UNIVERSITY OF SOUTHAMPTON

RESPIRATORY SYMPTOMS IN THE ELDERLY AND THEIR CLINICAL SIGNIFICANCE IN THE RECOGNITION OF ASTHMA

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ABSTRACT
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Doctor of Medicine
RESPIRATORY SYMPTOMS IN THE ELDERLY AND THEIR CLINICAL SIGNIFICANCE IN THE RECOGNITION OF ASTHMA
by John Robert Horsley

This study was carried out to estimate the prevalence of respiratory symptoms amongst the elderly in the community and relate symptoms to objective lung function measurements, including bronchial hyperreactivity. A respiratory symptoms questionnaire was sent to 2011 subjects (957 male) drawn by age-stratified random sampling from the age-sex registers of 4 group practices in Lymington, Sway and Brockenhurst. All were age >65 yrs (mean 77 ± 8 yrs; oldest 102 yrs) representing a 1:3.3 sample. 1803 (90%) replied, 1665 from the first mailing and a further 138 after a reminder (96% response excluding 136 who had died or moved). The accuracy of replies was verified for a randomly selected 20%, either by formal interview or telephone.

Only 14% were current smokers. Morning chest tightness was experienced by 203 (11.3%), lasting >1 hour in 44; 131 (7.3%) had episodes of nocturnal breathlessness; 437 (24.2%) experienced occasional wheezing. Only 296 (16.4%) had chronic bronchitis and 151 (8.4%) gave a history of asthma, of whom half (76) had active asthma. 489 (27.1%) had seen their doctor with chest symptoms within the preceding 2 years. Sub-dividing by symptoms:

I No respiratory symptoms 715 (40%)
II Exertional dyspnoea only 185 (10%)
III Wheeze, cough or mild chest tightness 289 (16%)
IV Symptoms of bronchial irritability 519 (29%)
V Unclassified (incomplete questionnaires) 95 (5%)

A random sample from each of groups I-IV was invited for examination, spirometry and methacholine inhalation bronchial challenge. The dose of methacholine producing a 20% fall in FEV_1 was termed the 'PD_{20}'. Of 180 attending, 20 were excluded (FEV_1 <1.0 *l* or spirometry not reproducible); 90 had a negative challenge and 69 (38%) had a positive challenge at or below a cumulative dose of 6.13 μmol methacholine, 19 (12% of total) of these having highly reactive airways (PD_{20} < 1.0 μmol).

Subjects with low baseline FEV_1 (1.0 - 1.5 *l*) were more likely to have a positive challenge result, and significantly more of these had highly reactive airways than to subjects with FEV_1 >1.5 *l* . The presence of respiratory symptoms (groups III, IV) correlated with increased airway reactivity, but the clear separation of subjects (group IV) with the bronchial irritability syndrome symptoms reported by Mortagy et al (1986) was not observed in the elderly. This has important implications for the assessment and treatment of elderly patients with respiratory symptoms, since bronchial hyperreactivity, which is closely associated with clinical asthma, is far more common amongst the elderly than previously recognised.

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B.I.S.	Bronchial Irritability Syndrome (Mortagy et al 1986)
CC	Closing capacity
CV	Closing volume
CO_2	Carbon dioxide
ERV	Expiratory reserve volume
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
H_20	Water
IRV	Inspiratory reserve volume
l	litre
μmol	micromoles
MBC	Maximum breathing capacity
PEFR	Peak expiratory flow rate
P_ACO_2	Alveolar partial pressure of carbon dioxide
RV	Residual volume
TLC	Total lung capacity
PD_{20}	Cumulative inhaled dose of methacholine (in μmol) producing a 20% decrease in FEV_1 from baseline (post-saline, diluent) value
Positive Challenge	20% (or greater) fall in FEV_1 at, or below, maximum cumulative dose of methacholine (6.13 μmol)
Negative Challenge	< 20% fall in FEV_1 at 6.13 μmol methacholine

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INTRODUCTION

INTRODUCTION

Respiratory problems are common amongst the elderly but often neglected. The elderly themselves tend to tolerate illhealth and, even when they do report their symptoms, relatives and doctors all too often just tell them "what can you expect at your age?" Williamson et al (1964) looked at a random sample of elderly subjects registered with 3 general practices in Edinburgh. They found a high level of respiratory disability in men (43% of sample), of whom half, with mild to moderate grades of disability, had not reported their symptoms to their doctor. Similarly, 25% of those with chronic bronchitis had not informed their doctor of their symptoms.

