calculation of $FEF_{25-75\%}$

$$FEF_{25-75\%} = \frac{v}{x} \text{ l/sec}$$

4. Maximum Expiratory Flow Volume (MEFV) Curves

Maximum expiratory flow volume curves were obtained with the subject first breathing air followed by an 80% helium/20% oxygen (He/O_2) mixture. The subject was seated wearing nose clips and breathed quietly through the mouthpiece extension of a Lloyd valve (Plates 7 & 8). After exhaling to residual volume, three successive vital capacity (VC) manouvres were performed. During the third, expiration was forced and complete into a "bag and box" arrangement with the displacement of air through a flow meter (Mercury Electronics Ltd). A linear relationship between flow and output voltage was achieved electronically (Tau Electronics). Linearity was checked weekly and rarely required adjustment.

Volume was obtained by integration of the linearised flow signal (Tau Electronics). Volume calibration was performed using a one-litre (BTPS) syringe and the flow meter calibrated using a rotameter (GEC-Elliott, Process Instruments Ltd). An identical volume signal was obtained for flow rates up to 500 1/min.

Flow was displayed against volume on the y-x co-ordinates of a storage oscilloscope (Tektronix Inc.). An electronic time marker indicated one second on the horizontal axis.

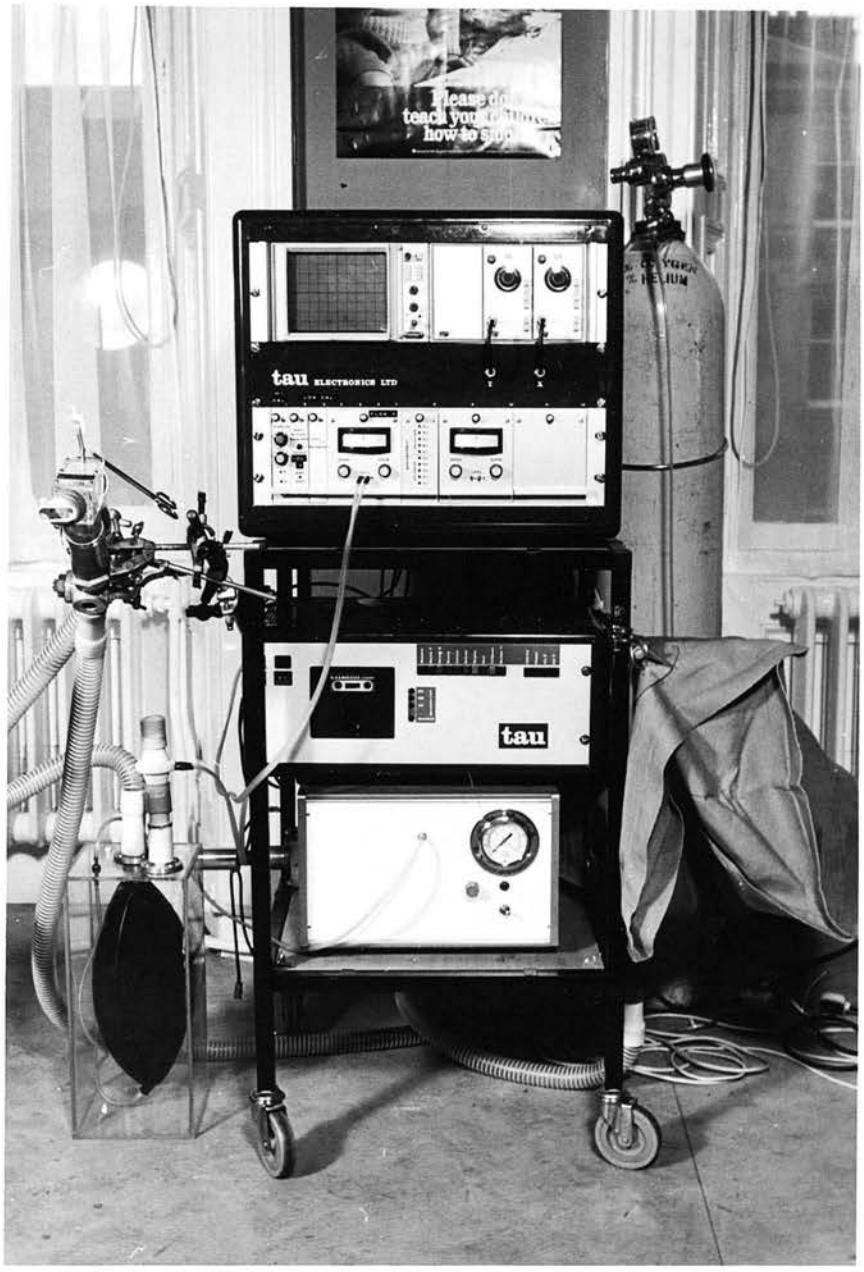


Plate 7

Equipment for measuring MEFV curves

Plate 8

Child performing forced expiratory manoeuvres

The VC manouvres were repeated with the subject breathing the He/O_2 mixture. Air and He/O_2 curves were compared when the FVC breathing He/O_2 was within 5% of FVC breathing air.

The MEFV curves of children from the first two winters were stored on magnetic tapes for subsequent computer analysis, while those obtained from the third winter period were photographed and analysed manually. Variables measured from the MEFV curves obtained in air and He/O_2 were $FEV_{1.0}$, FVC, maximal flow at 50% VC ($\dot{V}_{50}$) and at 25% VC ($\dot{V}_{25}$). The change in flow while breathing He/O_2 was obtained by subtraction ($\Delta \dot{V}_{50}$ and $\Delta \dot{V}_{25}$)(Figure 6).

Results were reported in BTPS units and expressed as percent predicted values for height and sex (Simpson, unpublished data; Appendix 10).

5. Exercise Study

The subject ran continuously for six minutes at a speed of approximately 5km/hr and a slope of 15% on a treadmill. The electrocardiograph was displayed continuously and in each case heart rate was maintained at above 160 beats/minute. PEFR was measured before, during (at 2 and 4 minutes) and after exercise (0, 2, 5, 10, 15 and 20 minutes). Nose clips were worn to ensure mouth breathing (Plates 9 & 10).

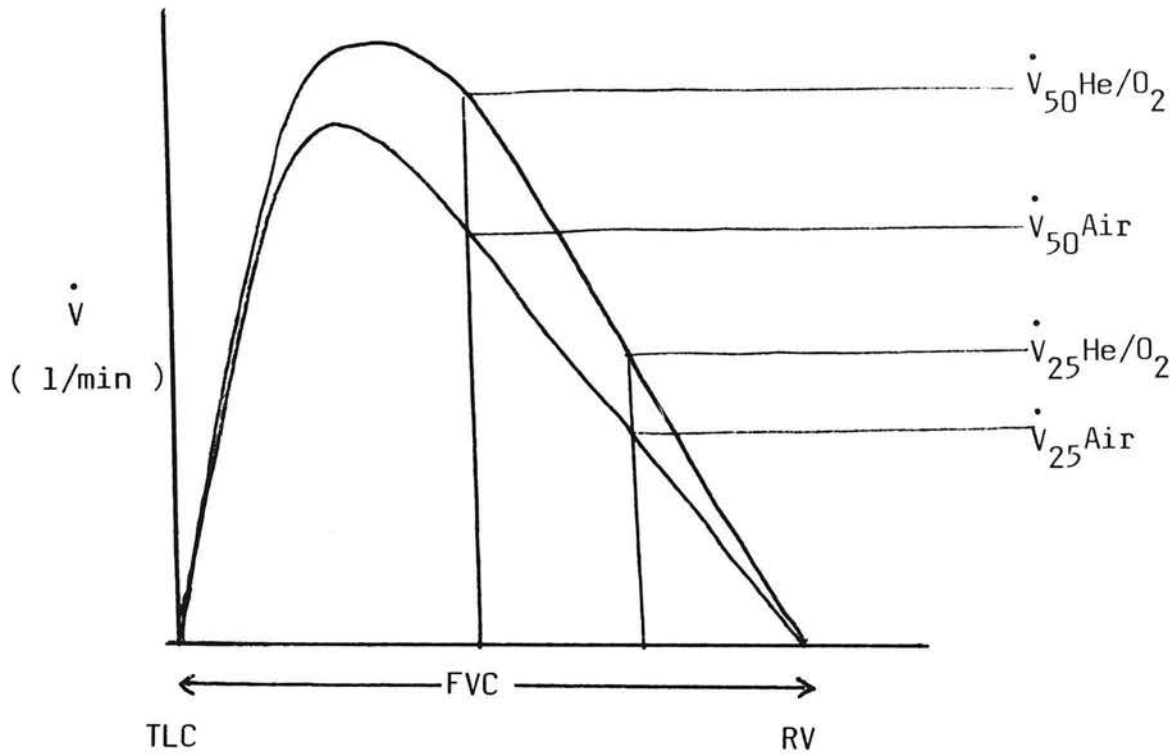


Figure 6

MEFV curves in air (bottom curve) and He/O_2 (top curve)

See text

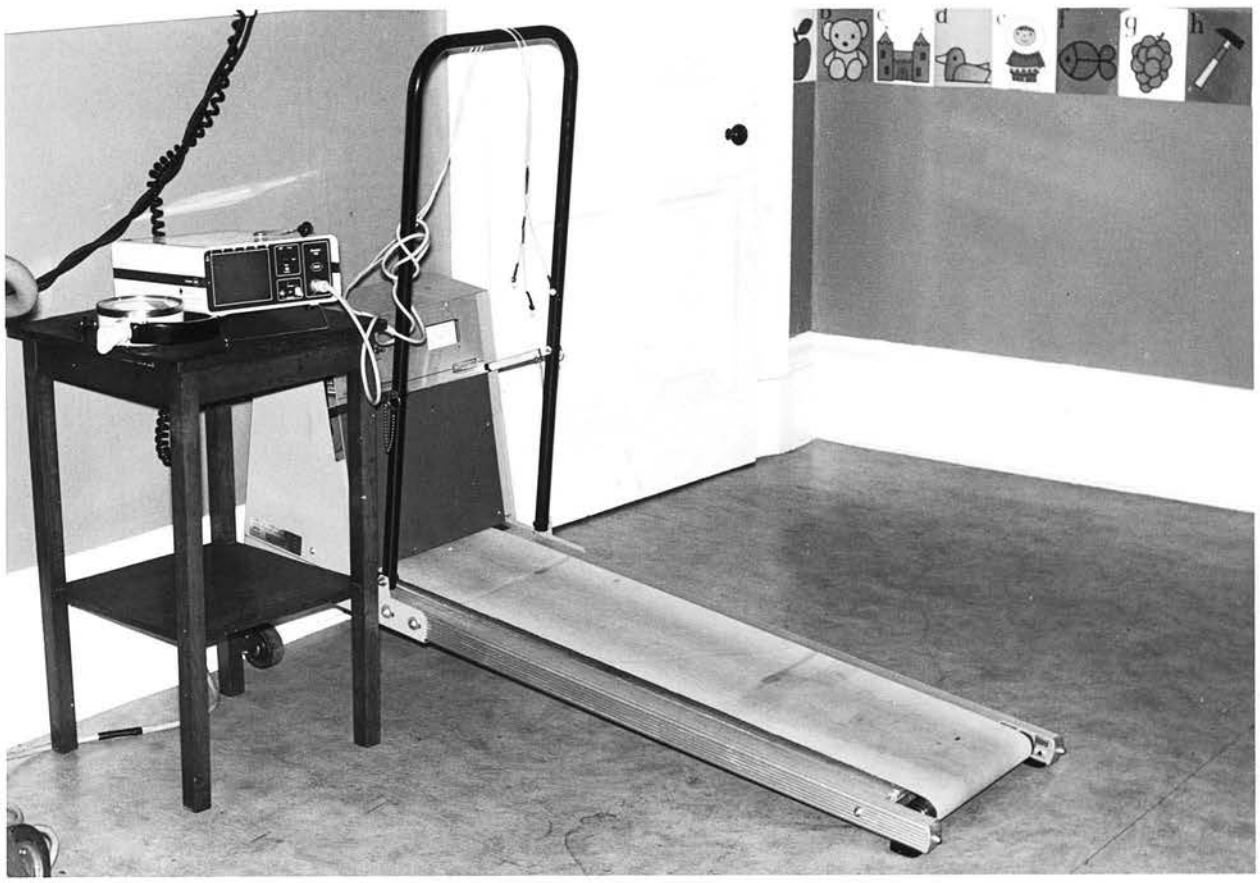


Plate 9

Equipment for exercise study - treadmill, ECG monitor, nose clips, peak flow meter and stopwatch.

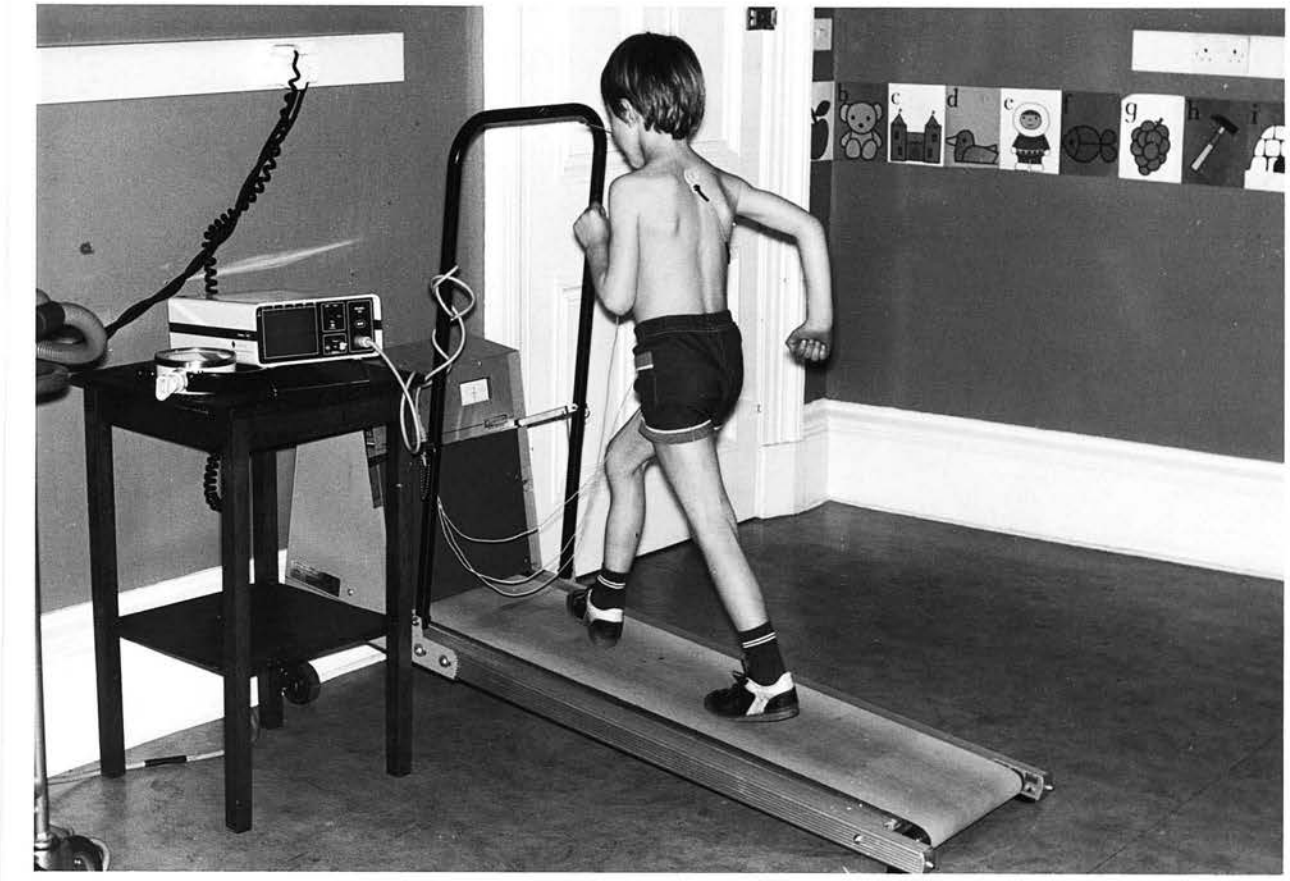


Plate 10

Child performing exercise test

The temperature and humidity in the room were noted during the test. Room temperatures ranged from 19-23°C while the relative humidity varied from 30-50%. From the data obtained, indices of bronchial lability were calculated as follows:

$$\% \text{ rise} = \frac{\text{Highest PEFR during exercise} - \text{Resting PEFR}}{\text{Resting PEFR}} \times 100$$

$$\% \text{ fall} = \frac{\text{Resting PEFR} - \text{lowest PEFR after exercise}}{\text{Resting PEFR}} \times 100$$

Exercise lability = % rise + % fall

Results were compared with values for normal children (Silverman and Anderson, 1972).

Validation of Respiratory Function Tests

Eight healthy subjects (children of hospital staff) with no history of recurrent respiratory illness, performed the series of respiratory function tests on five different days. The subject attended for the tests at approximately the same time each day, and repeated the same sequence of tests three times during the session. Therefore each child performed each test a total of fifteen times.

There were four boys and four girls, of mean age 6.96 years (range 6.08-7.58 years). Analyses of variance were performed and the results displayed on Table 4. For each

TABLE 4

ANALYSES OF VARIANCE

	Error Variation σ^2_E	Day Variation σ^2_D	Subject Variation σ^2_S	$\frac{\sigma^2_E + \sigma^2_D}{\sigma^2_E + \sigma^2_D + \sigma^2_S}$
PEFR	64.2	145.7	485.5	0.3018
R_T	0.0055	0.0025	0.0038	0.6808
$FEV_{0.75}$	0.0091	0.0060	0.0424	0.2623
$FEV_{1.0}$	0.0098	0.0068	0.0394	0.2966
FVC	0.0178	0.0141	0.0316	0.5021
$FEF_{25-75\%}$	1200	879	2995	0.4097
$FEV_{1.0}^{Air}$	0.0078	0.0139	0.0282	0.4361
$FEV_{1.0}^{He-O_2}$	0.0095	0.0162	0.0272	0.4858
FVC Air	0.0061	0.0122	0.0259	0.4142
FVC $He-O_2$	0.0072	0.0136	0.0310	0.4016
$\dot{V}_{50}^{Air}$	249	310	1399	0.2855
$\dot{V}_{50}^{He-O_2}$	250	339	1997	0.2278
$\dot{V}_{25}$ Air	123	211	891	0.2744
$\dot{V}_{25}$ $He-O_2$	180	236	1121	0.2707

test, there were three sources of variance. The error variation (σ^2_E), an index of precision of measurement, indicated variability within a session. Day variation (σ^2_D) measured variation in the same subject on different days. The subject variation (σ^2_S) characterised a subject. So that subject differences can be maximised, variation within sessions and between days would have to be eliminated. A value was derived by summing the error and day variations, and dividing this by the sum of all three sources of variance ie $\frac{\sigma^2_E + \sigma^2_D}{\sigma^2_E + \sigma^2_D + \sigma^2_S}$

Those respiratory function tests with the lowest values would be the most discriminate in detecting subject differences. The derived values for the tests are depicted in the last column of Table 4. It is seen that most of the tests of respiratory function used will detect subject differences, with R_T and FVC the least sensitive.

Statistical Methods

For matched pairs, continuous data were analysed using Student's paired t test, with the Wilcoxon test used for non-parametric data. Categorical or qualitative data were analysed using McNemar's test (McNemar, 1947).

Continuous data from unmatched pairs were analysed using Student's unpaired t test. The Mann-Whitney U test was used for non-parametric data and x^2 test for categorical data.

S E C T I O N II

Chapter 4

LIMITATIONS OF THE STUDY

1. Virological Studies

All house physicians at the Royal Hospital for Sick Children in Edinburgh are instructed on the techniques of obtaining nose and throat swabs as well as naso-pharyngeal secretions. During the study period, our isolation rate for respiratory syncytial virus increased from 50% in the first year to about 70% in the third, as methods of collection, transport and laboratory techniques improved. Fluorescent antibody techniques were used in the latter part of the study, thereby increasing the accuracy of diagnosis. It can be argued that some of our RSV- cases could have been ones where the RSV was the causative agent despite the result of viral studies.

2. The Questionnaire

The answers could be influenced to a certain extent by the person who asked them, as well as the exact phrasing of the questions. Therefore the actual printed wording was always used, and the questionnaire was always administered by one person (JM).

It is recognised that enquiry into past events in the child's life rely on parental recall. Depending on the parent's observation and interest, and on the family's attitude to illness, replies could be biased. It was hoped that scrutiny of general practitioner records might

corroborate the parent's account of respiratory illness. By enquiring into the frequency of symptoms in the preceding year only, most parents were able to provide accurate information.

3. Atopic Background

The diagnosis of atopy based on history alone is incomplete. Skin testing, which would provide a more sensitive guide to atopy, was considered unjustified, especially in symptom-free control children. It might also have deterred a lot of children from attending.

The diagnosis of asthma in the children was based on the frequency of wheezy episodes which necessitated medical attention, ie were noted in the general practitioner's records. This may have been too stringent, as some children could have wheezed at home and not been attended to by the general practitioner. We may have excluded some mildly affected children.

4. MEFV Curves

Our studies were carried out without whole body plethysmography, which makes matching curves obtained in air and He-0_2 difficult. The three-breath method for administering He-0_2 could lead to incomplete equilibrium and contribute to any impairment of response to breathing He-0_2.

Finally, measurements made from photographs of MEFV curves could lead to error at low flow rates, as the calibration factor for flow was usually 1mm per 2 l/min flow. Computer analysis would obviate this error, but technical difficulties encountered in curves from the first two winter periods necessitated manual analysis for curves obtained from children in the third winter.

S E C T I O N I I I

Chapter 1

THE INDEX ILLNESS

There were 123 males and 77 females, a male:female ratio of 1.6:1. During the index illness, the mean age of the children was 4.45 ± 2.96 months. The interval between the index illness and follow-up was 6.74 ($\pm$ 1.51) years.

Forty-five children had had bronchitis (15 RSV+ and 30 RSV-), 104 bronchiolitis (56 RSV+ and 48 RSV-) while 51 were found to have had pneumonia (29 RSV+, 22 RSV-) (Table 5).

Fifteen "RSV negative" children had other viruses isolated. Table 6 lists these and the clinical syndromes caused. Of the "RSV positive" children, double infections were seen in two - both children had bronchiolitis clinically, one had an adenovirus type 1 infection coexisting with RSV, while the other had a rhinovirus infection.

One hundred and forty-one children (70.5%) had received antibiotics from their general practitioners prior to hospital admission; while one hundred and fifty-two (76%) were prescribed antibiotics in hospital. Bacteriological studies were performed on blood culture (45 patients), bronchial secretions (7 patients) and sputum (6 patients). Positive cultures were found in only one of the blood cultures (2.2%), three of the bronchial secretion specimens (42.9%) and four sputum samples (66.7%). Pathogens included

TABLE 5

INDEX ILLNESS: RSV DETECTION AND CLINICAL DIAGNOSIS

	Diagnosis			
Virology	Bronchitis	Bronchiolitis	Pneumonia	
RSV+	15	56	29	(100)
RSV-	30	48	22	(100)
	45	104	51	

Haemophilus influenzae (3), Streptococcus pneumoniae (1), Staphylococcus aureus (2) and Escherichia coli (3).

During the index illness all but one of the children were weighed. The weights were about the fiftieth centile in 102 children (51.2%); around the tenth centile in 61 (30.7%) and the ninetieth centile in 36 (18.1%). Only seventy children had their lengths measured at the time of the index illness; of these 33 (47.1%) lay around the fiftieth centile, 23 (32.9%) about the tenth centile while 14 (20%) were on the ninetieth centile.

Blood gas analyses were performed in 64 children (32%) and five (2.5%) required assisted ventilation at the time of their illness.

Sixty-seven children (33.5%) had received some form of immunisation prior to the index illness. Sixty had triple antigen and oral polio vaccine, three diphtheria and tetanus with oral polio vaccine, while four had received measles immunisation. The immunisation history of one child who lived in a children's home, was unknown.

S E C T I O N I I I

Chapter 2

INDEX-CONTROL COMPARISONS

1. Clinical characteristics

Clinical characteristics of the index and control children are summarised in Table 7. No differences were found between the two groups with respect to birth weight, gestational age or the weight at follow-up. A greater proportion of control children were breast-fed at any time when compared to the index children ($p = 0.05$). At follow-up, the control children were significantly taller than the index children, and slightly older.

Examination of the upper respiratory tract (ears, nose and throat) did not reveal any significant differences between the two groups of children. Intercurrent upper respiratory tract infections were found in 27 (13.5%) index cases and 38 (19%) controls (NS). No differences were noted between the two groups of children when the fingers, nails, skin or chest shape were compared.

2. Other respiratory illness

Neonatal respiratory disorders were present in 14 index children (7%) compared with five (2.5%) controls (NS). Four of these index children required assisted ventilation during the neonatal period, while two controls were ventilated. These numbers were too small for meaningful statistical analysis.

TABLE 7

CLINICAL CHARACTERISTICS - INDEX AND CONTROL CHILDREN

	Index (n = 200)	Control (n = 200)	p Value
Sex (M:F)	123:77	123:77	
Age (years) at follow-up	7.20 ± 0.44	7.38 ± 0.44	<0.01*
Weight at follow-up (Kg)	23.1 ± 3.6	23.4 ± 3.3	>0.2 *
Height at follow-up (cm)	119.8 ± 6.1	121.8 ± 5.1	<0.001*
Birth weight (Kg)	3.18 ± 0.64	3.23 ± 0.50	>0.4 *
Gestational age (weeks)	39.4 ± 2.4	39.7 ± 1.9	>0.1 *
Breast feeding (%)	12.5	21	= 0.05+

* Student's paired t test

\+ McNemar's test

Table 8 summarises other respiratory illnesses suffered by the children prior to inclusion in the study.

No differences were noted in the proportion of children who had had whooping cough, chicken pox with chest involvement or pneumonia (other than during the index illness). However, significantly more index cases had suffered from measles, either with or without chest involvement (54.5% index children had measles, compared with 38% controls, $p < 0.01$; 29.5% index children were chesty during measles, compared with 7.5% controls, $p < 0.05$).

3. Respiratory symptoms/established respiratory disease

The respiratory status of the two groups of children are listed in Table 9.

Cough

When asked about cough and wheeze, parents were first asked if the child had the symptom. The frequency of attacks in the first two years of life was enquired into, followed by the frequency in the year prior to review so that it could be assessed if the symptom was improving in nature, getting worse or staying the same.

Cough "at any time" in the child's life was when the answer to the question on cough was in the affirmative. Sixty-nine index children (34.5%) were reported by their

TABLE 8

OTHER RESPIRATORY ILLNESSES PRIOR TO REVIEW

	Index (%) (n = 200)	Control (%) (n = 200)	p Value
Whooping Cough	10.0	8.5	> 0.05*
Measles	54.5	38.0	< 0.01*
Measles with chestiness	29.5	7.5	< 0.05*
Chickenpox with chestiness	8.0	2.5	> 0.05*
Pneumonia (other than index)	4.0	2.0	> 0.05*

* McNemar's test

TABLE 9

RESPIRATORY STATUS - INDEX AND CONTROL CHILDREN

	Index (n = 200)	Control (n = 200)	p Value
"Tendency" to cough (%)			
At any time	34.5	13.0	< 0.01*
In past year	17.0	5.5	< 0.01*
Established bronchitis (%)	3.5	0.5	NS*
Sputum (%)	5.0	1.0	< 0.05*
"Tendency" to wheeze (%)			
At any time	47.0	17.0	< 0.01*
In past year	10.5	1.0	< 0.01*
Established asthma (%)	8.5	2.5	< 0.05*
Recurrent nasal blockage or discharge (%)	35.0	22.0	< 0.01*
Colds going to chest (%)	52.5	20.5	< 0.01*
Hearing difficulties (%)	18.5	10.5	= 0.05*
Tonsils removed (%)	9.5	9.0	NS*
Adenoids removed (%)	17.5	12.5	NS*
Medication in past year (%)	45.1	17.5	< 0.01*
Antibiotics (%)	41.5	15.5	NS*
Bronchodilators (%)	11.0	4.5	NS*
School absenteeism in past year (weeks)	1.9 ± 3.7	0.8 ± 1.3	< 0.001+
GP consultations for respiratory illness in past year (times)	2.1 ± 4.8	0.9 ± 1.6	< 0.005+

* McNemar's test

+ Wilcoxon test

parents to have this symptom compared with twenty-six (13%) controls ($p < 0.01$). Only ten index children were said to have coughed prior to the index illness. The same proportion of index and control children coughed in their first two years of life, while cough which had persisted to the year prior to review was reported more often in index children (17% compared with 5.5% controls, $p < 0.01$). Examination of general practitioner records, however, revealed no significant differences in the proportion of children from either group who had been labelled as having "established bronchitis" (four or more consultations in the preceding year with "cough", "bronchitis", "chest infection" or "respiratory infection"; 3.5% index children, 0.5% controls; $p > 0.05$).

Sputum

Ten index children (5%) were said to produce sputum for more than three months each year, while two controls (1%) were reported to produce sputum. This result with such small numbers was statistically significant ($p < 0.05$).

Wheeze

More index children (47%) were reported to have wheezed at some stage in their lives compared to controls (17%), $p < 0.01$. This symptom occurred more frequently in the first two years of lives amongst index children, when 13.5% of them wheezed compared with 3% controls ($p < 0.01$). Wheeze antedated the index illness in 23 index children.

Wheeze continued into the year prior to review in 10.5% index children, compared to 1% controls ($p < 0.01$). Established asthma (four or more episodes of wheeze requiring medical attention in the preceding year) was present in 17 (8.5%) index cases and five (2.5%) controls. This result was statistically significant ($p < 0.05$).

Upper respiratory symptoms

Recurrent rhinitis (nasal blockage or discharge) was reported in 70 (35%) index children and 44 (22%) controls ($p < 0.01$). More index cases were subject to colds (8.5% index children, 1.5% controls having more than seven colds/year, $p < 0.01$) and also to colds "going to the chest" (52.5% index, 20.5% controls, $p < 0.01$).

No differences in ear trouble (earache or discharging ears) were noted between index and control children; but difficulties with hearing was reported significantly more often in index children (18.5% index, 10.5% controls, $p = 0.05$).

Sore throats (up to six episodes per year) were reported very frequently in both groups of children - 197 matched pairs were concordant for this symptom. No differences were apparent in the proportion of children in either group who had had tonsils (9.5% index; 9.0% controls) or adenoids (17.5% index; 12.5% controls) removed.

The general practitioner records revealed the same proportion of children who had recurrent upper respiratory sepsis (tonsillitis, otitis or pharyngitis on six or more occasions in the preceding year) - 4.5% index, 4% controls.

Medication for respiratory symptoms

A significantly greater proportion of index cases (45.1%) received medications in the preceding year for respiratory illnesses. This compared with 17.5% of the control children ($p < 0.01$). Five index and four control children required constant medication, intermittent therapy was given to 86 index cases and 31 controls. Bronchodilators were prescribed for 22 index children and 9 controls (McNemar's test NS) while 83 index children received antibiotics compared with 31 controls (McNemar's test NS). Two index cases were on inhaled steroid therapy, while none of the control children received steroids.

School absenteeism for respiratory illness

Respiratory illness in the preceding year caused school absenteeism of an average of 1.9 ($\pm$ 3.7) weeks in the index cases and 0.8 ($\pm$ 1.3) weeks in the controls. This was highly significant ($p < 0.001$).

GP consultations

The general practitioners of index children were consulted more often for respiratory problems - an average

of 2.1 ($\pm$ 4.8) occasions in the preceding year, compared with 0.9 ($\pm$ 1.6) times for the control children ($p < 0.005$).

The number of hospital admissions in the past year was small for both groups of children (index 0.04 $\pm$ 0.57 times; controls 0.01 $\pm$ 0.14). This was not statistically significant.

Table 10 shows the average number of general practitioner consultations throughout the children's lives, and depicts these against the category of respiratory illness diagnosed by the GP. Index children were seen by their family doctors more often for upper and lower respiratory tract infections ($p < 0.05$ and <0.001 respectively).

A combined x^2 test was performed on the total number of respiratory illnesses per year for each group and again, this showed a significant increase in respiratory illnesses in the index children ($p < 0.001$). Figure 7 depicts this trend graphically.

A similar test was performed for the total number of hospital admissions for respiratory illnesses per year (Table 11). Although the trend in the early years (1972-1975) showed more index cases to require hospitalisation, with interaction between the years and the subjects, trends changed and the combined x^2 test was invalid.

TABLE 10

RESPIRATORY ILLNESSES RECORDED BY GENERAL PRACTITIONERS

Diagnosis made by GP	Mean Number of GP Consultations		
	Index (n = 200)	Control (n = 200)	p Value
URTI	4.1 ± 5.8	3.1 ± 5.2	< 0.05*
MRTI	0.3 ± 0.8	0.2 ± 0.7	> 0.2 *
LRTI	5.2 ± 8.4	2.7 ± 5.8	< 0.001*

* paired t test

URTI = Upper respiratory tract infection ("common cold", rhinitis, otitis, tonsillitis, pharyngitis)

MRTI = Middle respiratory tract infection (croup, laryngitis, tracheitis)

LRTI = Lower respiratory tract infection (bronchitis, bronchiolitis, pneumonia, "chest infection", "respiratory infection")

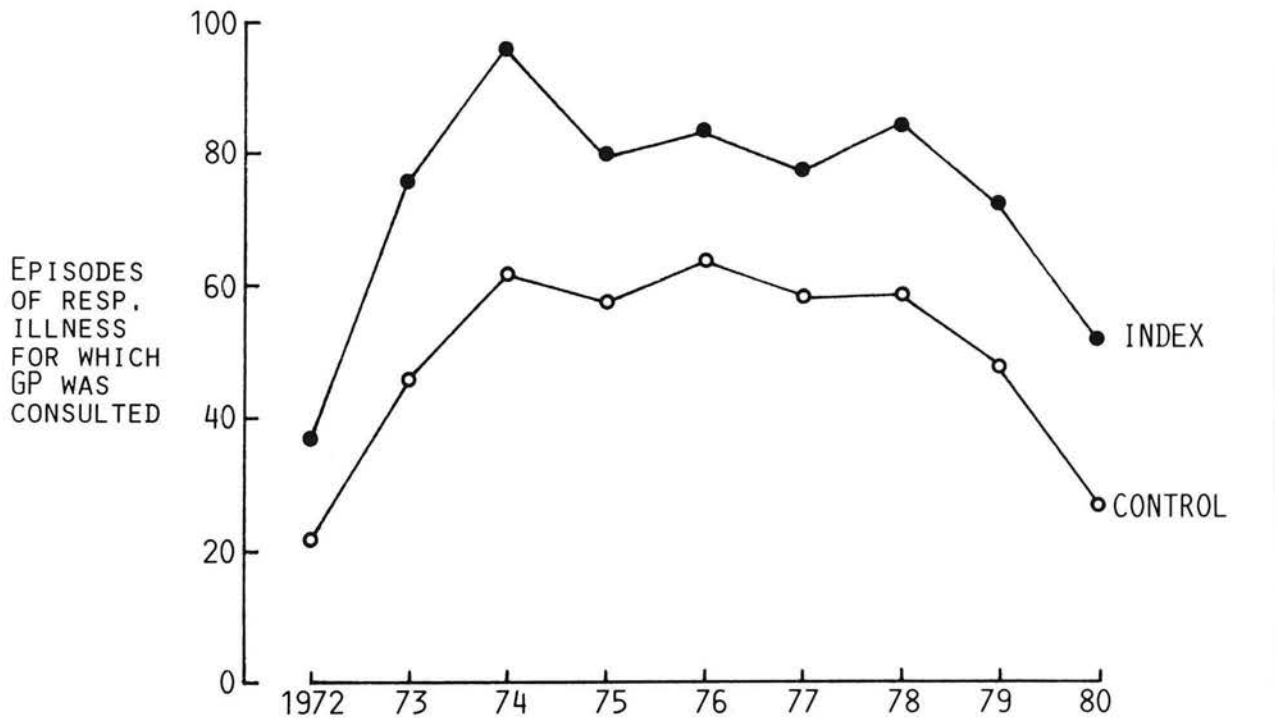


Figure 7

Trend of GP consultations for respiratory illness in index and control children.

TABLE 11

FREQUENCY OF HOSPITAL ADMISSIONS FOR RESPIRATORY ILLNESSES PER YEAR (EXCLUDING INDEX ILLNESSES)

Year	Index	Control
1972	6	0
1973	16	0
1974	15	1
1975	7	2
1976	5	4
1977	4	3
1978	1	3
1979	1	1
1980	1	0

The total number of admissions in each year is shown, for index and control children

4. Social and Family Characteristics

Social and family factors are listed in Table 12. There were no discrepancies in the numbers of matched pairs where the father was the head of the household, whether the head of the household was employed, the type of housing lived in, the number of rooms in each house, the presence of a garden, the number of moves in the last five years or in the number of adults in each dwelling unit. At follow-up, 80.5% of the index children had both parents living at home, compared with 90% controls (NS). However, there were fewer firstborns among the index children (29%) compared to the controls (45%); $p < 0.01$. Index children also had more siblings (mean 1.9 ± 1.8; controls 1.4 ± 1.0; $p < 0.001$).

The social class distribution is also shown. Although evenly distributed, more index children came from the lower social classes ($p < 0.05$).

Central heating was present less frequently in the homes of index children (44.5%) compared to the homes of controls (57%) $p<0.05$. The numbers of children in each group were comparable in terms of the type of fuel used to heat the living room (Table 13). Table 14 shows McNemar's test applied to the matched pairs, and it was seen that more pairs were present where the control children had electric, gas or oil heating ($p < 0.05$).

TABLE 12

SOCIAL AND FAMILY CHARACTERISTICS
INDEX AND CONTROL CHILDREN

	Index	Control	p Value
Father head of household (%)	84.0	89.0	>0.05 *
Head of household employed (%)	85.5	86.0	>0.05 *
Housing			
Tenement/Flat (%)	28.5	30.0)	
Terraced (%)	42.0	39.0)	>0.05 *
Semi-detached (%)	29.0	30.5)	
<5 rooms/house (%)	80.0	77.0	>0.05 *
Garden (%)	78.0	74.5	>0.05 *
>2 moves in last 5 years (%)	10.0	10.5	>0.05 *
>2 adults in house (%)	8.5	4.5	>0.05 *
Both parents at home (%)	80.5	90.0	>0.05 *
Firstborn (%)	29.0	45.0	<0.01 *
Siblings (number)	1.9 ± 1.8	1.4 ± 1.0	<0.001 +
Social class distribution			
I & II	15.0	21.5)	
III	23.0	28.0)	<0.05 *
IV & V	61.5	50.0)	
Central heating (%)	44.5	57.0	$= 0.01$ *
Own bedroom (%)	29.0	41.0	<0.05 *
Mother smoked at some time (%)	71.0	66.0	>0.05 *
Father smoked at some time (%)	74.0	65.0	>0.05 *
Mother's age at follow-up (years)	32.2 ± 5.3	33.1 ± 5.1	<0.05 +
Father's age at follow-up (years)	34.9 ± 6.2	34.9 ± 6.2	>0.05 +

* McNemar's test

+ Student's paired t test

TABLE 13

TYPE OF HEATING IN LIVING ROOM

Main Fuel	Index (n = 200)	Control (n = 200)
Electric	42	46
Gas	73	84
Oil	5	3
Coal	72	61
Paraffin	8	6

The actual numbers of children in index and control groups are shown

TABLE 14

MAIN FUEL IN LIVING ROOM

INDEX	CONTROL		
	Electricity	Gas/Oil	Coal/Paraffin
Electricity	11	16	15
Gas/Oil	24	41	13
Coal/Paraffin	11	30	39

This table shows the distribution of pairs according to the type of fuel used in the living room. Using McNemar's test, $p < 0.05$

Fewer index children had their own bedroom (29% index, 41% controls; $p < 0.05$). When the room was shared, there was no difference in the proportion of children in both groups who had a "chesty" person in the bedroom. The types of animals present at home were similar in both groups. No differences were seen in the proportion of children from either group who attended nursery school, the age at entry to nursery or the period spent there.

5. The Parents

"Father"

There were similar proportions of children in both groups who had the real father, step father, foster father or guardian staying at home. The mean age of fathers of index children was 34.9 ($\pm$ 6.2) years, identical to that of the fathers of control children. No differences were noted in the proportion of children whose fathers had cough, sputum, wheeze or any chest illnesses in the last three years. The smoking habits of fathers in the two groups were also similar - 74% of index children compared with 65% of control children had fathers who smoked at some time in their lives. The amount smoked (cigarettes/day; ounces of tobacco per week or cigars per week) were also similar.