Unfortunately this negative attitude towards health amongst the elderly, their relatives and their medical attendants has hampered research amongst the elderly. Studies of diseases such as asthma have often tended to either exclude the elderly or to have few elderly subjects - an inevitable problem with simple cross-sectional community studies of the prevalence of any disease or symptom.

As the impact of increased life expectation is felt, with better health education, reduction of disability amongst the elderly is becoming an important issue, both for the caring relatives and for political parties. Gray (1982) has suggested that 'handicap' and disability amongst the elderly may be reduced by maintenance of activity, weight control, anti-smoking campaigns and improved pensions. Additionally, better targeting of services is vital. Much disability appears to result from widely varying expectations between the different social classes, Ebrahim et al (1988) finding many changes in habit being socially rather than medically determined - for example, council tenants faring less well than private home owners. This was particularly true for reduction in physical activity, as previously documented by Shepherd (1978). Increasing symptom scores were noted by Ebrahim (1988) to be strongly associated with decreasing physical activity over the preceding 5 years, the least active having most symptoms. Physical fitness is therefore to be encouraged if the health of the elderly is to be improved (Gray 1987).

Ageing affects virtually every system of the body, the respiratory system not escaping. However, most of these changes are within the context of changing life-style, so that the elderly subject will often manage with significantly reduced respiratory reserves until stressed - when he rapidly becomes symptomatic. With reduced respiratory reserves the effect of even mild chest problems can be extremely serious, the patient's progress often also complicated by the scars of previous disease (eg. pulmonary tuberculosis).

Unfortunately diagnosis may also be hampered by atypical presentations of disease in the elderly, hence the need for a high level of clinical suspicion in dealing with the "ill" elderly (Exton-Smith 1965). This has been further highlighted by Isaacs (1981) in his description of the classic "geriatric giants" as modes of presentation.

The elderly, and in particular the very elderly, represent "the survivors" of society, having avoided diseases or accidents that have led to the demise of their less fortunate contemporaries. They may represent a more resilient sub-group of the population, so that predictions of age-related functional change based on cross-sectional population sampling may differ from conclusions drawn from longitudinal studies.

If the health needs of the increasing retirement population (Clarke 1986) is to be met, detailed estimates of the prevalence of disability within the community are essential. However, it must be recognised that studies undertaken in one part of the United Kingdom may have little bearing on the problems being faced elsewhere in the country. In the United States, the Seattle Home Health Care Service provides a lot of support to the elderly, 65% of the problems being respiratory in origin (Personal communication: Dr J Foley, Case Western Reserve University, Ohio). If a similar demand was encountered by the community services in most parts of the United Kingdom it would place considerable burden on the finite resources of the National Health Service.

In order to assess the needs of a population, as many individuals as possible should be assessed if the data is to be meaningful. Unfortunately good community surveys are extremely time-consuming to conduct, the number of subjects interviewed being limited unless considerable time and a large number of interviewers are available. An alternative approach is to screen a larger randomly selected sample from the general population with a simple postal questionnaire, then select subgroups from the respondents to study in greater detail. This avoids one of the risks of random sampling which may,

for example, entirely by chance produce either an excessive number of "disabled" individuals or, conversely, a disproportionately large number of "healthy" subjects - although this error can be minimised by adequate sample size.