"Mother"

The majority (97%) of the matched pairs had their real mother at home. Mothers of the index children were significantly younger (32.2 $\pm$ 5.3 years) than those of controls (33.1 $\pm$ 5.1 years, $p < 0.05$). No differences were reported in the proportions of mothers who were housewives or who worked, either at any time after the child was born or at the time of follow-up. Similar proportions of children from each group had mothers who reported cough, sputum, wheeze, or a chest illness in the last three years. Smoking habits of both groups of mothers were also similar, with 71% of mothers of index children and 66% control mothers having smoked at some stage of their children's lives. In the first year of the children's lives, similar proportions of index and control mothers smoked (index 9.8 $\pm$ 10.7 cigarettes/day, controls 8.3 $\pm$ 9.7, NS). Maternal smoking habits were also similar in the preceding year (index 11.9 $\pm$ 11.9 cigarettes/day; controls 10.0 $\pm$ 10.4, NS), although the number of cigarettes smoked per day, averaged over the years, was higher (17.9 $\pm$ 9.4) in mothers of index children than in controls (15.7 $\pm$ 8.6, $p < 0.03$).

6. Atopic Background

The atopic background of the two groups of children are demonstrated in Table 15. This shows no differences in the proportion of children with either personal or family

TABLE 15

ATOPIC BACKGROUND - INDEX AND CONTROLS

Personal History	Index (n = 200)	Control (n = 200)	p Value
Eczema (%)	18.0	12.5	>0.05*
Hay fever (%)	6.0	7.5	>0.05*
Food allergy (%)	6.5	5.0	>0.05*
Family History			
Eczema (%)	23.5	20.5	>0.05*
Hay fever (%)	27.5	32.0	>0.05*
Food allergy (%)	15.0	13.0	>0.05*
Asthma (%)	55.0	45.0	>0.05*

* McNemar's test

history of atopic disorders. A high percentage of children in both groups had first-degree relatives who had asthma.

7. Tests of Respiratory Function

These are shown in Table 16, and expressed as the percent predicted values, thereby eliminating any effects due to the height difference between the patients and controls. PEFR, $FEV_{0.75}$, $FEV_{1.0}$, $FEV_{1.0}/FVC$ and $FEF_{25-75\%}$ were all significantly reduced in the index cases while FVC and R_T were similar in both groups.

Results of the exercise study are tabulated as shown in Table 17. No differences were noted in the proportion of matched pairs with a greater than 7.5% rise in PEFR during exercise, while a significantly greater proportion of index children (34.5% compared with 23% controls, $p < 0.05$) showed bronchoconstriction (PEFR falling >10% resting value) following exercise. When the exercise lability was examined similar proportions of children from both groups were found to have a lability index of >22%.

MEFV curves were reliably documented in matched pairs where the patients' index illness fell in the "third winter" ie 1.11.73-30.4.74, and these were the only ones analysed. No significant differences were noted between index and control children when $FEV_{1.0}$, FVC, $\dot{V}_{50}$ and $\dot{V}_{25}$ in both air and $He-0_2$ were compared. The changes in flow

TABLE 16

TESTS OF RESPIRATORY FUNCTION - INDEX AND CONTROLS

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	199	97.3	- 3.64	1.59	< 0.05 +
Control	199	100.9			
$FEV_{0.75}$ (% predicted)					
Index	197	88.7	- 4.14	1.31	< 0.005 +
Control	197	92.8			
$FEV_{1.0}$ (% predicted)					
Index	197	91.3	- 3.70	1.24	< 0.005 +
Control	197	95.0			
FVC (% predicted)					
Index	197	86.3	- 0.73	1.24	NS +
Control	197	87.1			
$FEF_{25-75\%}$ (% predicted)					
Index	197	91.8	-10.58	3.08	< 0.001 +
Control	197	102.3			
$FEV_{1.0}$/FVC					
Index	197	0.88	- 0.03	0.008	< 0.001 +
Control	197	0.01			
R_T (Kp/l/s)					
Index	194	0.58	- 0.01	0.016	NS +
Control	194	0.60			

+ Student+s paired t test

TABLE 17

EXERCISE TEST (AFTER SILVERMAN AND ANDERSON 1972)

(n = 200)

a) Percentage rise in PEFR during exercise

		CONTROL		
		≤ 7.5%	> 7.5%	N/D
INDEX	≤ 7.5%	75	55	1
	> 7.5%	44	20	0
	N/D	5	0	0

NS*

b) Percentage fall in PEFR following exercise

		CONTROL		
		≤ 10%	> 10%	N/D
INDEX	≤ 10%	99	26	1
	> 10%	50	19	0
	N/D	4	1	0

$p < 0.05$*

c) Exercise lability (% rise + % fall)

		CONTROL		
		≤ 22%	> 22%	N/D
INDEX	≤ 22%	152	16	1
	> 22%	23	3	0
	N/D	5	0	0

NS*

* McNemar's test

N/D = not done

NS = not significant

rate noted between breathing air and He-0_2 at 50% and 25% VC - absolute values as well as % rise - were also similar in both groups. Conventional tests of ventilatory function, however, revealed differences in $FEV_{0.75}$ ($p < 0.05$) and $FEV_{1.0}$ ($p < 0.05$).

Summary

Children who had suffered acute lower respiratory tract infections in infancy were of similar gestational age and birth weight compared to their matched controls. Breast feeding was observed more frequently amongst control children. With the possible exception of measles, the occurrence of other respiratory illnesses were similar in index and control groups. Index children reported more respiratory symptoms, asthma, as well as other indices of respiratory ill health. Although index children appeared to be a socially disadvantaged group, parental respiratory symptoms and smoking habits were comparable in both groups of children. The atopic background was similar in index and control populations. At follow-up, index children were shorter than their controls, although weights were comparable.

Tests of respiratory function were diminished in index children, who also had evidence of bronchial hyperreactivity.

S E C T I O N I I I

Chapter 3

THE ROLE OF RESPIRATORY SYNCYTIAL VIRUS

Comparisons were made between index children who had suffered RSV infection (RSV+) and those who had not (RSV-), (Table 18). The age at presentation with the index illness was similar in both groups. Neonatal respiratory problems and the history of breast feeding were also similar. At follow-up, the mean heights and weights of these children were comparable. Cough was reported in similar numbers of RSV+ (31) and RSV- (38) children, with very few children in either group diagnosed as having established bronchitis. Wheeze was found in almost identical numbers of children (49 RSV+, 45 RSV-), with established asthma in six RSV+ and 11 RSV- children. The social class distribution was similar in both groups, with no differences observed in the atopic background of RSV+ or RSV- children.

Tests of respiratory function (Table 19) were comparable in both groups, as was the response to exercise testing.

Summary

RSV+ and RSV- index children showed similar clinical characteristics and atopic background. No significant differences were found in the age at which the index illness occurred or in the proportion who were breast fed. The results of tests of respiratory function and exercise test were comparable in the two groups of children.

TABLE 18

COMPARISON OF RSV+ AND RSV- INDEX CASES

	RSV+ (n = 100)	RSV- (n = 100)	p Value
Age at index (months)	4.5 ± 3.0	4.4 ± 2.9	>0.9*
Breast fed (%)	14	11	>0.4+
Neonatal resp. problems (%)	9	5	>0.4+
Age at study (years)	7.1 ± 2.1	7.1 ± 0.4	>0.8*
Height at study (cm)	119.7 ± 6.7	119.8 ± 5.4	>0.8*
Weight at study (Kg)	23.2 ± 4.0	23.0 ± 3.2	>0.6*
Cough (%)	31	38	>0.3+
Established bronchitis (%)	3	4	>1.0+
Wheeze (%)	49	45	>0.3+
Established asthma (%)	6	11	>0.3+
Established upper respiratory sepsis (%)	3	6	>0.4+
Social class I & II (%)	15	15	>0.6+
III (%)	21	25	
IV & V (%)	63	60	
Not known	1	0	
Atopic history (%)			
- personal	22	29	>0.3+
- family	75	81	>0.3+

* Student's unpaired t test

+ x^2 test

TABLE 19

RESPIRATORY FUNCTION TESTS
RSV+ AND RSV- INDEX CHILDREN

	RSV+ (n = 100)	RSV- (n = 100)	p Value
PEFR (% pred)	98.1 ± 14.2	96.5 ± 14.9	>0.5*
$FEV_{0.75}$ (% pred)	89.2 ± 14.2	88.1 ± 12.4	>0.5*
$FEV_{1.0}$ (% pred)	91.3 ± 13.5	91.2 ± 12.2	>1.0*
$FEV_{1.0}$/FVC (%)	89.0 ± 9.0	88.0 ± 9.0	>0.4*
FVC (% pred)	85.7 ± 13.3	86.9 ± 12.9	>0.5*
FEF_{25-75} (% pred)	91.8 ± 34.5	91.7 ± 36.8	>1.0*
R_T (Kp/l/s)	0.60 ± 0.17	0.56 ± 0.18	>0.1*
PEFR >10% fall after exercise (%)	14	15	>0.3*

* Student's unpaired t test

S E C T I O N I I I

Chapter 4

THE TYPE OF INDEX ILLNESS

A) Index children with bronchitis

The male:female ratio was 1.6:1. No differences were observed in the gestational age, birth weight or proportion who were breast fed between index sub-group and controls (Table 20). The tendency to cough was reported more often in the index children, at any time of the child's life as well as in the preceding year. Wheeze was also reported significantly more often, but the tendency had lessened in the year prior to study. Established respiratory disorders such as bronchitis or asthma were not found in excess in the index children who had had bronchitis, although more children were said to have colds "going to the chest", and to require medications for respiratory complaints. General practitioner consultations for respiratory illnesses in index children exceeded those in the controls (Table 21). The social class distribution was similar in index and control sub-groups. No significant differences were noted in the proportion who were firstborn, the number of siblings per child, or in the percentages of homes with central heating. Fewer index children had their own bedrooms. Parental ages and smoking habits were similar (Table 22). Asthma was reported significantly more often in the first-degree relatives of index children (Table 23). When the respiratory function tests were compared (Table 24) no differences were noted between index and control sub-groups. Following exercise, PEFR fell >10% of the resting value in

TABLE 20

CLINICAL CHARACTERISTICS
INDEX CHILDREN WITH BRONCHITIS (n = 45)

	Index	Control	p Value
Sex (M:F)	28:17	28:17	
Age at follow-up (years)	7.38 ± 0.45	7.53 ± 0.46	<0.001*
Height at follow-up (cm)	119.4 ± 7.1	122.1 ± 6.2	<0.001*
Weight at follow-up (Kg)	23.2 ± 4.4	23.6 ± 3.8	NS*
Birth weight (Kg)	3.26 ± 0.72	3.14 ± 0.53	NS*
Gestational age (weeks)	39.7 ± 2.3	39.8 ± 1.4	NS*
Breast feeding (%)	20.0	15.6	NS+

* Student's paired t test

+ McNemar's test

TABLE 21

RESPIRATORY STATUS

INDEX CHILDREN WITH BRONCHITIS (n = 45)

	Index	Control	p Value
"Tendency" to cough (%)			
At any time	42.2	11.1	< 0.01*
In past year	15.6	0	<0.05*
Established bronchitis (%)	0	0	NS*
Sputum (%)	4.4	0	NS*
"Tendency" to wheeze (%)			
At any time	60.0	8.9	<0.001*
In past year	6.7	2.2	NS*
Established asthma (%)	13.3	2.2	NS*
Recurrent nasal blockage or discharge (%)	33.3	17.8	NS*
Colds going to chest (%)	60.0	17.8	= 0.001*
Hearing difficulties (%)	11.1	2.2	NS*
Tonsils removed (%)	8.9	2.2	NS*
Adenoids removed (%)	8.9	2.2	NS*
Medication in past year (%)	42.2	15.6	<0.05*
Antibiotics (%)	37.8	13.3	NS*
Bronchodilators (%)	11.1	4.4	NS*
School absenteeism in past year (weeks)	1.4 ± 2.2	0.7 ± 1.0	NS+
GP consultations for respiratory illness in past year (times)	1.9 ± 2.5	0.9 ± 1.8	<0.05+

* McNemar's test

+ Wilcoxon test

TABLE 22

SOCIAL AND FAMILY FACTORS
INDEX CHILDREN WITH BRONCHITIS (n = 45)

	Index	Control	p Value
Both parents at home (%)	77.8	88.9	NS*
First born (%)	35.6	44.4	NS*
Siblings (number)	2.1 $\pm$ 3.1	1.3 $\pm$ 0.9	NS^{+}
Social class Distribution (%)			
I & II	15.6	20.0	
III	31.1	28.9	NS*
IV & V	51.1	48.2	
Central heating (%)	51.1	62.2	NS*
Own bedroom (%)	20.0	51.1	<0.005*
Mother smoked at some time (%)	75.6	57.8	NS*
Father smoked at some time (%)	68.8	55.6	NS*
Mother's age (years)	31.4 $\pm$ 5.7	33.5 $\pm$ 6.1	NS^{+}
Father's age (years)	33.7 $\pm$ 5.1	35.2 $\pm$ 6.9	NS^{+}

* McNemar's test

$^{+}$ Student's paired t test

TABLE 23

ATOPIC BACKGROUND

INDEX CHILDREN WITH BRONCHITIS (n = 45)

	Index	Control	p Value
Personal History			
Eczema (%)	20.0	15.6	NS*
Hayfever (%)	8.9	8.9	NS*
Food allergy	6.7	2.2	NS*
Family History			
Eczema (%)	26.7	20.0	NS*
Hayfever (%)	28.9	37.8	NS*
Food allergy (%)	17.8	8.9	NS*
Asthma (%)	60.0	28.9	<0.01*

* McNemar's test

TABLE 24

TESTS OF RESPIRATORY FUNCTION - INDEX CHILDREN WITH BRONCHITIS (n = 45)

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	45	98.3	- 0.80	3.44	NS*
Control	45	99.1			
$FEV_{0.75}$ (% predicted)					
Index	44	89.2	- 2.01	2.61	NS*
Control	44	91.2			
$FEV_{1.0}$ (% predicted)					
Index	44	90.4	- 4.16	2.55	NS*
Control	44	94.5			
FVC (% predicted)					
Index	44	83.7	- 2.94	2.45	NS*
Control	44	86.6			
$FEF_{25-75\%}$ (% predicted)					
Index	44	96.1	- 2.96	7.33	NS*
Control	44	99.1			
$FEV_{1.0}$/FVC					
Index	44	0.90	- 0.01	0.02	NS*
Control	44	0.91			
R_T (Kp/l/s)					
Index	45	0.58	- 0.03	0.04	NS*
Control	45	0.61			

* Student's paired t test

TABLE 25

EXERCISE TEST

INDEX CHILDREN WITH BRONCHITIS (n = 45)

a) Percentage rise in PEFR during exercise

		CONTROL			
		≤7.5%	>7.5%	N/D	
INDEX	≤7.5%	16	13	0	
	>7.5%	9	7	0	
	N/D	0	0	0	NS*

b) Percentage fall in PEFR following exercise

		CONTROL			
		≤10%	>10%	N/D	
INDEX	≤10%	22	6	0	
	>10%	14	3	0	
	N/D	0	0	0	NS*

c) Exercise lability (% rise + % fall)

		CONTROL			
		≤22%	>22%	N/D	
INDEX	≤22%	34	6	0	
	>22%	4	1	0	
	N/D	0	0	0	NS*

* McNemar's test

N/D = Not done

NS = Not significant

37.8% of the bronchitis children, compared with 20% controls. This just failed to reach statistical significance (Table 25).

b) Index children with bronchiolitis

There were sixty-nine boys and thirty-five girls, a male:female ratio of almost 2:1. Significantly fewer index children had been breast fed (Table 26). Although more index children were reported to cough, the tendency had improved in the preceding year of the study. Wheeze, however, continued to be reported more frequently in the index sub-group, right up to the year before the study, but established asthma was not observed more often. The bronchiolitis sub-group of children were more prone to colds "going to the chest". A greater proportion required medications, were absent from school or consulted their own doctors for respiratory illnesses more often than their controls (Table 27).

There were fewer index children who were firstborn or who came from the higher social classes. The numbers of siblings were similar in index and control children, as were other social and family factors and atopic background (Tables 28 and 29).

TABLE 26

CLINICAL CHARACTERISTICS
INDEX CHILDREN WITH BRONCHIOLITIS (n = 104)

	Index	Control	p Value
Sex (M:F)	69:35	69:35	
Age at follow-up (years)	7.12 ± 0.40	7.31 ± 0.41	< 0.001*
Height at follow-up (cm)	119.9 ± 5.5	121.7 ± 4.6	< 0.001*
Weight at follow-up (Kg)	23.1 ± 3.2	23.2 ± 3.2	NS*
Birth weight (Kg)	3.20 ± 0.57	3.20 ± 0.53	NS*
Gestational age (weeks)	39.3 ± 2.4	39.5 ± 2.3	NS*
Breast feeding (%)	8.7	21.2	< 0.02+

* Student's paired t test

+ McNemar's test

TABLE 27

RESPIRATORY STATUS

INDEX CHILDREN WITH BRONCHIOLITIS (n = 104)

	Index	Control	p Value
"Tendency" to cough (%)			
At any time	29.8	14.4	<0.05*
In past year	15.4	7.7	NS*
Established bronchitis (%)	4.8	0	NS*
Sputum (%)	4.8	1.9	NS*
"Tendency" to wheeze (%)			
At any time	44.2	18.3	<0.001*
In past year	10.6	0	<0.01*
Established asthma (%)	6.7	1.0	NS*
Recurrent nasal blockage or discharge	34.6	26.9	NS*
Colds going to chest (%)	51.9	19.2	<0.001*
Hearing difficulties (%)	20.2	12.5	NS*
Tonsils removed (%)	7.7	10.6	NS*
Adenoids removed (%)	18.3	15.4	NS*
Medication in past year (%)	46.2	15.4	<0.001*
Antibiotics (%)	42.3	14.4	NS*
Bronchodilators (%)	10.6	4.8	NS*
School absenteeism in past year (weeks)	1.8 ± 2.6	0.8 ± 1.5	<0.01+
GP consultations for respiratory illness in past year (times)	1.6 ± 2.5	0.8 ± 1.3	<0.01+

* McNemar's test

\+ Wilcoxon test

TABLE 28

SOCIAL AND FAMILY FACTORS
INDEX CHILDREN WITH BRONCHIOLITIS (n = 104)

	Index	Control	p Value
Both parents at home (%)	77.9	86.5	NS*
First born (%)	29.8	47.1	< 0.01*
Siblings (number)	1.7 ± 1.1	1.5 ± 1.1	NS+
Social class Distribution (%)			
I & II	13.4	22.1	
III	21.2	24.0	< 0.05*
IV & V	64.4	52.9	
Central heating (%)	42.3	53.8	NS*
Own bedroom (%)	32.7	39.4	NS*
Mother smoked at some time (%)	68.3	63.4	NS*
Father smoked at some time (%)	68.2	61.5	NS*
Mother's age (years)	32.6 ± 5.5	33.1 ± 5.0	NS+
Father's age (years)	35.3 ± 6.9	34.8 ± 6.3	NS+

* McNemar's test

+ Student's paired t test

TABLE 29

ATOPIC BACKGROUND
INDEX CHILDREN WITH BRONCHIOLITIS (n = 104)

	Index	Control	p Value
Personal History			
Eczema (%)	16.3	13.5	NS*
Hayfever (%)	5.8	6.7	NS*
Food allergy (%)	7.7	3.8	NS*
Family History			
Eczema (%)	21.2	22.1	NS*
Hayfever (%)	29.8	32.7	NS*
Food allergy (%)	12.5	13.5	NS*
Asthma (%)	58.7	49.0	NS*

* McNemar's test

TABLE 30

TESTS OF RESPIRATORY FUNCTION - INDEX CHILDREN WITH BRONCHIOLITIS (n = 104)

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	103	95.7	- 6.03	2.17	<0.01 *
Control	103	101.8			
$FEV_{0.75}$ (% predicted)					
Index	102	87.0	- 5.60	1.89	<0.005*
Control	102	92.6			
$FEV_{1.0}$ (% predicted)					
Index	102	90.7	- 4.16	1.78	<0.05 *
Control	102	94.8			
FVC (% predicted)					
Index	102	86.2	- 0.18	1.75	NS*
Control	102	86.4			
$FEF_{25-75\%}$ (% predicted)					
Index	102	89.1	-12.24	3.92	<0.005*
Control	102	101.3			
$FEV_{1.0}/FVC$					
Index	102	0.88	- 0.04	0.01	<0.005*
Control	102	0.91			
R_T (Kp/l/s)					
Index	101	0.59	- 0.00	0.02	NS*
Control	101	0.59			

* Student's paired t test

TABLE 31

EXERCISE TEST

INDEX CHILDREN WITH BRONCHIOLITIS (n = 104)

a) Percentage rise in PEFR during exercise

		CONTROL			
		≤7.5%	>7.5%	N/D	
INDEX	≤7.5%	40	26	1	
	>7.5%	23	10	0	
	N/D	4	0	0	NS*

b) Percentage fall in PEFR following exercise

		CONTROL			
		≤10%	>10%	N/D	
INDEX	≤10%	51	14	1	
	>10%	23	11	0	
	N/D	3	1	0	NS*

c) Exercise lability (% rise + % fall)

		CONTROL			
		≤22%	>22%	N/D	
INDEX	≤22%	79	5	1	
	>22%	14	1	0	
	N/D	4	0	0	$p < 0.05$*

* McNemar's test

N/D = Not done

NS = Not significant

Significant differences were noted in respiratory function tests between the bronchiolitis children and their controls (Table 30), with the PEFR, $FEV_{0.75}$, $FEV_{1.0}$, $FEF_{25-75\%}$ and $FEV_{1.0}/FVC$ all reduced in the bronchiolitis sub-group. More index children had an exercise lability in excess of 22% ($p < 0.05$) (Table 31).

c) Index children with pneumonia

An identical number of boys and girls were affected (male:female ratio 1:1). The index children were of a lower birthweight than the controls, with no differences noted in the gestational age (Table 32). The tendency to cough and wheeze were reported more often in index cases. Again, more index children had colds "going to the chest", with medications and school absenteeism (but not general practitioner consultations) for respiratory illnesses reported more frequently (Table 33). Social and family factors were less favourable, with fewer index children being firstborn, more siblings in the family and more families from the lower social classes (Table 34). The atopic background were similar in index and control children (Table 35). Respiratory function tests (Table 36) revealed a significant difference in $FEF_{25-75\%}$ only. The response to exercise was similar in both groups of children (Table 37).

TABLE 32

CLINICAL CHARACTERISTICS
INDEX CHILDREN WITH PNEUMONIA (n = 51)

	Index	Control	p Value
Sex (M:F)	26:25	26:25	
Age at follow-up (years)	7.22 ± 0.48	7.41 ± 0.46	<0.001*
Height at follow-up (cm)	199.8 ± 6.5	121.7 ± 4.8	<0.02*
Weight at follow-up (Kg)	23.0 ± 3.6	23.5 ± 3.3	NS*
Birth weight (Kg)	3.08 ± 0.70	3.34 ± 0.42	<0.025*
Gestational age (weeks)	39.2 ± 2.5	39.8 ± 1.2	NS*
Breast feeding (%)	13.7	25.5	NS+

* Student's paired t test

+ McNemar's test

TABLE 33

RESPIRATORY STATUS

INDEX CHILDREN WITH PNEUMONIA (n = 51)

	Index	Control	p Value
"Tendency" to cough (%)			
At any time	37.3	11.8	<0.05 *
In past year	21.6	5.9	NS *
Established bronchitis (%)	3.9	2.0	NS *
Sputum (%)	5.9	0	NS *
"Tendency" to wheeze (%)			
At any time	41.2	21.6	<0.001*
In past year	13.7	2.0	<0.01 *
Established asthma (%)	7.8	5.9	NS *
Recurrent nasal blockage or discharge (%)	37.3	15.7	NS *
Colds going to chest (%)	47.1	25.5	<0.001*
Hearing difficulties (%)	15.7	11.8	NS *
Tonsils removed (%)	13.7	11.8	NS *
Adenoids removed (%)	23.5	15.7	NS *
Medication in past year (%)	47.1	23.5	<0.001*
Antibiotics (%)	43.1	19.6	NS *
Bronchodilators (%)	11.8	3.9	NS *
School absenteeism in past year (weeks)	2.4 $\pm$ 6.0	0.8 $\pm$ 1.1	<0.01 +
GP consultations for respiratory illness in past year (times)	3.1 $\pm$ 8.6	1.3 $\pm$ 2.0	NS +

* McNemar's test

+ Wilcoxon test

TABLE 34

SOCIAL AND FAMILY FACTORS
INDEX CHILDREN WITH PNEUMONIA (n = 51)

	Index	Control	p Value
Both parents at home (%)	88.2	92.2	NS *
First born (%)	21.6	41.2	<0.05 *
Siblings (number)	2.1 ± 1.1	1.4 ± 1.0	<0.001 +
Social class Distribution			
I & II	15.7	19.6	
III	19.6	35.3	<0.05 *
IV & V	64.7	45.1	
Central heating (%)	43.1	58.8	NS *
Own bedroom (%)	29.4	35.3	NS *
Mother smoked at some time (%)	70.6	76.5	NS *
Father smoked at some time (%)	74.5	68.6	NS *
Mother's age (years)	32.0 ± 4.6	32.9 ± 4.2	NS +
Father's age (years)	34.9 ± 5.8	34.7 ± 5.8	NS +

* McNemar's test

+ Student's paired t test

TABLE 35

ATOPIC BACKGROUND
INDEX CHILDREN WITH PNEUMONIA (n = 51)

	Index	Control	p Value
Personal History			
Eczema (%)	19.6	7.8	NS*
Hayfever (%)	3.9	7.8	NS*
Food allergy (%)	3.9	9.8	NS*
Family History			
Eczema (%)	25.5	15.7	NS*
Hayfever (%)	21.6	25.5	NS*
Food allergy (%)	17.6	15.7	NS*
Asthma (%)	43.1	51.0	NS*

* McNemar's test

TABLE 36

TESTS OF RESPIRATORY FUNCTION - INDEX CHILDREN WITH PNEUMONIA (n = 51)

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	51	99.6	- 1.32	3.13	NS*
Control	51	100.9			
$FEV_{0.75}$ (% predicted)					
Index	51	91.5	- 3.04	2.53	NS*
Control	51	94.6			
$FEV_{1.0}$ (% predicted)					
Index	51	93.3	- 2.39	2.40	NS*
Control	51	95.7			
FVC (% predicted)					
Index	51	88.7	0.08	2.47	NS*
Control	51	88.6			
$FEF_{25-75\%}$ (% predicted)					
Index	51	93.4	-13.84	6.31	<0.05*
Control	51	107.2			
$FEV_{1.0}/FVC$					
Index	51	0.89	- 0.02	0.02	NS*
Control	51	0.91			
R_T (Kp/l/s)					
Index	48	0.58	- 0.02	0.03	NS*
Control	48	0.60			

* Student's paired t test

TABLE 37

EXERCISE TEST

INDEX CHILDREN WITH PNEUMONIA (n = 51)

a) Percentage rise in PEFR during exercise

		CONTROL			
		≤7.5%	>7.5%	N/D	
INDEX	≤7.5%	19	16	0	
	>7.5%	12	3	0	
	N/D	1	0	0	NS*

b) Percentage fall in PEFR following exercise

		CONTROL			
		≤10%	>10%	N/D	
INDEX	≤10%	26	6	0	
	>10%	13	5	0	
	N/D	1	0	0	NS*

c) Exercise lability (% rise + % fall)

		CONTROL			
		≤ 22%	>22%	N/D	
INDEX	≤22%	39	5	0	
	>22%	5	1	0	
	N/D	1	0	0	NS*

* McNemar's test

N/D = Not done

NS = Not significant

Summary

Clinical characteristics were similar in index children who had suffered bronchitis, bronchiolitis or pneumonia when compared with their controls. Index children who had suffered pneumonia were, on average, of lower birth weight. Fewer children who had bronchiolitis were breast fed.

All the sub-groups of index children reported more respiratory symptoms and ill health than their controls. Social and family factors were comparable in the index sub-groups but were less favourable when compared to control children. The pneumonia sub-group of index children seemed worst off socially.

The atopic backgrounds were remarkably similar in the index sub-groups of children, with the exception that more asthma was reported amongst first-degree relatives of children who had had bronchitis. The similarity in atopic histories is also seen between index and control children.

Tests of respiratory function were significantly reduced only in the children who had bronchiolitis, although the trend in the bronchitis and pneumonia children was also towards poorer function. A one-way analysis of variance between disease categories (bronchitis, bronchiolitis and pneumonia) on the differences between case and control for each respiratory function measurement showed no significant

differences. In other words, the differences within a disease category for each variable assessed was greater than differences between disease categories; and that the significant differences in respiratory function between bronchiolitis children and their controls is a reflection of the greater numbers in this disease category.

S E C T I O N I I I

Chapter 5

SUBSEQUENT RESPIRATORY SYMPTOMS

Following the index illness, children either reported subsequent respiratory symptoms, or remained asymptomatic. Those with subsequent symptoms had recurrent cough (including bronchitis) or recurrent wheeze (including asthma). A small proportion reported both symptoms. The three sub-groups of index children were compared with their case controls.

a) Index children with recurrent cough

There were 72 children, 47 boys and 25 girls of similar birth weight, gestational age and infant feeding history to their controls (Table 38). Wheeze was reported significantly more often in the index children, at any time in the child's life as well as in the past year. Physician-confirmed asthma was also found more often. Index children had more nasal blockage and chesty colds, compared to controls. Other indices of respiratory ill health, such as medications, school absenteeism or general practitioner consultations were more common in index children (Table 39).

There were fewer firstborns amongst the index children and more siblings in the family. Parents of index children were younger, and more fathers had smoked (Table 40). No significant differences were found in the atopic histories of index and control children (Table 41). Tests of respiratory function revealed significantly lower $FEV_{0.75}$, $FEV_{1.0}$, and $FEF_{25-75\%}$ in children with recurrent cough (Table 42). A higher percentage of index cases showed a

TABLE 38

CLINICAL CHARACTERISTICS

INDEX CHILDREN WITH RECURRENT COUGH (n = 72)

	Index	Control	p Value
Sex (M:F)	47:25	47:25	
Age at follow-up (years)	7.12 ± 0.41	7.29 ± 0.43	<0.001*
Height at follow-up (cm)	118.1 ± 5.6	121.0 ± 4.6	<0.001*
Weight at follow-up (Kg)	22.5 ± 3.2	23.0 ± 2.9	NS*
Birth weight (Kg)	3.10 ± 0.63	3.24 ± 0.48	NS*
Gestational age (weeks)	39.4 ± 2.4	39.7 ± 1.9	NS*
Breast feeding (%)	15.3	19.4	NS+

* Student's paired t test

+ McNemar's test

TABLE 39

RESPIRATORY STATUS

INDEX CHILDREN WITH RECURRENT COUGH (n = 72)

	Index	Control	p Value
Sputum (%)	12.5	2.8	NS*
"Tendency" to wheeze (%)			
At any time	63.9	19.4	<0.001*
In past year	22.2	0	<0.001
Established asthma (%)	19.4	1.4	<0.01 *
Recurrent nasal blockage (%)	59.7	22.2	<0.001*
Colds going to chest (%)	84.7	22.2	<0.001*
Hearing difficulties (%)	18.1	11.1	NS*
Tonsils removed (%)	9.7	9.7	NS*
Adenoids removed (%)	16.7	12.5	NS*
Medication in past year (%)	73.6	16.7	<0.001*
Antibiotics (%)	68.1	15.3	NS*
Bronchodilators (%)	22.2	2.8	NS*
School absenteeism in past year (weeks)	3.9 ± 5.4	0.8 ± 1.2	$<0.001^{+}$
GP consultations for respiratory illness in past year (times)	4.3 ± 7.4	1.1 ± 1.9	$<0.001^{+}$

* McNemar's test

+ Wilcoxon test

TABLE 40

SOCIAL AND FAMILY CHARACTERISTICS

INDEX CHILDREN WITH RECURRENT COUGH (n = 72)

	Index	Control	p Value
Both parents at home (%)	86.1	90.3	NS*
First born (%)	38.9	58.3	<0.05*
Siblings (number)	1.8 ± 1.3	1.3 ± 1.1	<0.01+
Social class Distribution			
I & II	18.1	20.8	
III	25.0	26.4	NS*
IV & V	56.9	51.4	
Central heating (%)	44.4	54.2	NS*
Own bedroom (%)	33.3	38.9	NS*
Mother smoked at some time (%)	69.4	61.1	NS*
Father smoked at some time (%)	80.6	63.9	<0.05*
Mother's age (years)	30.8 ± 4.9	32.6 ± 4.6	<0.01+
Father's age (years)	33.0 ± 5.5	34.5 ± 5.7	<0.05+

* McNemar's test

+ Student's paired t test

TABLE 41

ATOPIC BACKGROUND

INDEX CHILDREN WITH RECURRENT COUGH (n = 72)

	Index	Control	p Value
Personal History			
Eczema (%)	18.1	12.5	NS*
Hayfever (%)	8.3	11.1	NS*
Food allergy (%)	8.3	5.6	NS*
Family History			
Eczema (%)	29.2	19.4	NS*
Hayfever (%)	25.0	37.5	NS*
Food allergy (%)	13.9	13.9	NS*
Asthma (%)	55.6	47.2	NS*

* McNemar's test

TABLE 42

RESPIRATORY FUNCTION TESTS - INDEX CHILDREN WITH RECURRENT COUGH (n = 72)

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	72	96.5	- 4.30	2.94	NS*
Control	72	100.8			
$FEV_{0.75}$ (% predicted)					
Index	72	86.8	- 5.41	2.38	<0.05*
Control	72	92.2			
$FEV_{1.0}$ (% predicted)					
Index	72	89.5	- 5.33	2.27	<0.05*
Control	72	94.9			
FVC (% predicted)					
Index	72	84.5	- 2.01	2.25	NS*
Control	72	86.5			
$FEF_{25-75\%}$ (% predicted)					
Index	72	94.9	-11.62	5.67	<0.05*
Control	72	106.6			
$FEV_{1.0}/FVC$					
Index	72	0.89	- 0.03	0.015	NS*
Control	72	0.91			
R_T (Kp/l/s)					
Index	71	0.58	- 0.01	0.026	NS*
Control	71	0.59			

* Student's paired t test

TABLE 43

EXERCISE TEST

INDEX CHILDREN WITH RECURRENT COUGH (n = 72)

a) Percentage rise in PEFR during exercise

		CONTROL			
		≤7.5%	>7.5%	N/D	
INDEX	≤7.5%	25	16	0	
	>7.5%	19	10	0	
	N/D	2	0	0	NS*

b) Percentage fall in PEFR following exercise

		CONTROL			
		≤10%	>10%	N/D	
INDEX	≤10%	39	6	0	
	>10%	17	8	0	
	N/D	2	0	0	$p < 0.05$*

c) Exercise lability (% rise + % fall)

		CONTROL			
		≤22%	>22%	N/D	
INDEX	≤22%	52	3	0	
	>22%	13	2	0	
	N/D	2	0	0	$p<0.05$*

* McNemar's test

N/D = Not done

NS = Not significant

fall in PEFR of greater than 10% following exercise, as well as an exercise lability in excess of 22% (Table 43).

b) Index children with recurrent wheeze

Ninety-four cases reported recurrent wheeze following the index illness, 65 boys and 29 girls. No differences were noted in the gestation, birth weight or proportion who were breastfed when compared with their controls (Table 44). Cough was reported more often in index children, along with recurrent nasal blockage, chesty colds and hearing difficulties. Medications were prescribed more frequently, although bronchodilators were not used in excess. School absenteeism and general practitioner consultations for respiratory illnesses also exceeded those in controls (Table 45). Fewer index children were firstborn, and more siblings were noted. Parents of index children were also younger (Table 46). The atopic background is depicted in Table 47, and shows a greater proportion of index children with a positive family history of asthma. Index children had diminished tests of respiratory function (Table 48), with a greater percentage demonstrating bronchoconstriction following exercise (Table 49).

c) Index children who remained asymptomatic

Seventy-nine children (44 boys and 35 girls) did not have respiratory symptoms following the index illness. Their clinical characteristics, with those of controls, are listed on Table 50. Index children were of similar birth weight, gestational age and proportion who were breastfed,

compared to controls. Upper respiratory symptoms, medications for respiratory problems, school absenteeism or general practitioner consultations were reported in proportions similar to control children (Table 51). Family and social factors were comparable in index and control children, with the exception that fewer index children were firstborn, they had more siblings and the fathers were older than those of control children (Table 52). The atopic background of the two groups of children were similar (Table 53). Tests of respiratory function showed no differences in the asymptomatic index children compared with controls, with the exception of $FEV_{1.0}$/FVC (Table 54). The response to exercise was comparable in both groups (Table 55), although more index children showed bronchoconstriction.

Summary

Following the index illness, children were reported to cough, wheeze or remain asymptomatic. Children with symptoms (cough or wheeze) were almost identical in terms of clinical, social and family characteristics as well as atopic background. However, they differed from their controls. Tests of respiratory function were diminished in both groups of symptomatic children, with evidence of bronchial hyperreactivity.

The asymptomatic group of index children did not differ from the asymptomatic groups with respect to social factors suggesting that these contribute little to the occurrence

of respiratory symptoms. Asymptomatic children were of similar height to their controls. Respiratory function was also comparable, although there was a slight trend to hyperreactive airways.

TABLE 44

CLINICAL CHARACTERISTICS

INDEX CHILDREN WITH RECURRENT WHEEZE (n = 94)

	Index	Control	p Value
Sex (M:F)	65:29	65:29	
Age at follow-up (years)	7.19 ± 0.44	7.36 ± 0.42	<0.001*
Height at follow-up (cm)	119.1 ± 6.2	121.7 ± 5.6	<0.001*
Weight at follow-up (Kg)	23.1 ± 3.7	23.1 ± 3.1	NS*
Birth weight (Kg)	3.16 ± 0.69	3.18 ± 0.55	NS*
Gestational age (weeks)	39.3 ± 2.5	39.5 ± 2.2	NS*
Breast feeding (%)	11.7	17.0	NS+

* Student's paired t test

+ McNemar's test

TABLE 45

RESPIRATORY STATUS

INDEX CHILDREN WITH RECURRENT WHEEZE (n = 94)

	Index	Control	p Value
"Tendency" to cough (%)			
At any time	48.9	14.9	<0.001*
In past year	26.6	5.3	= 0.001*
Sputum (%)	8.5	2.1	NS*
Established bronchitis (%)	3.2	1.1	NS*
Recurrent nasal blockage (%)	45.7	26.6	<0.01 *
Colds going to chest (%)	74.5	21.3	<0.001*
Hearing difficulties (%)	16.0	5.3	<0.05 *
Tonsils removed (%)	9.6	10.6	NS*
Adenoids removed (%)	18.1	11.7	NS*
Medication in past year (%)	60.6	23.4	<0.001*
Antibiotics (%)	56.4	22.3	NS*
Bronchodilators (%)	22.3	5.3	NS*
School absenteeism in past year (weeks)	2.5 ± 3.1	0.9 ± 1.3	<0.001+
GP consultations for respiratory illness in past year (times)	2.5 ± 3.2	1.1 ± 1.8	<0.001+

* McNemar's test

+ Wilcoxon test

TABLE 46

SOCIAL AND FAMILY CHARACTERISTICS

INDEX CHILDREN WITH RECURRENT WHEEZE (n = 94)

	Index	Control	p Value
Both parents at home (%)	81.9	88.3	NS *
First born (%)	31.9	47.9	<0.05 *
Siblings (number)	1.7 ± 1.1	1.4 ± 1.1	<0.05 +
Social class Distribution (%)			
I & II	11.7	21.3	
III	23.4	23.4	<0.05 *
IV & V	64.9	54.3	
Central heating (%)	45.7	53.2	NS *
Own bedroom (%)	26.6	38.3	NS*
Mother smoked at some time (%)	74.5	63.8	NS *
Father smoked at some time (%)	74.5	63.8	NS *
Mother's age at follow-up (years)	30.5 ± 4.3	32.9 ± 5.2	<0.001 +
Father's age at follow-up (years)	32.9 ± 4.9	34.6 ± 6.4	<0.05 +

* McNemar's test

+ Student's paired t test

TABLE 47

ATOPIC BACKGROUND

INDEX CHILDREN WITH RECURRENT WHEEZE (n = 94)

	Index	Control	p Value
Personal History			
Eczema (%)	20.2	13.8	NS*
Hayfever (%)	9.6	6.4	NS*
Food allergy (%)	6.4	4.3	NS*
Family History			
Eczema (%)	25.5	21.3	NS*
Hayfever (%)	27.7	34.0	NS*
Food allergy (%)	14.9	17.0	NS*
Asthma (%)	63.8	43.6	< 0.05*

* McNemar's test

TABLE 48

RESPIRATORY FUNCTION TESTS - INDEX CHILDREN WITH RECURRENT WHEEZE (n = 94)

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	94	96.6	- 3.16	2.41	NS *
Control	94	99.7			
$FEV_{0.75}$ (% predicted)					
Index	94	86.7	- 5.12	1.88	<0.01 *
Control	94	91.8			
$FEV_{1.0}$ (% predicted)					
Index	94	89.7	- 4.35	1.84	<0.05 *
Control	94	94.1			
FVC (% predicted)					
Index	94	85.2	- 1.15	1.74	NS *
Control	94	86.4			
$FEF_{25-75\%}$ (% predicted)					
Index	94	86.2	-13.9	4.1	= 0.001*
Control	94	100.2			
$FEV_{1.0}/FVC$					
Index	94	0.88	- 0.03	0.012	<0.05 *
Control	94	0.91			
R_T (Kp/l/s)					
Index	92	0.60	- 0.002	0.024	NS *
Control	92	0.60			