The prevalence of different diseases changes considerably with age. Amongst the very elderly, for example, smoking-related diseases are not a major problem, since most with these disease types will not have survived to old age (Baylis et al 1986). Amongst those developing such diseases in old age, increased case fatality amongst smokers may lead to their selective loss from a cross-sectional study (Ebrahim 1988). This presents a particular problem when studying the elderly as part of a random sample, since smoking is more prevalent amongst men and random cross-sectional studies often yield few elderly (particularly very elderly) men. This can be overcome by age stratified sampling techniques, so that equal numbers of males and females are selected at random within pre-defined age bands.

Few detailed studies of respiratory problems amongst the elderly have been undertaken and, because of inter-regional variations in disease, care must be taken when applying findings from one part of the country (or world) with another area. This study was therefore set up to provide current data of the prevalence of respiratory symptoms in a section of the area served by the Southampton Geriatric Department, also assessing the value of postal health questionnaire surveys for the elderly.

When elderly patients are admitted to hospital, the author has observed that there is a tendency for breathlessness and other respiratory symptoms to be diagnosed as "chronic airways disease" by the junior medical staff. Had the same symptoms been present in a younger adult, one of the first questions would have been "could this be asthma?". Having observed this trend during postgraduate training, both in the United Kingdom and North America, a further question to be answered is "how much unrecognised reversible airflow obstruction ('asthma') is present amongst the elderly?". This study attempts to answer this question by looking at subgroups of those replying to a postal respiratory symptoms questionnaire, including physical examination as well as pulmonary function assessment of those agreeing to attend for study.

Mortagy et al (1986) found that a cluster of certain respiratory symptoms had a strong correlation to the presence of markedly increased bronchial reactivity. His study was in a much younger section of the population (mean age of study group 44 yrs). If these symptoms of the 'Bronchial Irritability Syndrome' had a similar correlation for the elderly, this would provide a useful tool for simple screening by general practitioners. The present study was therefore designed to include assessment of non-specific bronchial reactivity in the elderly, allowing correlation of outcome to reported symptoms as well as basic pulmonary function data.

PART 1:
Literature Survey

CHAPTER 1

PATHOPHYSIOLOGY OF THE AGEING LUNG

1.1 Introduction

Laennec (1834) in his famous "Treatise in diseases of the chest" reported autopsy findings in great detail for a variety of lung conditions. When discussing the structure of pulmonary tissue he noted changes in the very elderly not observed in young adults:

> *"..... in very old subjects .... the lungs present some other remarkable characters: the caliber of all their vessels seems diminished; they become in some sort exsanguine; the partitions of the air cells appear thinner than natural, on which account their substance, rendered more rare, becomes less elastic, and thus yielding to the atmospheric pressure on the opening of the body, they are found to occupy not more than one-third of the cavity of the pleura. They may be said to bear the same relation to the lungs of an adult, that muslin bears to a finer cloth, which is of a texture at once strong and close. These characters are especially observable in the lungs of octogenarians."*

It is also interesting to note, in view of the more recent findings of Shepherd (1978) and Ebrahim (1988), that physical activity was noted to be helpful in reducing the rate of deterioration in lung function 30 years ago by Mayer, Blazsig and Rappaport (1958):

> *".... we inescapably gained the impression that in the aged who had led physically active lives, the involutional lung changes were less marked than in those who had not. Indeed, enforced idleness seemed in a few instances to have accelerated senile pulmonary changes."*

These 'senile pulmonary changes' were particularly noted in patients aged over 80 yrs, confirming Laennec's observations, and were observed in females more often than in male patients. Possibly this observation was due to greater fitness amongst the men who had survived the First and Second World Wars, their less fit contemporaries having already died from war or other diseases.

Throughout life the lungs are constantly exposed to environmental influences causing repeated minor (or major) damage, so that it becomes quite difficult to establish what changes are solely due to the ageing process and which

have been produced or accelerated by environmental factors. As observed by Laennec (1834), the lungs of the elderly are smaller, weigh less and are more flabby than those of younger subjects. In addition the lungs are less collapsible on opening the chest at autopsy with a tendency for apical emphysema, although there are few other major macroscopic changes (McKeown 1965). The effects of ageing must therefore be considered at the cellular level.