* Student's paired t test

TABLE 49

EXERCISE TEST

INDEX CHILDREN WITH RECURRENT WHEEZE (n = 94)

a) Percentage rise in PEFR during exercise

		CONTROL			
		≤7.5%	>7.5%	N/D	
INDEX	≤7.5%	34	29	0	
	>7.5%	17	11	0	
	N/D	3	0	0	NS*

b) Percentage fall in PEFR following exercise

		CONTROL			
		≤10%	>10%	N/D	
INDEX	≤10%	44	10	0	
	>10%	28	9	0	
	N/D	3	0	0	$p < 0.01$*

c) Exercise lability (% rise + % fall)

		CONTROL			
		≤22%	>22%	N/D	
INDEX	≤22%	67	9	0	
	>22%	12	3	0	
	N/D	3	0	0	NS*

* McNemar's test

N/D = Not done

NS = Not significant

TABLE 50

CLINICAL CHARACTERISTICS

INDEX CHILDREN WHO REMAINED ASYMPTOMATIC (n = 79)

	Index	Control	p Value
Sex M:F)	44:35	44:35	
Age at follow-up (years)	7.26 $\pm$ 0.5	7.45 $\pm$ 0.5	<0.001*
Height at follow-up (cm)	121.1 $\pm$ 6.3	121.7 $\pm$ 4.8	NS*
Weight at follow-up (Kg)	23.4 $\pm$ 3.7	23.8 $\pm$ 3.8	NS*
Birth weight (Kg)	3.25 $\pm$ 0.6	3.24 $\pm$ 0.5	NS*
Gestational age (weeks)	39.3 $\pm$ 2.5	39.8 $\pm$ 1.6	NS*
Breast feeding (%)	11.4	24.1	NS+

* Student's paired t test

+ McNemar's test

TABLE 51

RESPIRATORY STATUS

INDEX CHILDREN WHO REMAINED ASYMPTOMATIC (n = 79)

	Index	Control	p Value
Sputum (%)	0	0	NS*
Recurrent nasal blockage or discharge (%)	20.3	20.3	NS*
Colds going to chest (%)	19.0	22.2	NS*
Hearing difficulties (%)	19.0	12.8	NS*
Tonsils removed (%)	8.9	7.6	NS*
Adenoids removed (%)	17.7	13.9	NS*
Medication in past year (%)	20.3	13.9	NS*
Antibiotics (%)	100.0	66.7	NS*
Bronchodilators (%)	0	33.3	NS*
School absenteeism in past year (weeks)	0.5 ± 1.2	0.6 ± 1.1	NS+
GP consultations for respiratory illness in past year (times)	0.7 ± 1.0	0.7 ± 1.2	NS+

* McNemar's test

+ Wilcoxon test

TABLE 52

SOCIAL AND FAMILY CHARACTERISTICS

INDEX CHILDREN WHO REMAINED ASYMPTOMATIC (n = 79)

	Index	Control	p Value
Both parents at home (%)	78.9	87.3	NS*
First born (%)	21.8	38.5	<0.05*
Siblings (number)	3.2 ± 2.4	2.4 ± 0.9	<0.01*
Social class Distribution (%)			
I & II	17.9	20.3	
III	21.8	33.3	NS*
IV & V	60.3	46.2	
Central heating (%)	44.3	60.8	NS*
Own bedroom (%)	31.6	44.3	NS*
Mother smoked at some time (%)	67.1	72.2	NS*
Father smoked at some time (%)	72.2	69.4	NS*
Mother's age at follow-up (years)	34.3 ± 5.8	33.4 ± 5.1	NS+
Father's age at follow-up (years)	37.5 ± 7.0	35.1 ± 6.5	<0.05+

* McNemar's test

+ Student's paired t test

TABLE 53

ATOPIC BACKGROUND

INDEX CHILDREN WHO REMAINED ASYMPTOMATIC (n = 79)

	Index	Control	p Value
Personal History			
Eczema (%)	16.5	12.7	NS*
Hay fever (%)	2.5	6.3	NS*
Food allergy (%)	5.1	6.3	NS*
Family History			
Eczema (%)	22.8	19.0	NS*
Hayfever (%)	29.1	25.3	NS*
Food allergy (%)	15.2	10.1	NS*
Asthma (%)	46.8	46.8	NS*

*McNemar's test

TABLE 54

RESPIRATORY FUNCTION TESTS - INDEX CHILDREN WHO REMAINED ASYMPTOMATIC (n = 79)

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	78	98.9	- 3.73	2.39	NS*
Control	78	102.6			
$FEV_{0.75}$ (% predicted)					
Index	76	92.3	- 2.72	2.04	NS*
Control	76	95.0			
$FEV_{1.0}$ (% predicted)					
Index	76	94.6	- 2.03	1.86	NS*
Control	76	96.7			
FVC (% predicted)					
Index	76	89.4	1.57	1.91	NS*
Control	76	87.8			
$FEF_{25-75\%}$ (% predicted)					
Index	76	95.2	- 9.78	5.14	NS*
Control	76	105.0			
$FEV_{1.0}/FVC$					
Index	76	0.88	- 0.03	0.11	<0.01*
Control	76	0.92			
R_T (Kp/l/s)					
Index	75	0.57	- 0.02	0.02	NS*
Control	75	0.59			

* Student's paired t test

TABLE 55

EXERCISE TEST

INDEX CHILDREN WHO REMAINED ASYMPTOMATIC (n = 79)

a) Percentage rise in PEFR during exercise

		CONTROL			
		≤ 7.5%	>7.5%	N/D	
INDEX	≤ 7.5%	32	21	1	
	>7.5%	17	6	0	
	N/D	2	0	0	NS*

b) Percentage fall in PEFR following exercise

		CONTROL			
		≤ 10%	>10%	N/D	
INDEX	≤ 10%	38	13	1	
	>10%	18	7	0	
	N/D	1	1	0	NS*

c) Exercise lability (% rise + % fall)

		CONTROL			
		≤ 22%	>22%	N/D	
INDEX	≤ 22%	63	6	1	
	>22%	7	0	0	
	N/D	2	0	0	NS*

* McNemar's test

N/D = Not done

NS = Not significant

S E C T I O N I I I

Chapter 6

THE ROLE OF ATOPY

To assess the effect of atopy on the outcome, index children were separated into two groups on the basis of a positive personal and/or family history of atopic disorders.

a) Non-atopic index children

Thirty-six children had no history of atopy. Their clinical details were similar to those of control children (Table 56). Although cough was reported more often at any time, this had improved so that equal proportions of index and control children had this symptom in the year prior to study. Wheeze was also reported in similar proportions amongst index and control populations. Medications (all antibiotics) were prescribed significantly more often in non-atopic index children, and more time was lost from school (Table 57). Social and family factors, shown in Table 58, seemed comparable between index and control children.

Tests of respiratory function (Table 59) showed lower trends in the non-atopic index subgroup, although not reaching statistical significance. Bronchial reactivity was seen in more index children (Table 60) but the numbers were small and did not reach statistical significance.

b) Atopic Index Children

One hundred and sixty-four children had either a personal and/or family history of atopy. Table 61 lists

TABLE 56

CLINICAL CHARACTERISTICS
NON-ATOPIC INDEX CHILDREN (n = 36)

	Index	Control	p Value
Sex (M:F)	20:16	20:16	
Age at follow-up (years)	7.3 ± 0.5	7.4 ± 0.5	NS*
Height at follow-up (cm)	121.1 ± 5.5	121.7 ± 5.2	NS*
Weight at follow-up (Kg)	23.7 ± 3.0	23.4 ± 3.2	NS*
Birth weight (Kg)	3.25 ± 0.55	3.37 ± 0.51	NS*
Gestational age (weeks)	39.6 ± 1.7	39.8 ± 1.6	NS*
Breast feeding (%)	13.9	22.2	NS+

* Student's paired t test

+ McNemar's test

TABLE 57

RESPIRATORY STATUS
NON-ATOPIC INDEX CHILDREN (n = 36)

	Index	Control	p Value
"Tendency" to cough (%)			
At any time	30.6	8.3	NS*
In past year	8.3	8.3	NS*
Sputum (%)	5.7	0	NS*
Established bronchitis (%)	2.8	0	NS*
"Tendency" to wheeze (%)			
At any time	20.0	17.1	NS*
In past year	3.1	3.1	NS*
Established asthma (%)	100.0	2.8	NS*
Recurrent nasal blockage (%)	16.7	8.3	NS*
Colds going to chest (%)	34.3	20.0	NS*
Hearing difficulties (%)	2.9	8.8	NS*
Tonsils removed (%)	2.8	8.3	NS*
Adenoids removed (%)	2.8	13.9	NS*
Medications in past year (%)	41.7	11.1	= 0.01*
Antibiotics (%)	100.0	100.0	NS*
Bronchodilators (%)	0	0	NS*
School absenteeism in past year (weeks)	2.3 $\pm$ 6.7	0.7 $\pm$ 1.3	<0.05+
GP consultations for respiratory illness in past year (times)	2.9 $\pm$ 9.9	0.9 $\pm$ 1.6	NS+

* McNemar's test
+ Wilcoxon test

TABLE 58

SOCIAL AND FAMILY CHARACTERISTICS
NON-ATOPIC INDEX CHILDREN (n = 36)

	Index	Control	p Value
Both parents at home (%)	77.1	97.1	<0.05*
First born (%)	34.2	42.9	NS*
Siblings (number)	3.1 ± 3.2	2.5 ± 0.9	NS+
Social class Distribution (%)			
I & II	17.1	24.3	
III	31.4	37.1	<0.05*
IV & V	2.9	34.2	
Central heating (%)	41.7	66.7	NS*
Own bedroom (%)	36.1	36.1	NS*
Mother smoked at some time (%)	80.0	65.7	NS*
Father smoked at some time (%)	66.7	66.7	NS*
Mother's age (years)	31.2 ± 4.0	32.5 ± 4.0	NS+
Father's age (years)	34.1 ± 5.6	34.2 ± 4.3	NS+

* McNemar's test

+ Student's paired t test

TABLE 59

TESTS OF RESPIRATORY FUNCTION - NON-ATOPIC INDEX CHILDREN (n = 36)

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	36	98.9	- 5.44	3.29	NS*
Control	36	104.3			
$FEV_{0.75}$ (% predicted)					
Index	35	92.3	- 2.44	2.99	NS*
Control	35	94.7			
$FEV_{1.0}$ (% predicted)					
Index	35	93.7	- 3.00	2.85	NS*
Control	35	96.7			
FVC (% predicted)					
Index	35	88.8	- 0.66	3.16	NS*
Control	35	88.2			
$FEF_{25-75\%}$ (% predicted)					
Index	35	93.6	- 9.38	7.22	NS*
Control	35	103.0			
$FEV_{1.0}$/FVC					
Index	35	0.88	- 0.03	0.02	NS*
Control	35	0.91			
R_T (kp/l/s)					
Index	35	0.56	- 0.01	0.03	NS*
Control	35	0.57			

* Wilcoxon test

TABLE 60

EXERCISE TEST

NON-ATOPIC INDEX CHILDREN (n = 36)

a) Percentage rise in PEFR during exercise

		CONTROL		
		≤7.5%	>7.5%	
INDEX	≤7.5%	13	12	
	>7.5%	10	1	NS*

b) Percentage fall in PEFR following exercise

		CONTROL		
		≤10%	>10%	
INDEX	≤10%	15	7	
	>10%	11	3	NS*

c) Exercise lability (% rise + % fall)

		CONTROL		
		≤22%	>22%	
INDEX	≤22%	31	3	
	>22%	2	0	NS*

*McNemar's test

NS = Not significant

their clinical characteristics and they showed differences in age and height as seen in the index group as a whole. Atopic index children had more respiratory symptoms and other indices of respiratory illhealth were reported significantly more often (Table 62). Social and family factors were also less favourable with fewer first-borns, more siblings and an increase in paternal smoking (Table 63). Significant differences were noted in tests of respiratory function, with the $FEV_{0.75}$, $FEV_{1.0}$, $FEF_{25-75\%}$ and $FEV_{1.0}/FVC$ being reduced in atopic index children (Table 64). Such children also had evidence of bronchial reactivity (Table 65).

Summary

Atopic index children reported more respiratory symptoms and had significantly lower tests of ventilatory function as well as increased bronchial reactivity when compared with controls.

Non-atopic children also had more symptoms, diminished respiratory function and evidence of bronchial reactivity although the results did not reach statistical significance.

These results suggest that atopy is a determinant of a poorer outcome, but are influenced by the discrepancy in numbers between the two index subgroups.

A one-way analysis of variance on the differences between index and control children for each respiratory function measurement showed no significant differences. This implied that differences within index-control comparisons exceeded those seen between the subgroups.

TABLE 61

CLINICAL CHARACTERISTICS
ATOPIC INDEX CHILDREN (n = 164)

	Index	Control	p Value
Sex (M:F)	103:61	103:61	
Age at follow-up (years)	7.19 ± 0.44	7.38 ± 0.44	<0.001*
Height at follow-up (cm)	119.5 ± 6.2	121.8 ± 5.0	<0.001*
Weight at follow-up (Kg)	22.9 ± 3.7	23.4 ± 3.4	NS*
Birth weight (Kg)	3.17 ± 0.66	3.20 ± 0.50	NS*
Gestational age (weeks)	39.3 ± 2.5	39.7 ± 1.9	NS*
Breast feeding (%)	12.2	20.7	NS*

* Student's paired t test

+ McNemar's test

TABLE 62

RESPIRATORY STATUS
ATOPIC INDEX CHILDREN (n = 164)

	Index	Control	p Value
"Tendency" to cough (%)			
At any time	35.6	14.1	<0.001*
In past year	18.5	4.9	<0.01 *
Sputum (%)	4.9	1.2	NS *
Established bronchitis (%)	3.7	0.6	NS *
"Tendency" to wheeze (%)			
At any time	53.0	17.1	<0.001*
In past year	12.7	0.6	<0.001*
Established asthma (%)	10.4	2.4	<0.01 *
Recurrent nasal blockage (%)	39.0	25.0	<0.01 *
Colds going to chest (%)	57.1	20.9	<0.001*
Hearing difficulties (%)	20.4	10.5	<0.05 *
Tonsils removed (%)	11.0	9.1	NS *
Adenoids removed (%)	20.7	12.1	= 0.05 *
Medications in past year (%)	46.3	18.9	<0.001*
Antibiotics (%)	93.8	87.5	NS*
Bronchodilators (%)	26.7	13.3	NS*
School absenteeism in past year (weeks)	1.8 ± 2.7	0.8 ± 1.3	<0.001+
GP consultations for respiratory illness in past year (times)	1.9 ± 2.7	1.0 ± 1.6	<0.001+

* McNemar's test

+ Wilcoxon test

TABLE 63

SOCIAL AND FAMILY CHARACTERISTICS
ATOPIC INDEX CHILDREN (n = 164)

	Index	Control	p Value
Both parents at home (%)	82.7	88.3	NS *
First born (%)	28.0	45.1	<0.01 *
Siblings (number)	2.9 ± 1.2	2.4 ± 1.0	<0.001 +
Social class Distribution (%)			
I & II	14.1	19.6	
III	21.4	26.4	<0.05 *
IV & V	64.4	54.0	
Central heating (%)	45.1	59.9	NS*
Own bedroom (%)	27.4	42.1	<0.05 *
Mother smoked at some time (%)	69.3	66.3	NS *
Father smoked at some time (%)	76.1	68.4	<0.05 *
Mother's age (years)	32.4 ± 5.6	33.3 ± 5.3	NS +
Father's age (years)	35.0 ± 6.4	35.0 ± 6.6	NS +

* McNemar's test

+ Student's paired t test

TABLE 64

TESTS OF RESPIRATORY FUNCTION - ATOPIC INDEX CHILDREN (n = 164)

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	163	97.0	- 3.25	1.80	NS*
Control	163	100.2			
$FEV_{0.75}$ (% predicted)					
Index	162	87.9	- 4.50	1.46	<0.01*
Control	162	92.4			
$FEV_{1.0}$ (% predicted)					
Index	162	90.8	- 3.85	1.38	<0.05*
Control	162	94.6			
FVC (% predicted)					
Index	162	85.7	- 1.03	1.34	NS*
Control	162	86.7			
$FEF_{25-75\%}$ (% predicted)					
Index	162	91.4	-10.8	3.41	<0.01*
Control	162	102.2			
$FEV_{1.0}$/FVC					
Index	162	0.88	- 0.03	0.01	<0.01*
Control	162	0.91			
R_T (Kp/l/s)					
Index	159	0.59	- 0.01	0.02	NS*
Control	159	0.60			

* Wilcoxon test

TABLE 65

EXERCISE TEST

ATOPIC INDEX CASES (n = 164)

a) Percentage rise in PEFR during exercise

		CONTROL			
		≤ 7.5%	> 7.5%	N/D	
INDEX	≤ 7.5%	62	43	1	
	> 7.5%	34	19	0	
	N/D	5	0	0	NS*

b) Percentage fall in PEFR following exercise

		CONTROL			
		≤ 10%	> 10%	N/D	
INDEX	≤ 10%	84	19	1	
	> 10%	39	16	0	
	N/D	4	1	0	$p < 0.05$*

c) Exercise lability (% rise + % fall)

		CONTROL			
		≤ 22%	> 22%	N/D	
INDEX	≤ 22%	121	13	1	
	> 22%	21	3	0	
	N/D	5	0	0	NS*

* McNemar's test

N/D = Not done

NS = Not significant

S E C T I O N I I I

Chapter 7

BRONCHIAL REACTIVITY

It was postulated that the inclusion of children who had hyperreactive airways would result in the respiratory function of the index group as a whole being diminished. Index children were therefore grouped separately into those who demonstrated bronchial reactivity, ie had a post-exercise fall in PEFR greater than 10% of the resting value, and those who showed less than or equal to a 10% fall in PEFR.

a) Index children with bronchial reactivity

Seventy-one children had evidence of hyperreactive airways, 47 boys and 30 girls. Table 66 shows that clinical characteristics were similar to their controls, with the age and height differences found as in the whole index group. More cough was reported, as well as wheeze and colds going to the chest (Table 67). Wheeze had persisted to the year prior to follow-up, and the percentage with asthma was also greater in the index children. Such children had received more medications (mostly antibiotics), and also lost more time from school, besides requiring more general practitioner consultations for respiratory problems.

Social and family characteristics are listed in Table 68. Index children had a higher percentage of single parent families, came from the lower social classes and had younger mothers than their controls.

TABLE 66

CLINICAL CHARACTERISTICS

INDEX CHILDREN WITH BRONCHIAL REACTIVITY (n = 77)

	Index	Control	p Value
Sex (M:F)	47:30	47:30	
Age at follow-up (years)	7.16 ± 0.40	7.32 ± 0.40	<0.01 *
Height at follow-up (cm)	119.7 ± 6.3	122.1 ± 4.9	<0.001*
Weight at follow-up (Kg)	22.9 ± 3.8	23.0 ± 2.8	NS *
Birth weight (Kg)	3.19 ± 0.6	3.20 ± 0.5	NS *
Gestational age (weeks)	39.5 ± 2.3	39.5 ± 2.1	NS *
Breast feeding (%)	14.3	20.8	NS +

* Student's paired t test

+ McNemar's test

TABLE 67

RESPIRATORY STATUS

INDEX CHILDREN WITH BRONCHIAL REACTIVITY (n = 77)

	Index	Control	p Value
"Tendency" to cough (%)			
At any time	36.4	13.0	<0.01 *
In past year	20.8	5.2	<0.05 *
Sputum (%)	5.3	1.3	NS *
Established bronchitis (%)	1.3	1.3	NS *
"Tendency" to wheeze			
At any time	52.6	14.5	<0.001*
In past year	15.3	1.4	<0.01 *
Established asthma (%)	18.2	1.3	<0.01 *
Recurrent nasal blockage (%)	36.4	23.4	NS *
Colds going to chest (%)	57.3	14.7	<0.001*
Hearing difficulties (%)	17.1	15.8	NS *
Tonsils removed (%)	9.1	9.1	NS *
Adenoids removed (%)	20.8	10.4	NS *
Medication in past year (%)	46.8	18.2	<0.001*
Antibiotics (%)	85.7	100.0	NS *
Bronchodilators (%)	57.1	0	NS *
School absenteeism in past year (weeks)	2.3 ± 5.1	0.8 ± 1.3	<0.01 +
GP consultations for respiratory illness in past year (times)	2.8 ± 7.2	1.0 ± 1.8	<0.05 +

* McNemar's test

+ Wilcoxon test

TABLE 68

SOCIAL AND FAMILY CHARACTERISTICS
INDEX CHILDREN WITH BRONCHIAL REACTIVITY (n = 77)

	Index	Control	p Value
Both parents at home (%)	80.0	93.3	<0.05*
First born (%)	38.2	48.7	NS*
Siblings (number)	3.0 ± 2.4	2.5 ± 1.1	NS+
Social class Distribution (%)			
I & II	17.3	29.3	<0.05*
III	25.3	26.7	
IV & V	57.3	44.0	
Central heating (%)	45.5	59.7	NS*
Own bedroom (%)	33.8	49.4	NS*
Mother smoked at some time (%)	63.2	65.8	NS*
Father smoked at some time (%)	70.4	66.2	NS*
Mother's age at follow-up (years)	31.6 ± 5.5	33.4 ± 4.9	<0.05+
Father's age at follow-up (years)	34.3 ± 6.4	35.1 ± 6.3	NS+

* McNemar's test

+ Student's paired t test

TABLE 69

ATOPIC BACKGROUND

INDEX CHILDREN WITH BRONCHIAL REACTIVITY (n = 77)

	Index	Control	p Value
Personal History			
Eczema (%)	18.2	11.7	NS*
Hayfever (%)	11.7	1.3	<0.05*
Food allergy (%)	6.5	5.2	NS*
Family History			
Eczema (%)	20.8	18.2	NS*
Hayfever (%)	32.5	32.5	NS*
Food allergy (%)	11.7	14.3	NS*
Asthma (%)	54.5	41.6	NS*

* McNemar's test

TABLE 70

RESPIRATORY FUNCTION TESTS - INDEX CHILDREN WITH BRONCHIAL REACTIVITY (n = 77)

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	76	95.9	- 2.13	2.56	NS *
Control	76	98.0			
$FEV_{0.75}$ (% predicted)					
Index	74	85.7	- 6.20	2.21	<0.05 *
Control	74	91.9			
$FEV_{1.0}$ (% predicted)					
Index	74	88.2	- 5.54	2.26	<0.05 *
Control	74	93.7			
FVC (% predicted)					
Index	74	86.7	0.11	2.28	NS *
Control	74	86.6			
$FEF_{25-75\%}$ (% predicted)					
Index	74	85.8	-17.3	5.27	<0.001*
Control	74	103.1			
$FEV_{1.0}/FVC$					
Index	74	0.85	- 0.06	0.01	<0.05 *
Control	74	0.90			
R_T (Kp/l/s)					
Index	74	0.58	- 0.005	0.275	NS *
Control	74	0.58			

* Student's paired t test

Hayfever was reported more often in index children (Table 69). However, the family history of atopic disorders was similar in both groups, with high reporting of asthma amongst relatives in index as well as control children.

Significantly lower respiratory function (Table 70) was found in index children with hyperreactive airways.

b) Index children without bronchial reactivity

Following the exercise test, 123 index children (76 boys and 47 girls) did not demonstrate evidence of bronchial reactivity. These children had similar clinical characteristics compared to controls (Table 71). Table 72 lists respiratory symptoms and disease. More index children were reported to cough, with 4.9% being labelled as having established bronchitis, while no control child had this diagnosis. Wheeze was reported more frequently in index children, although the occurrence of asthma was not significantly different between index and controls. Index children had more nasal symptoms, chesty colds and hearing difficulties. Medications were prescribed more often, more time lost from school and also more medical consultations for respiratory illnesses.

When social and family factors were compared (Table 73), index children had more siblings, fewer were firstborn, more

came from the lower social classes and more fathers smoked. No differences were noted in the family history of atopic disorders (Table 74) although index children had a higher incidence of hayfever.

Tests of respiratory function in index children without bronchial reactivity were similar to those of control children, with PEFR only being diminished (Table 75).

Summary

Index children with bronchial reactivity showed similar clinical, atopic, social and family characteristics to those with no evidence of hyperreactive airways, but these two groups differed clinically and in social and family background from control children.

Children with bronchial reactivity appeared to wheeze more, and there was a greater percentage of asthmatics. Respiratory function was significantly diminished compared to controls. There was no excess of atopic disorders in the index children with hyperreactive airways.

Index children with no evidence of bronchial reactivity also reported more respiratory symptoms, but bronchitis rather than asthma was diagnosed in these children. Except for a lower PEFR, all other tests of respiratory function were similar between index and control children.

TABLE 71

CLINICAL CHARACTERISTICS

INDEX CHILDREN WITHOUT BRONCHIAL REACTIVITY (n = 123)

	Index	Control	p Value
Sex (M:F)	76:47	76:47	
Age at follow-up (years)	7.24 ± 0.44	7.43 ± 0.44	<0.001*
Height at follow-up (cm)	119.8 ± 6.0	121.6 ± 5.2	<0.001*
Weight at follow-up (Kg)	23.2 ± 3.5	23.7 ± 3.6	NS*
Birth weight (Kg)	3.18 ± 0.7	3.24 ± 0.5	NS*
Gestational age (weeks)	39.3 ± 2.4	39.8 ± 1.7	NS*
Breast feeding (%)	11.4	21.1	NS+

* Student's paired t test

+ McNemar's test

TABLE 72

RESPIRATORY STATUS

INDEX CHILDREN WITHOUT BRONCHIAL REACTIVITY (n = 123)

	Index	Control	p Value
"Tendency" to cough (%)			
At any time	33.6	13.0	<0.001*
In past year	14.0	5.8	NS *
Sputum (%)	4.9	0.8	NS *
Established bronchitis (%)	4.9	0	<0.05 *
"Tendency" to wheeze (%)			
At any time	43.9	18.7	<0.001*
In past year	8.5	0.8	<0.05 *
Established asthma (%)	2.4	3.3	NS *
Recurrent nasal blockage (%)	34.1	21.1	<0.05 *
Colds going to chest (%)	50.4	24.4	<0.001*
Hearing difficulties (%)	17.5	6.7	<0.05 *
Tonsils removed (%)	9.8	8.9	NS *
Adenoids removed (%)	15.4	13.8	NS *
Medication in past year (%)	44.7	17.1	<0.001*
Antibiotics (%)	100.0	81.8	NS *
Bronchodilators (%)	0	20.0	NS *
School absenteeism in past year (weeks)	1.6 ± 2.5	0.8 ± 1.3	<0.01 +
GP consultations for respiratory illness in past year (times)	1.6 ± 2.3	0.9 ± 1.4	<0.01 +

* McNemar's test

+ Wilcoxon test

TABLE 73

SOCIAL AND FAMILY CHARACTERISTICS
INDEX CHILDREN WITHOUT BRONCHIAL REACTIVITY (n = 123)

	Index	Control	p Value
Both parents at home (%)	82.8	87.7	NS *
First born (%)	23.6	43.1	<0.01 *
Siblings (number)	2.9 ± 1.1	2.3 ± 0.9	<0.001 +
Social class Distribution (%)			
I & II	13.0	16.3	
III	22.0	29.3	<0.05 *
IV & V	65.0	54.5	
Central heating (%)	43.9	55.3	NS *
Own bedroom (%)	26.0	35.8	NS *
Mother smoked at some time (%)	76.2	66.4	NS *
Father smoked at some time (%)	81.1	67.6	<0.05 *
Mother's age at follow-up (years)	32.5 ± 5.2	33.0 ± 5.2	NS +
Father's age at follow-up (years)	35.1 ± 6.2	34.7 ± 6.2	NS +

* McNemar's test

+ Student's paired t test

TABLE 74

ATOPIC BACKGROUND

INDEX CHILDREN WITHOUT BRONCHIAL REACTIVITY (n = 123)

	Index	Control	p Value
Personal History			
Eczema (%)	17.9	13.0	NS*
Hayfever (%)	2.4	11.4	<0.05*
Food allergy (%)	6.5	4.9	NS*
Family History			
Eczema (%)	25.2	21.1	NS*
Hayfever (%)	24.4	31.7	NS*
Food allergy (%)	17.1	12.2	NS*
Asthma (%)	55.3	47.2	NS*

* McNemar's test

TABLE 75

RESPIRATORY FUNCTION TESTS - INDEX CHILDREN WITHOUT BRONCHIAL REACTIVITY (n = 123)

	No of matched pairs	Mean Value	Mean Difference	Standard error of difference	p Value
PEFR (% predicted)					
Index	123	98.0	- 4.95	2.02	<0.05*
Control	123	103.0			
$FEV_{0.75}$ (% predicted)					
Index	123	90.4	- 3.14	1.64	NS*
Control	123	93.5			
$FEV_{1.0}$ (% predicted)					
Index	123	93.0	- 2.83	1.48	NS*
Control	123	95.8			
FVC (% predicted)					
Index	123	85.8	- 1.59	1.47	NS*
Control	123	87.4			
$FEF_{25-75\%}$ (% predicted)					
Index	123	95.1	- 6.86	3.66	NS*
Control	123	101.9			
$FEV_{1.0}/FVC$					
Index	123	0.91	- 0.009	0.009	NS*
Control	123	0.91			
R_T (Kp/l/s)					
Index	123	0.59	- 0.018	0.018	NS*
Control	123	0.60			

* Student's paired t test

It would appear that, at the age of seven, two groups of index children exist. Those with bronchial reactivity have limitation in respiratory function as well as an increased incidence of asthma; while those without evidence of hyperreactive airways have bronchitis diagnosed more frequently, but do not have abnormal respiratory function.

SECTION IV

D I S C U S S I O N

The results indicate that children who have suffered acute lower respiratory tract infections in infancy severe enough to merit hospitalisation have an increase in respiratory symptoms, an increased tendency to bronchitis and asthma, impairment of respiratory function and increased bronchial hyperreactivity when compared with case controls seven years later. This might reflect a "genetic predisposition" in our index cases, increasing susceptibility to respiratory infection as well as the subsequent development of symptoms. One might except such children to start off life with poorer lung function. In a prospective study, Colley et al. (1976) showed that children who suffered chest infections in infancy had lung function at birth (crying PEFR) comparable to those who escaped such illnesses. By the age of one, differences in crying PEFR were apparent and it is tempting to ascribe this to the direct effects of infection on airways or lung parenchyma.

Index children reported a greater tendency to cough and wheeze and this was not explained by other antecedent respiratory problems such as neonatal respiratory disease, whooping cough or pneumonia. Although measles with or without chest involvement was reported more frequently by mothers of index children, virological confirmation of the disease was lacking. Children with cough who were

prescribed antibiotics could subsequently develop a rash and be labelled as having had "measles with chest involvement". The tendency to cough and wheeze had lessened considerably by the age of seven, which is in agreement with the findings of previous workers (Sims et al., 1978; Pullan and Hey, 1982). The prevalence of asthma amongst index children in our study (8.5%) is lower than in most reported series (Eisen and Bacal, 1963; Hyde and Saed, 1966; Rooney and Williams, 1971). Boesen (1953) attempted to predict an outcome as regards wheeze in children who had suffered "asthmatoid bronchitis". Children aged under a year during their index illness had a 6% occurrence of asthma subsequently, and our findings would be in keeping with his.

We defined asthma purely on clinical grounds as "four or more episodes of wheeze requiring medical attention in the year preceding the study". The discrepancy between the prevalence of asthma and that of bronchial hyperreactivity suggests that our criteria for diagnosing asthma were too stringent. Not all children with hyperreactive bronchi wheezed in the year prior to study, whereas all those with significant clinical asthma had hyperreactive airways. We may therefore have excluded some mildly affected asthmatic children. Looked at slightly differently, 22 index cases and 9 controls had been treated with broncho-

dilators at some time during the year prior to study: none of these cases had more than mild symptoms at that time. It seems therefore, that about 10% of index cases had asthma at review.

When other types of medications were looked at, more index children had received antibiotics in the preceding year, compared to controls. Index children were also more prone to upper respiratory symptoms. Other indices of illhealth from respiratory problems such as school absenteeism and general practitioner consultations were found more frequently in index children.

It could be argued that social, family and environmental factors were the main determinants of outcome in our study. Colley and Holland (1967) reported a direct relationship between respiratory illness in young children and the number of siblings. Although our index children had more siblings statistically, the differences of 0.5 sibling could hardly have biological importance. Respiratory symptoms of parents were also reported to exert some, albeit a lesser, effect on children's respiratory symptoms (Leeder et al., 1976). We found no differences in the reporting of respiratory symptoms or illhealth in either parent of index or control children. Parental smoking habits were also similar in both groups of children.

A greater proportion of control children came from higher social classes. However, social class designation based on the occupation of the head of the household gives no extra information on parental education, standards of maternal care, family size or housing conditions which are perhaps more sensitive indicators. Housing standards were similar in index and control groups, as were the number of adults in each household. More index children had to share their bedroom with another person, and fewer were firstborn. Fewer homes of index children were centrally heated. Yarnell and St Leger (1977) found an excess of upper respiratory tract infections in children from centrally heated houses, and these children also had the worst lung function compared to children from houses where coal was used for heating. If central heating was responsible for these findings, we might expect a greater proportion of control children to report respiratory symptoms.

The difficulties of assessing the effects of social and environmental variables is further highlighted in the study by Sims et al. (1978), where children with RSV bronchiolitis in infancy were found to have diminished respiratory function when compared to controls. Their index children also came from poorer social backgrounds where overcrowding and parental smoking habits might have contributed to lower lung function. This led to the suggestion that environmental factors provided a link between respiratory infection in

infancy and subsequent respiratory illness in childhood or even adult life. Our choice of controls from the same class at the same school as the index case would eliminate some socio-economic and environmental differences between the two groups of children.

Due to the design of the study, control children were not seen until all the index cases were traced and assessed, and on average were three months older than the index children. This age difference does not fully explain the height difference between index and control children. As the weights were comparable, it could be that increased respiratory problems in the index children accounted for their smaller stature. During the index illness, about 70% of infants were adequately nourished, as judged by weights taken during admission to hospital. Only 35% of the children had their heights measured during the index illness, so that there was insufficient data to determine if index children started off by being smaller in stature. The fact that index children who remained asymptomatic were similar in height to their controls is further evidence that respiratory symptoms may have retarded growth.

Breast feeding is reported to protect against RSV infections (Downham, 1976; Evans-Jones et al., 1978). The duration of breast feeding had been shown to protect against respiratory illnesses (Cunningham, 1979). We were unable to

comment on the duration of breast feeding in index and control children, as the wide scatter of results obtained made statistical analysis impossible. Meaningful analysis was possible only by dividing children into those who had been breastfed, and those who had not. Index children had a lower incidence of breast feeding compared to their matched controls. This might have contributed to the occurrence of respiratory illness in the index children, or could merely reflect differences in feeding practices amongst social classes.

The Role of Respiratory Syncytial Virus

Comparison of index children who had suffered respiratory syncytial virus infections (RSV+) with those who had not (RSV-) did not reveal differences in clinical characteristics, atopic background or tests of respiratory function. Our findings would not, therefore, support the hypothesis of Simon and Jordan (1967) that epidemic RSV+ bronchiolitis was an infectious disease with a good prognosis, while sporadic, RSV- bronchiolitis could be a forerunner of asthma.

Our results must, however, be interpreted with caution, as we may have failed to isolate RSV in some children designated RSV-. The two groups may not be distinct, and it is quite possible that the respiratory syncytial virus was responsible for the index illness in the majority of the children.

Few other viruses were isolated, and double infection seen in only two cases. The small number of children with infections caused by viruses apart from RSV makes it difficult to draw conclusions on the part played by other viruses on the outcome of lower respiratory infections in infancy.

A large proportion of children (70.5%) had received antibiotics prior to hospital admission, making interpretation of bacteriological study difficult. Assuming that such studies were performed on children only when a bacterial cause was suspected for the respiratory infection, the yield of pathogens was still low. This could be due to prior antibiotic therapy, but does not allow meaningful comment on the role of bacteria in childhood respiratory infections.

Specific Index Illness

The clinical outcome was unaffected by the type of index illness suffered. Although asthma was reported more often in first-degree relatives of children who had bronchitis, the personal histories of all three groups of index children revealed no greater incidence of atopy than their controls. This finding would therefore not support the hypothesis that infection in childhood allergises the individual (Frick et al., 1979). Children who had bronchiolitis appeared to have the worst residual effect, in terms of

respiratory function and bronchial reactivity, only because of the large numbers involved. Children who suffered bronchitis and pneumonia showed trends towards diminished lung function, and no significant differences were shown between disease categories when a one-way analysis of variance was performed.

Subsequent Respiratory Symptoms

Index children who reported subsequent respiratory symptoms (cough or wheeze) differed from their controls as regards clinical, social and family characteristics as well as tests of respiratory function. No clear distinction existed between those who coughed and those who wheezed, suggesting that there is an overlap in these symptoms and such children may belong to a homogenous population.

Burrows and Lebowitz (1975) found that almost three quarters of children with a diagnosis of bronchitis also wheezed. Other workers (McFadden, 1975; Cloutier et al., 1981) have shown that chronic cough in children may be the primary or sole manifestation of asthma. The paediatric literature contains scanty information regarding childhood bronchitis, with no clear picture of the clinical manifestations, aetiological factors, diagnostic criteria or appropriate therapy for this condition.

The differences found between children with symptoms and their controls are not explained by differences in the atopic background or social conditions. As the asymptomatic children tended to come from poorer social backgrounds, this would suggest that social factors may not be solely responsible for the increase in symptoms found in the index group as a whole.

Although the asymptomatic index children did not have abnormal lung function, bronchial reactivity was present in excess (33% compared with 26% controls) and could be the result of an acute infection in infancy.

Atopy and Bronchial Reactivity

Previous workers reported an increased incidence of atopic disorders amongst children who had suffered from bronchiolitis, with a higher incidence of atopy amongst first-degree relatives (Wittig et al., 1959; Eisen and Bacal, 1963; Hyde and Saed, 1966; Zweiman et al., 1971; Rooney and Williams, 1971). However, no controls were used in these studies. This case-control study revealed no differences in the personal or family histories of atopic disorders between index and control children. Index children with a history of atopy had more respiratory symptoms, diminished ventilatory function and hyperreactive airways when compared with their controls; while non-atopic index children appeared to compare favourably with their controls

in terms of respiratory symptom and function. It can be argued that the use of history alone is not a sensitive indicator of atopy. Skin tests, measurements of eosinophils, IgE or other more sophisticated tests were considered invasive (and therefore unjustified) in symptom-free control children.

Bronchial reactivity was present in excess in both atopic and non-atopic index cases, although statistical significance was demonstrated in the atopic group only. This would imply that atopy is not the sole determinant of outcome. Children with bronchial hyperreactivity, on the other hand, had atopic backgrounds similar to non-reactive children and no different from controls. This observation suggests that atopy may not be related to bronchial reactivity, and confirms the work of Sims et al. (1981).

Frick et al. (1979) postulated that viral infections could cause bronchial reactivity in atopic individuals, and the findings of positive skin tests in babies admitted to hospital with bronchiolitis would support that hypothesis (Laing et al., 1982). Abnormal lymphocyte responses in releasing chemical mediators were identified as mechanisms by which viral infections caused wheezing (Welliver et al., 1979, 1981). Such a genetic predisposition might explain the association of family history

of atopy and recurrent wheezing following RSV bronchiolitis. Other workers demonstrated hyperreactive airways in children following bronchiolitis (Sims et al., 1978; Gurwitz et al., 1981; Pullan and Hey, 1982). Bronchial reactivity has been demonstrated in a variety of respiratory disorders, being pathognomonic in asthma but also found to a lesser extent in cystic fibrosis (Mellis and Levison, 1978) and croup (Loughlin and Taussig, 1979). It has been reported following surgery for tracheo-eosophageal fistula (Milligan and Levison, 1979); ventilation for idiopathic respiratory distress syndrome (Smyth et al., 1981); a past history of inhaled foreign body (Givan et al., 1981) and near-drowning (Laughlin and Eigen, 1982). All these reports suggest that infection as well as pulmonary insult can cause damage and lead to bronchial reactivity.

The question posed is whether ventilatory dysfunction is paralleled by an increase in bronchial reactivity. Flow variables at rest were related to the post-exercise fall in PEFR, and an inverse relationship was seen between resting respiratory function and bronchial reactivity. In other words, children with low respiratory function at rest experienced greater bronchoconstriction following exercise. It is not clear, however, which is of primary importance, or indeed if there is a cause-and-effect relationship between ventilatory dysfunction and bronchial reactivity. These abnormalities could have predated the

acute respiratory infection, and even predispose susceptible children to the infection. Equally, they may have been the result of the infection. The data so far does not permit these questions to be answered.

The relationship of lower respiratory tract infections in infancy to respiratory symptoms and function later in childhood or even adult life may be due to anatomic changes induced by the early infections, as well as to immunological events. Host differences, genetic factors or environmental influences may predispose to the development of lower respiratory infections, atopy and chronic lung disease either by themselves or in some combination.

We have demonstrated an increase in respiratory symptoms and impaired respiratory function seven years following acute lower respiratory tract infections in infancy. Although our index and control populations were not closely matched for some social and family factors, the findings could not be attributed solely to social and environmental differences. Though available evidence is inconclusive, infection of the respiratory tract during a vulnerable period of lung growth in infancy may cause direct injury or induce changes that lead to increased symptoms with impairment of lung function. Whether such children ultimately outgrow their respiratory symptoms with full functional recovery, or whether they become more vulnerable

to the effects of environmental factors such as smoking and atmospheric pollution as they grow older is not known. This study emphasises the need for more longitudinal studies into adult life to trace the clinical course of chest infections in early childhood.

1. Children who suffered acute lower respiratory tract infection in infancy severe enough to merit hospitalisation have an increase in respiratory symptoms, established bronchitis and asthma; impairment of respiratory function; and bronchial hyperreactivity when compared to matched controls seven years later.

2. Index children who had respiratory syncytial virus infections (RSV+) showed similar clinical characteristics, social background and atopic histories to those who did not have respiratory syncytial virus infections (RSV-). Tests of respiratory function and the response to exercise were comparable in RSV+ and RSV- index cases.

3. Clinical outcome was not influenced by the type of index illness suffered. Differences within a disease category were greater than those between disease categories. Tests of respiratory function were reduced in all three subgroups of index children, although statistical significance was demonstrated only in the bronchiolitis subgroup.

4. Children who wheezed subsequent to the index illness showed similar clinical characteristics, social, family and atopic backgrounds to those who coughed. Both groups

of symptomatic index children differed from their controls in these respects. Lung function was abnormal, and there was evidence of hyperreactive airways.

5. Index children who remained asymptomatic following their illness did not differ clinically from their controls. Although tests of respiratory function were also comparable, bronchial reactivity was present in excess even in asymptomatic index children.

6. Social factors were less favourable in the asymptomatic index children, implying that differences in outcome seen between the index and control populations as a whole were not totally related to differences in social backgrounds.

7. A positive history of atopic disorders in either the child or first-degree relatives gave rise to increased respiratory symptoms and diminished respiratory function. Bronchial reactivity was present also in non-atopic index children, suggesting that atopy is not the sole determinant of outcome.

8. On the basis of bronchial reactivity, two populations were identified amongst the index children - one with asthma and the other, bronchitis. Atopy was not related to bronchial reactivity.

9. Ventilatory dysfunction paralleled bronchial reactivity. It is not clear which is of primary importance, or if there is any cause-and-effect relationship between the two.

10. Acute respiratory infection may have caused both these abnormalities; or they could have predated the event, rendering children more susceptible to infection.

SECTION VI

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SECTION VII

A P P E N D I X

ROYAL HOSPITAL FOR SICK CHILDREN

SCIENNES ROAD EDINBURGH,

EH9 1LF

Telephone: 031-667 1991

Dear Mr and Mrs .....

Several years ago, your child ..... was admitted to the Royal Hospital for Sick Children with a chest infection. We have been reviewing children recently with similar illnesses to find out whether they have had further chest problems. We have also been carrying out breathing tests on these children which could not be done at a younger age when they were less cooperative. The tests tell how forcefully each child can blow, and the changes which occur after exercise.

We would like to include ..... in our follow-up study. This would involve attending one of our-patient clinics where you would be asked some simple questions regarding ..... general health and that of the rest of your family. He/she will then be examined and the breathing tests carried out. No jags are involved.

We would greatly appreciate your cooperation as this study has been planned with a view to the possible prevention of severe chest infections in babies of the future. The whole session will last approximately two hours and we shall be pleased to repay your travelling expenses to and from the clinic.

Yours sincerely

Dr Hamish Simpson
Consultant Paediatrician

Dr Jacqueline Mok
Research Fellow

Name of Child: ..... Ref No: .....

Correct Address: ..... Tel No: .....

.....

Name and Address of School your child attends: .....

.....

I am / am not* willing to allow my Child to participate in the follow-up study.

I would prefer a morning / afternoon* appointment.

Signature of Parent / Guardian* ..... Date: .....

* Delete as appropriate

APPENDIX 2

ROYAL HOSPITAL FOR SICK CHILDREN

SCIENNES ROAD EDINBURGH,

EH9 1LF

Telephone: 031-667 1991

The Headmaster/Headmistress,

Dear Sir/Madam,

We are in receipt of a grant from the National Chest, Heart and Stroke Association to carry out a survey on children who have suffered chest infections in the first year of life. Our cases have been carefully selected and, in order to interpret our results, we propose to study a control group of normal children from the same class in school as our cases.

The Divisional Education Officer from the Lothian Regional Council has approved the project and granted us permission to approach head teachers regarding the selection of control children. We would be grateful if you could supply us with four names and addresses of children of the same sex, age (to within three months) and approximate height as the child named on the accompanying sheet. Permission will then be sought from the parents of these children. We enclose a copy of the letter we will be sending to parents.

If you have any queries regarding the project, we would be most grateful if you would contact either of us at 667 1991, extension 204, any weekday morning.

Thank you for your cooperation.

Yours sincerely,

Dr. Hamish Simpson, Consultant Paediatrician.

Dr. Jacqueline Mok, Research Fellow.

Name of Case: ..... Ref. No: .....

Date of Birth: ..... Height: .....

Address: .....

.....

.....

"Control Children"

1. Name: .....

Date of Birth: ..... Height: .....

Address: .....

.....

.....

2. Name: .....

Date of Birth: ..... Height: .....

Address: .....

.....

.....

3. Name: .....

Date of Birth: ..... Height: .....

Address: .....

.....

.....

4. Name: .....

Date of Birth: ..... Height: .....

Address: .....

.....

.....

APPENDIX 4

ROYAL HOSPITAL FOR SICK CHILDREN

SCIENNES ROAD EDINBURGH,

EH9 1LF

Telephone: 031-667 1991

Dear Mr / Mrs .....

We are at present reviewing a large number of children who were admitted to the Royal Hospital for Sick Children in Edinburgh with severe chest infections in the first year of life, to find out if they have developed further chest problems. This is an important study which we hope will lead to improved methods of preventing chest infections in young babies. It has the full support of the National Chest, Heart and Stroke Association.

In order to evaluate our findings, it is essential that we also have information about children who did not have chest infections in the first year of life. For each child in our study group, we have chosen for comparison another child in the same class at school. Your child is one of those chosen, and we would greatly appreciate your permission to include him / her in our survey.

If you are agreeable, this would involve attending one of our out-patient clinics when you would be asked some simple questions regarding ..... general health and that of the rest of your family. We would then examine his / her chest and carry out some breathing tests, which show how the lungs work. No jags are involved. The whole session will last approximately two hours. We shall be pleased to repay your travelling expenses to and from the clinic.

We would greatly appreciate your cooperation and request that you return the enclosed slip in the envelope provided. Should you agree to participate in the study, an appointment will be sent to you in the near future.

Yours sincerely

Dr Hamish Simpson
Consultant Paediatrician

Dr Jacqueline Mok
Research Fellow

APPENDIX 5

ROYAL HOSPITAL FOR SICK CHILDREN

SCIENNES ROAD EDINBURGH,

EH9 1LF

Telephone: 031-667 1991

Name of Child: .....

Ref No: .....

Correct Address: .....

.....

Tel No (if any): .....

Please tick the appropriate:

1. I am willing to allow my Child to participate in the survey.
2. I am unwilling to allow my Child to participate in the survey.
3. My Child was admitted to another hospital with a chest infection in the first year of life and is therefore not eligible for the survey.

If you have ticked 1. please indicate:

I would prefer a morning / afternoon* appointment. (delete as appropriate)

..... Date: .....

Signature of Parent / Guardian

APPENDIX 6

ROYAL HOSPITAL FOR SICK CHILDREN

SCIENNES ROAD EDINBURGH,

EH9 1LF

Telephone: 031-667 1991

PATIENT

Dear Dr.

Follow-up study of children with lower respiratory tract infection in infancy

re: , ... Ref No: . . . .

. . . . . .

. . . . . .

The above-named child has been included in a follow-up study which we are at present conducting in children six years after pneumonia or bronchiolitis in infancy. This project is being supported by the Chest, Heart and Stroke Association and has the approval of local Hospital and General Practitioner committees.

When we saw . . . . . recently, his/her mother mentioned that he/she had had no respiratory illnesses of note since the index illness on . . . . . We would be most grateful if you would confirm from your records that this is indeed so and indicate in the space below. If, on the other hand, he/she has had respiratory problems since the index illness which have required your attention, we would be grateful for your permission to peruse the records some time at your convenience. A stamped addressed envelope is enclosed for the return of this letter.

We look forward to hearing from you in due course.

Yours sincerely,

Hamish Simpson, Consultant Paediatrician.

Jacqueline Mok, Research Fellow.

The above child has/has not* had any respiratory illnesses of note since the index illness.

I agree/do not agree* to the case records being perused. (if there have been respiratory problems)

(* Delete as necessary)

. . . . . .

General Practitioner.

APPENDIX 7

ROYAL HOSPITAL FOR SICK CHILDREN

SCIENNES ROAD EDINBURGH,

EH9 1LF

Telephone: 031-667 1991

CONTROL

Dear Dr.

Follow-up study of children with lower respiratory tract infection in infancy

re: . . . . . Ref No: . . . .

. . . . . .

. . . . . .

The above-named child has been included as a control in a follow-up study which we are at present conducting in children six years after pneumonia or bronchiolitis in infancy. This project is being supported by the Chest, Heart and Stroke Association and has the approval of local Hospital and General Practitioner committees.

When we saw . . . . . recently, his/her mother mentioned that he/she had had no respiratory illnesses of note since early infancy. We would be most grateful if you would confirm from your records that this is indeed so and indicate in the space below. A stamped addressed envelope is enclosed for the return of this letter. If, on the other hand, he/she has had respiratory problems which have required your attention, we would be grateful for your permission to peruse the records some time at your convenience.

We look forward to hearing from you in due course.

Yours sincerely,

Hamish Simpson, Consultant Paediatrician.

Jacqueline Mok, Research Fellow.

The above child has/has not* had any respiratory illnesses of note since early infancy.

I agree/do not agree* to the case records being perused. (if there have been respiratory problems)

(* Delete as necessary)

. . . . . .

General Practitioner.

APPENDIX 8

ROYAL HOSPITAL FOR SICK CHILDREN

SCIENNES ROAD EDINBURGH,

EH9 1LF

Telephone: 031-667 1991

PATIENT

Dear Dr.

Follow-up study of children with lower respiratory tract infection in infancy

re: . . . . . Ref No: . . . .

. . . . . .

. . . . . .

The above-named child has been included in a follow-up study which we are at present conducting in children six years after pneumonia or bronchiolitis in infancy. This project is being supported by the Chest, Heart and Stroke Association and has the approval of local Hospital and General Practitioner committees.

When we saw . . . . . recently, his/her mother mentioned that the child has required medical attention from you on a number of occasions in the past because of recurrent respiratory problems. We would be most grateful for your permission to peruse the child's records. Would you indicate your approval or otherwise in the space below and return this letter in the stamped addressed envelope provided. We would then arrange for the records to be reviewed at your surgery at a time convenient to you.

We look forward to hearing from you in the near future.

Yours sincerely,

Hamish Simpson, Consultant Paediatrician.

Jacqueline Mok, Research Fellow.

I agree/do not agree* to the case records being perused.

(* Delete as appropriate)

. . . . . .

General Practitioner.

APPENDIX 9

ROYAL HOSPITAL FOR SICK CHILDREN

SCIENNES ROAD EDINBURGH,

EH9 1LF

Telephone: 031-667 1991

CONTROL

Dear Dr.

Follow-up study of children with lower respiratory tract infection in infancy

re: . . . . . Ref No: . . . .

. . . . . .

. . . . . .

The above-named child has been included as a control in a follow-up study which we are at present conducting in children six years after pneumonia or bronchiolitis in infancy. This project is being supported by the Chest, Heart and Stroke Association and has the approval of local Hospital and General Practitioner committees.

When we saw . . . . . recently, his/her mother mentioned that the child has required medical attention from you on a number of occasions in the past because of recurrent respiratory problems. We would be most grateful for your permission to peruse the child's records. Would you indicate your approval or otherwise in the space below and return this letter in the stamped addressed envelope provided. We would then arrange for the records to be reviewed at your surgery at a time convenient to you.

We look forward to hearing from you in the near future.

Yours Sincerely,

Hamish Simpson, Consultant Paediatrician.

Jacqueline Mok, Research Fellow.

I agree/do not agree* to the case records being perused.

(*Delete as appropriate)

. . . . . .

General Practitioner.

REGRESSION EQUATIONS

SPIROMETRY (Cotes, 1979)

$FEV_{0.75}$ (1)

M $= 0.780\ h\ (m)^{2.67}$

F $= 0.744\ h\ (m)^{2.66}$

$FEV_{1.0}$ (1)

M $= 0.812\ h\ (m)^{2.77}$

F $= 0.788\ h\ (m)^{2.73}$

VC (1)

M $= 1.004\ h\ (m)^{2.72}$

F $= 0.946\ h\ (m)^{2.61}$

$FEF_{25-75\%}$ (l/min)

M & F $= -207.7 + 2.621\ h\ (cm)$

MEFV CURVES (Simpson, unpublished data)

$FEV_{1.0}$ (l/min)

Air $= -3.7163 + 0.04121\ h\ (cm)$

He/O_2 $= -3.6752 + 0.04121\ h\ (cm)$

FVC (1)

Air $= -4.0017 + 0.04514\ h\ (cm)$

He/O_2 $= -4.0540 + 0.04514\ h\ (cm)$

$\dot{V}_{50}$ (l/min)

Air $= -268.5206 + 3.1819\ h\ (cm)$

He/O_2 $= -239.3804 + 3.1819\ h\ (cm)$

$\dot{V}_{25}$ (l/min)

Air = -181.4013 + 1.8998 h (cm)

He/O_2 = -165.2114 + 1.8998 h (cm)

PEFR (l/min) (Cotes, 1979)

M & F = (-5.53 + 7.59 h (m) 60

KEY:

h = height

m = metres

cm = centimetres

FOLLOW-UP STUDY OF CHILDREN WITH ACUTE LOWER RESPIRATORY TRACT INFECTION IN INFANCY

SURNAME

FORENAMES

Coding:

1 = Yes
2 = No
9 = Not known
8 = Not applicable

Unless otherwise coded

PATIENT NUMBER	1-3		1-3	
RECORD NUMBER	4,5	0 1	4,5	0 1
SEX 1. Male 2. Female	6		6	
DATE OF BIRTH	7-12		7-12	
RACE	13		13	

RACE

1. Caucasian
2. African/West Indian
3. Asiatic
4. Mixed
5. Other, specify .....

ADDRESS

GENERAL PRACTITIONER

Name:

Address:

HOSPITAL INDEX NUMBER				
DATE OF INDEX ILLNESS	14-19		14-19	
DATE OF STUDY	20-25		20-25	

THE INDEX ILLNESS

DIAGNOSTIC CODE

1. Bronchitis
2. Bronchiolitis
3. Pneumonia

26 ☐ 26 ☐

PATIENT GROUP

1. RSV +ve
2. RSV -ve
3. Control

27 ☐ 27 ☐

OTHER VIRUSES ISOLATED 28 ☐ 28 ☐

If Yes:

Parainfluenza 1	29 ☐	29 ☐
Parainfluenza 3	30 ☐	30 ☐
Adenovirus	31 ☐	31 ☐
Rhinovirus	32 ☐	32 ☐
Others, specify	33 ☐	33 ☐

WEIGHT DURING ADMISSION (Kg)

34,35 ☐☐ centile 34,35 ☐☐

HEIGHT DURING ADMISSION (cm)

36,37 ☐☐ centile 36,37 ☐☐

BLOOD GASES DONE

38 ☐ 38 ☐

MECHANICAL VENTILATION

39 ☐ 39 ☐

ANTIBIOTICS

Prior to admission 40 ☐ 40 ☐

During admission 41 ☐ 41 ☐

Patient No:

.....

BACTERIOLOGY

BLOOD CULTURE:
1. Positive pathogen
2. Positive contaminant
3. Negative
4. Not done

42 ☐ 42 ☐

BRONCHIAL SECRETIONS:
1. Positive pathogen
2. Positive commensal
3. Negative
4. Not done

43 ☐ 43 ☐

SPUTUM:
1. Positive pathogen
2. Positive commensal
3. Negative
4. Not done

44 ☐ 44 ☐

"POSITIVE PATHOGEN":

H. influenza	45 ☐	45 ☐
Pneumococcus	46 ☐	46 ☐
Strept. pyogenes	47 ☐	47 ☐
Staph. aureus	48 ☐	48 ☐
E. coli	49 ☐	49 ☐
Others, specify _____	50 ☐	50 ☐

THE CHILD

BIRTH WEIGHT (lbs oz) 51-54 ☐☐☐☐ gms 51-54 ☐☐☐☐

GESTATIONAL AGE 55,56 ☐☐ weeks 55,56 ☐☐

INFANT FEEDING

1. Breast fed < 1/12
2. Breast fed 1-3/12
3. Breast fed > 3/12
4. Bottle fed from outset
5. Mixture of breast and bottle from outset
6. Not known 57 ☐ 57 ☐

IMMUNISATION (prior to index illness)

Dip/Tet/Pert	58 ☐	58 ☐
Dip/Tet only	59 ☐	59 ☐
OPV	60 ☐	60 ☐
Measles	61 ☐	61 ☐
Other, specify	62 ☐	62 ☐

	1-3	4,5		1-3	4,5	
RESPIRATORY ILLNESS	☐☐☐	0	2	☐☐☐	0	2
Did he/she have breathing problems within a week of birth?	6 ☐			6 ☐		
If Yes, did he/she require assistance with breathing as a result of these problems?	7 ☐			7 ☐		
If he/she did have assistance with breathing, was this 1. CPAP 2. IPPV 3. Both	8 ☐			8 ☐		
Has he/she had whooping cough (or an illness with bouts of coughing, at the end of which he/she vomited or made a noise that sounded like a whoop)?	9 ☐			9 ☐		
If Yes, how old was he/she during the illness?	10,11 ☐☐ months			10,11 ☐☐		
Has he/she had measles?	12 ☐			12 ☐		
If Yes, how old was he/she during the illness?	13,14 ☐☐ months			13,14 ☐☐		

Was he/she chesty during the illness?	15	☐	15 ☐
Has he/she had chickenpox?	16	☐	16 ☐
If Yes, how old was he/she during the illness?	17,18	☐☐ months	17,18 ☐☐
Was he/she chesty during the illness?	19	☐	19 ☐
Has he/she had pneumonia ? (Other than index illness)	20	☐	20 ☐
If Yes, how old was he/she during the first attack, apart from the index illness?	21,22	☐☐ months	21,22 ☐☐
How many times has he/she had pneumonia, excluding the index illness?	23	☐	23 ☐
Has he/she had pulmonary tuberculosis?	24	☐	24 ☐
Has he/she had any other chest problems?	25	☐	25 ☐
If yes, was this chest injury	26	☐	26 ☐
chest operation	27	☐	27 ☐
chest tumour	28	☐	28 ☐
other, specify	29	☐	29 ☐

RESPIRATORY SYMPTOMS

COUGH

Since the index illness, has he/she had a tendency to cough first thing in the morning or during the night in the winter?		☐
Does he/she usually cough during the day in the winter?		☐
If Yes to the above, does he/she cough like this on most days for as much as three months each year?		☐
COUGH CONFIRMED	30	☐ 30 ☐

In the year following the index illness, how many episodes of cough did he/she have?	31,32 ☐☐	31,32 ☐☐
In the past year, how many episodes of cough has he/she had?	33 ☐☐	33 ☐☐
Is this tendency to cough 1. Getting better 2. Getting worse 3. Staying much the same	34 ☐	34 ☐
Did he/she have this tendency to cough prior to the index illness?	35 ☐	35 ☐

SPUTUM

Since the index illness, has he/she had a tendency to bring up phlegm (spit) from the chest first thing in the morning - or at night - during the winter?	☐	☐
Does he/she usually bring up any phlegm from the chest during the day in the winter?	☐	☐
If Yes to the preceding two questions, does he/she bring up phlegm like this on most days for as much as three months each year?	☐	☐
SPUTUM CONFIRMED	36 ☐	36 ☐
Is this tendency to bring up phlegm: 1. Getting better 2. Getting worse 3. Staying much the same	37 ☐	37 ☐

WHEEZE

Does his/her chest ever sound wheezy or whistling?	38 ☐	38 ☐
If Yes, did this start 1. Before the index illness 2. After the index illness 3. Same time as index illness	39 ☐	39 ☐
Does he/she get this on most days or nights, regardless of the time of year?	40 ☐	40 ☐

If No, is the wheeze worse:
1. In summer
2. In spring
3. In autumn
4. In winter

41 ☐ 41 ☐

Has he/she ever had attacks of shortness of breath with wheezing?

42 ☐ 42 ☐

If Yes, is his/her breathing absolutely normal between attacks?

43 ☐ 43 ☐

In the year following the index illness, how many episodes of wheeze did he/she have?

44,45 ☐☐ 44,45 ☐☐

In the past year, how many episodes of wheeze has he/she had?

46,47 ☐☐ 46,47 ☐☐

Is this wheezing tendency:
1. Getting better
2. Getting worse
3. Staying much the same

48 ☐ 48 ☐

BREATHLESSNESS

Is he/she troubled by shortness of breath during active play (eg hopping, running, skipping)? ☐

If Yes, does he/she get short of breath when walking with children his/her own age on level ground? ☐

If Yes, does he/she have to stop for breath when walking at his/her own pace on level ground? ☐

BREATHLESSNESS CONFIRMED 49 ☐ 49 ☐

UPPER RESPIRATORY SYMPTOMS

Does he/she have a blocked or running nose on most days of the year? 50 ☐ 50 ☐

Does he/she snore at night, on most nights of the year? 51 ☐ 51 ☐

How often does he/she get a cold per year? 52 ☐ 52 ☐

Do his/her colds usually go to his/her chest? 53 ☐ 53 ☐

How often does he/she get earache per year? 54 ☐ 54 ☐

How often does he/she suffer from a running ear per year? 55 ☐ 55 ☐

Has he/she ever had difficulties with hearing? 56 ☐ 56 ☐

If Yes, comment: .....

How often does he/she get a sore throat per year? 57 ☐ 57 ☐

Has he/she had his/her tonsils removed? 58 ☐ 58 ☐

Has he/she had his/her adenoids removed? 59 ☐ 59 ☐

MEDICATION

In the last year, has he/she been on medications for chest problems?
1. Yes - all the time
2. Yes - intermittently
3. No 60 ☐ 60 ☐

If Yes, is this Bronchodilators 61 ☐ 61 ☐
Antibiotics 62 ☐ 62 ☐
Steroids 63 ☐ 63 ☐

SCHOOL ABSENTEEISM

In the last year, how many weeks has he/she been kept off school because of colds, coughs or other chest problems? 64,65 ☐☐ weeks 64,65 ☐☐

GP CONSULTATIONS

In the last year, how often have you had to get your own doctor because of his/her colds, coughs or other chest problems? 66,67 ☐☐ times 66,67 ☐☐

HOSPITAL ADMISSIONS

In the last year, how many times has he/she been admitted to hospital because of colds, coughs, wheeze, pneumonia or other chest problems? 68,69 ☐☐ 68,69 ☐☐

Which hospital? When?

NON-RESPIRATORY ILLNESS

Does he/she suffer from any other illness?

If Yes, specify .....

Illness involves:
1. Cardiovascular system
2. Gastrointestinal system
3. Central nervous system
4. Musculo skeletal system
5. Haematological system
6. Genito urinary system
7. Endocrine system
8. No other illness 70 ☐ 70 ☐

SOCIAL INFORMATION

HEAD OF HOUSEHOLD

1. Father
2. Mother
3. Other, specify: ..... 71 ☐ 71 ☐

OCCUPATION OF HEAD OF HOUSEHOLD
(main life-time occupation)

Job title:

Job description:

Industry/organisation:

Status: Self-employed > 25 employees
Self-employed < 25 employees
Self employed without employees
Manager of > 25 people
Manager of < 25 people
Foreman
Other employee

	1-3		
	4,5	0	3

	1-3		
	4,5	0	3

EMPLOYED AT PRESENT 6 ☐ 6 ☐

SOCIAL CLASS 7 ☐ 7 ☐

SOCIO-ECONOMIC GROUP 8,9 ☐☐ 8,9 ☐☐

HOUSING

1. Tenement/Flat
2. Terraced house/maisonette
3. Semi-detached
4. Detached
5. Institution
6. Other, specify: ..... 10 ☐ 10 ☐

GARDEN 11 ☐ 11 ☐

HOW MANY MOVES IN THE LAST FIVE YEARS? 12 ☐ 12 ☐

NUMBER OF ROOMS IN DWELLING UNIT
(excluding bathroom, kitchen and lavatory) 13 ☐ 13 ☐

NUMBER OF ADULTS IN DWELLING UNIT 14,15 ☐☐ 14,15 ☐☐

PLACE OF CHILD IN FAMILY 16,17 ☐☐ 16,17 ☐☐

NO OF CHILDREN IN DWELLING UNIT 18,19 ☐☐ 18,19 ☐☐

HEATING

Central Heating 20 ☐ 20 ☐

Main fuel in living room:

1. Electricity
2. Gas
3. Oil
4. Coal
5. Paraffin
6. None
7. Other, specify: ..... 21 ☐ 21 ☐

CHILD'S ROOM (in last year)

1. Own
2. Shared with parent(s)
3. Shared with sibling(s)
4. Shared with grandparent(s)
5. Shared with other adult(s)
6. Shared with other child(ren) — 22 ☐ — 22 ☐

If shared, is this with a person with bronchitis or chest trouble? — 23 ☐ — 23 ☐

ANIMALS/PETS AT HOME

1. Dog
2. Cat
3. Bird(s)
4. More than one type
5. Other, specify: ..... — 24 ☐ — 24 ☐

RESIDENT PARENTS (at follow-up)

1. Both parents resident
2. Mother only
3. Father only
4. Mother/father and other partner — 25 ☐ — 25 ☐

DAY TIME CARE OF CHILD

Nursery school
1. Yes, full-time
2. Yes, part-time
3. No — 26 ☐ — 26 ☐

If Yes, age at entry — 27,28 ☐☐ months — 27,28 ☐☐
period spent — 29,30 ☐☐ months — 29,30 ☐☐

Child minding
1. Yes, full-time
2. Yes, part-time
3. No — 31 ☐ — 31 ☐

If Yes, age when begun — 32,33 ☐☐ months — 32,33 ☐☐
period spent — 34,35 ☐☐ months — 34,35 ☐☐

Foster home — 36 ☐ — 36 ☐

If Yes, age when fostered — 37,38 ☐☐ months — 37,38 ☐☐
period spent — 39,40 ☐☐ months — 39,40 ☐☐

HAS CHILD EVER BEEN IN RESIDENTIAL CARE? 41 ☐ 41 ☐

If Yes, age when taken into care 42,43 ☐☐ months 42,43 ☐☐

period spent 44,45 ☐☐ months 44,45 ☐☐

SMOKING HABITS IN THE HOME

MOTHER: No of cigarettes smoked per day in first year of child's life? 46,47 ☐☐ 46,47 ☐☐

No of cigarettes smoked per day in last year. 48,49 ☐☐ 48,49 ☐☐

TOTAL NUMBER OF SMOKERS AT HOME:

During first year of child's life 50 ☐ 50 ☐

During the last year? 51 ☐ 51 ☐

"FATHER'S" HEALTH

Relationship to child:
1. Father
2. Step-father
3. Adoptive father
4. Foster father
5. Guardian
6. Other, specify: .....

52 ☐ 52 ☐

Age: 53,54 ☐☐ years 53,54 ☐☐

Do you usually cough first thing in the morning in the winter? ☐

Do you usually cough during the day or at night in the winter? ☐

If Yes to the above, do you cough like this on most days for as much as three months per year? ☐

COUGH CONFIRMED 55 ☐ 55 ☐

Do you usually bring up any phlegm (spit) from your chest first thing in the morning in the winter? ☐

Do you usually bring up any phlegm from your chest during the day or at night in the winter? ☐

If Yes to the preceding two questions, do you bring up any phlegm like this on most days for as much as three months each year? ☐

SPUTUM CONFIRMED 56 ☐ 56 ☐

Does your chest ever sound wheezy or whistling? 57 ☐ 57 ☐

If Yes, do you get this on most days or nights? 58 ☐ 58 ☐

Do you/did you ever smoke? 59 ☐ 59 ☐

If Yes, how many cigarettes per day? 60,61 ☐☐ 60,61 ☐☐

How many ounces of tobacco per week? 62 ☐ 62 ☐

How many cigars per week? (Large) 63,64 ☐☐ 63,64 ☐☐
(Small) 65,66 ☐☐ 65,66 ☐☐

Have you ever smoked as much as one cigarette per day or an ounce of tobacco per month for as long as a year? 67 ☐ 67 ☐

For ex-smokers, when did you last smoke regularly? 68,69 ☐☐ months 68,69 ☐☐

For current smokers, have your smoking habits in the last five years
1. Stayed the same
2. Increased
3. Decreased 70 ☐ 70 ☐

In the last three years, have you had a chest illness which has kept you off work, indoors or in bed for as much as a week? 71 ☐ 71 ☐

Do you suffer any other illnesses, apart from chest problems?
1. Yes - cardiovascular system
2. Yes - gastrointestinal system
3. Yes - central nervous system
4. Yes - musculo skeletal system
5. Yes - haematological system
6. Yes - genitourinary system
7. Yes - endocrine system
8. Yes - psychiatric
9. No 72 ☐ 72 ☐

Describe Illness: .....

.....

"MOTHER'S" HEALTH

1-3 ☐☐☐ 1-3 ☐☐☐
4,5 0 4 4,5 0 4

Relationship to child:
1. Mother
2. Step-mother
3. Adoptive mother
4. Foster mother
5. Guardian
6. Other, specify ..... 6 ☐ 6 ☐

Age: 7,8 ☐☐ years 7,8 ☐☐

Employment:
1. Housewife
2. Working part-time
3. Working full-time 9 ☐ 9 ☐

Since the child was born, have you:
1. Worked continuously
2. Worked intermittently
3. Not worked at all 10 ☐ 10 ☐

If you worked since the child was born, how old was he/she when you went back to work? 11,12 ☐☐ months 11,12 ☐☐

Do you usually cough first thing in the morning in the winter? ☐

Do you usually cough during the day or at night in the winter? ☐

If Yes to the above, do you cough like this on most days for as much as three months per year? ☐

COUGH CONFIRMED 13 ☐ 13 ☐

Do you usually bring up any phlegm (spit) from your chest first thing in the morning in the winter? ☐

Do you usually bring up any phlegm from your chest during the day or at night in the winter? ☐

If Yes to the preceding two questions, do you bring up any phlegm like this on most days for as much as three months each year ? ☐

SPUTUM CONFIRMED	14	☐	14 ☐
Does your chest ever sound wheezy or whistling?	15	☐	15 ☐
If Yes, do you get this on most days or nights?	16	☐	16 ☐
Do you/did you ever smoke?	17	☐	17 ☐
If Yes - how many cigarettes per day?	18,19	☐☐	18,19 ☐☐
How many ounces of tobacco per week?	20	☐	20 ☐
How many cigars per week? (large)	21,22	☐☐	21,22 ☐☐
(small)	23,24	☐☐	23,24 ☐☐
Have you ever smoked as much as one cigarette per day or an ounce of tobacco per month for as long as a year?	25	☐	25 ☐
For ex-smokers - When did you last smoke regularly?	26,27	☐☐ months	26,27 ☐☐
For current smokers - Have your smoking habits in the last five years: 1. Stayed the same 2. Increased 3. Decreased	28	☐	28 ☐
In the past three years, have you had a chest illness which has kept you off work, indoors or in bed for as much as a week?	29	☐	29 ☐
Do you suffer any other illnesses, **apart** from chest problems? 1. Yes - cardiovascular system 2. Yes - gastrointestinal system 3. Yes - central nervous system 4. Yes - musculo skeletal system 5. Yes - haematological system 6. Yes - genitourinary system 7. Yes - endocrine system 8. Yes - psychiatric 9. No	30	☐	30 ☐

Describe illness: .....

OPIC STATUS

Family Tree

First degree relatives

Pedigree Number	Living/Dead	Total
I		
II		
III		

Total number of first degree relatives: 31,32 ☐☐ 31,32 ☐☐

Eczema

Do any of the family listed above suffer from a condition where the skin is rough, chapped and dry, with red itchy areas that sometimes crack or weep?

Yes No Not Known

Pedigree No:

TOTAL NUMBER OF FIRST DEGREE RELATIVES WITH ECZEMA 33,34 ☐☐ 33,34 ☐☐

HAYFEVER/ALLERGIC RHINITIS

Do any of the family listed above usually sneeze, or have a runny nose in the presence of flowers, grass or dust?

Yes No Not Known

Pedigree No:

TOTAL NUMBER WITH HAYFEVER/RHINITIS 35,36 ☐☐ 35,36 ☐☐

RECURRENT RHINITIS

Do any of the family listed above usually have a blocked or runny nose on most days of the year?

Yes No Not Known

Pedigree No:

TOTAL NUMBER WITH RECURRENT RHINITIS 37,38 ☐☐ 37,38 ☐☐

FOOD ALLERGY

Is any of the family listed above "allergic" to any particular food, so that eating it makes him/her develop a rash or hives; have diarrhoea and vomiting, or wheeze?

Yes No Not Known

Pedigree No:

TOTAL NUMBER WITH FOOD ALLERGY 39,40 ☐☐ 39,40 ☐☐

ASTHMA

Do any of the family listed above, excluding the child, suffer from recurrent episodes of wheeze or whistling breathing, that resolve spontaneously or at times may require relief with medicines?

Yes No Not Known

Pedigree No:

TOTAL NUMBER WITH ASTHMA 41,42 ☐☐ 41,42 ☐☐

RECORDS

NAME OF CHILD

NHS NO

ADDRESS

GENERAL PRACTITIONER

ESTABLISHED RESPIRATORY DISORDER

Asthma/wheezy bronchitis	43	43
Recurrent bronchitis	44	44
Bronchiectasis	45	45
Recurrent URT sepsis	46	46

NO OF EPISODES OF RESPIRATORY ILLNESS PER YEAR

Year	URTI	MRTI	LRTI		
1972				47	47
1973				48	48
1974				49	49
1975				50	50
1976				51	51
1977				52	52
1978				53	53
1979				54	54
1980				55	55

TOTAL NUMBER OF URTI	56,57	56,57
MRTI	58,59	58,59
LRTI	60,61	60,61

HOSPITAL ADMISSIONS WITH RESPIRATORY ILLNESS

Year	Hospital	URTI	MRTI	LRTI		
1972					62	62
1973					63	63
1974					64	64
1975					65	65
1976					66	66
1977					67	67
1978					68	68
1979					69	69
1980					70	70

TOTAL NUMBER OF URTI	71,72		71,72	
MRTI	73,74		73,74	
LRTI	75,76		75,76	

CLINICAL EXAMINATION

1-3 ☐☐☐ 4,5 0 5

1-3 ☐☐☐ 4,5 0 5

NAME OF CHILD

DATE OF EXAMINATION

TIME OF EXAMINATION

HEIGHT (cm) 6,7 ☐☐ centile 6,7 ☐☐

WEIGHT (Kg) 8,9 ☐☐ centile 8,9 ☐☐

EARS Right Left

1. Normal drum
2. Discharge, drum not visible
3. Drum perforation
4. Discharge and perforation
5. Scarring of drum
6. Not examined, waxy
7. Not examined, uncooperative

10 ☐ 10 ☐

NOSE

Result of blowing into disposable handkerchief:

1. No discharge
2. Mucus
3. Mucopurulent discharge
4. Purulent discharge
5. Won't blow

11 ☐ 11 ☐

TONSILS

1. Healthy
2. Unhealthy
3. Removed

12 ☐ 12 ☐

INTERCURRENT URTI 13 ☐ 13 ☐

FINGERS

1. Normal
2. Clubbing

14 ☐ 14 ☐

NAILS

1. Normal
2. Shiny

15 ☐ 15 ☐

SKIN

1. Normal
2. Roughened and dry
3. Red and scaly areas
4. Cracked/weeping/infected areas

16 ☐ 16 ☐

CHEST APPEARANCE

1. Normal
2. Abnormal

17 ☐ 17 ☐

If Abnormal - sternal prominence 18 ☐ 18 ☐

sternal depression 19 ☐ 19 ☐

lateral sulci 20 ☐ 20 ☐

WHEEZE 21 ☐ 21 ☐

RHONCHI 22 ☐ 22 ☐

CREPITATIONS 23 ☐ 23 ☐

OTHER, specify: .....

RESPIRATORY FUNCTION TESTS

1-3 [ ][ ][ ]
4,5 [0][6]

1-3 [ ][ ][ ]
4,5 [0][6]

SPIROMETRY

FEV 0.75 sec:	Actual	6-8 [ ][ ][ ]	litres	6-8 [ ][ ][ ]
	Predicted	9-11 [ ][ ][ ]	litres	9-11 [ ][ ][ ]
FEV 1.0 sec:	Actual	12-14 [ ][ ][ ]	litres	12-14 [ ][ ][ ]
	Predicted	15-17 [ ][ ][ ]	litres	15-17 [ ][ ][ ]
FVC :	Actual	18-20 [ ][ ][ ]	litres	18-20 [ ][ ][ ]
	Predicted	21-23 [ ][ ][ ]	litres	21-23 [ ][ ][ ]
FEV 1.0/FVC :		24-25 [ ][ ]	%	24-25 [ ][ ]
MMEFR :	Actual	26-28 [ ][ ][ ]	l/min	26-28 [ ][ ][ ]
	Predicted	29-31 [ ][ ][ ]	l/min	29-31 [ ][ ][ ]

MEFV CURVES

AIR

FEV 1.0 sec :	Actual	32-34 [ ][ ][ ]	litres	32-34 [ ][ ][ ]
	Predicted	35-37 [ ][ ][ ]	litres	35-37 [ ][ ][ ]
FVC :	Actual	38-40 [ ][ ][ ]	litres	38-40 [ ][ ][ ]
	Predicted	41-43 [ ][ ][ ]	litres	41-43 [ ][ ][ ]
$\dot{V}$max 50 :	Actual	44-46 [ ][ ][ ]	l/min	44-46 [ ][ ][ ]
	Predicted	47-49 [ ][ ][ ]	l/min	47-49 [ ][ ][ ]
$\dot{V}$max 25 :	Actual	50-52 [ ][ ][ ]	l/min	50-52 [ ][ ][ ]
	Predicted	53-55 [ ][ ][ ]	l/min	53-55 [ ][ ][ ]
Slope :	Actual	56-58 [ ][ ][ ]	l/min/unit vol	56-58 [ ][ ][ ]
	Predicted	59-61 [ ][ ][ ]	l/min/unit vol	59-61 [ ][ ][ ]
		62-64 [ ][ ][ ]		62-64 [ ][ ][ ]

MEFV CURVES

1-3 | | | |
4,5 | 0 | 7 |

1-3 | | | |
4,5 | 0 | 7 |

HELIUM - OXYGEN

FEV 1.0 sec	:	Actual	6-8		litres	6-8
		Predicted	9-11		litres	9-11
FVC	:	Actual	12-14		litres	12-14
		Predicted	15-17		litres	15-17
$\dot{V}$max 50	:	Actual	18-20		l/min	18-20
		Predicted	21-23		l/min	21-23
$\dot{V}$max 25	:	Actual	24-26		l/min	24-26
		Predicted	27-29		l/min	27-29
Slope	:	Actual	30-32		l/min/unit vol	30-32
		Predicted	33-35		l/min/unit vol	33-35
			36-38			36-38
$\Delta\dot{V}$max 50	:	Actual	39-41		l/min	39-41
		Predicted	42-44		l/min	42-44
$\Delta\dot{V}$max 25	:	Actual	45-47		l/min	45-47
		Predicted	48-50		l/min	48-50

EXERCISE STUDY

PEFR

Pre-exercise (resting):	Actual	51-53			1/min	51-53			
	Predicted	54-56			1/min	54-56			
During exercise:	2 minutes				1/min				
	4 minutes				1/min				
After exercise:	Immediate				1/min				
	2 minutes				1/min				
	5 minutes				1/min				
	10 minutes				1/min				
	15 minutes				1/min				
	20 minutes				1/min				
	30 minutes				1/min				
% Rise		57-59				57-59			
% Fall		60-62				60-62			
Exercise lability		63-65				63-65			
Mouth 1. Open		66				66			
2. Closed									
Bronchodilator given - within last 4 hrs?		67				67			
- after test?		68				68			
Heart Rate									
Rhonchi heard									
Temperature of Room									
Relative humidity									
Atmospheric pressure									