1.2 Biochemical and structural changes in the ageing lung

The 'senile lung' changes described by Laennec (1834) have been shown to be due to changes occuring in several lung tissues , with changes in the thoracic cage itself also playing an important part in altered lung function (the latter is described in section 1.3). The elasticity of the respiratory tract itself is dependent on changes within the complex network made up from all of the following:

(i) collagen and reticulin fibres
(ii) elastic tissue fibres
(iii) smooth muscle
(iv) blood vessels
(v) alveolar epithelium

The connective tissue providing the framework for the lung parenchyma is largely composed of extracellular substances produced by fibroblasts or closely related cells. It contains mucopolysaccharides as well as fibrous proteins, principally collagen, reticulin and elastin. The principle mucopolysaccharide is hexosamine comprising approximately 0.6% of the lung dry weight, this proportion not changing significantly with age (Saltzman 1961). The alterations in function of the lung must therefore depend on age-related changes in the other connective tissue components.

Collagen and elastin fibres are distributed between the alveolar and capillary lining cells and also through the alveolar walls, providing a supportive network for the capillaries (Loosli and Baker 1962). In addition, collagen is the principle structural protein of the pleura, large vessels and airways (Kohn 1964). Collagen is also the principle component within the lung solid (Laurent 1986) and the changes in the functional properties of collagen that have been demonstrated to occur with ageing, combined with changes in elastin, provide part of the explanation for the observed age-related changes in lung tissue elasticity.

Mead (1961) suggested that collagen and elastin fibres run in the same direction within the lung parenchyma. He suggested that because collagen fibres are curled, distension of the lungs produces straightening of the collagen fibres, in turn preventing over-distension of the pulmonary airspaces once the elastic limit of the collagen had been reached. There is no change in concentration of collagen in lung tissue with age. Kohn (1964) showed that the ability of collagen to swell in acidic solutions is markedly impaired with progressive ageing (Fig. 1). This is due to increased crosslinkage between collagen fibrils which occurs progressively after the age of 30.

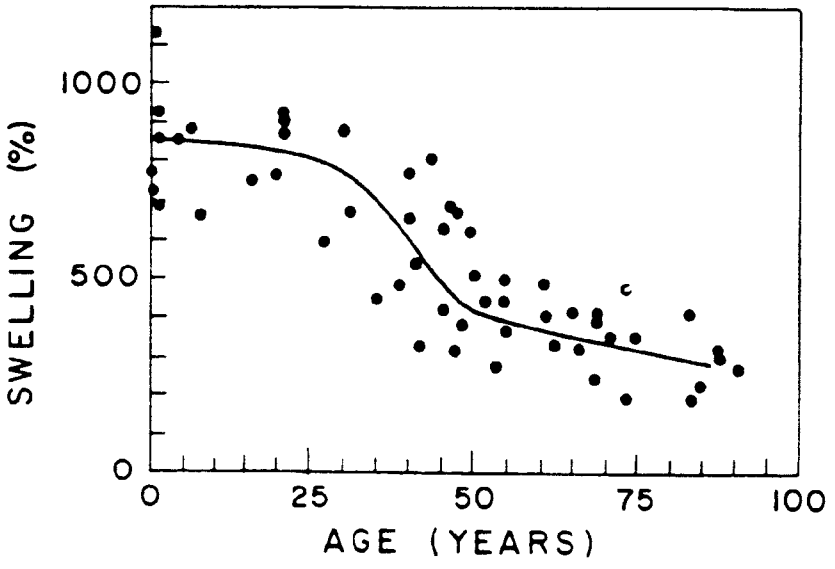


Fig 1: Osmotic swelling at pH 2.5 of human tendon related to age (Kohn 1964)

Increased crosslinkage of the collagen fibrils makes the structure more rigid and therfore less easily deformed under stress (Fig. 2). In combination with changes in elastin, changing collagen crosslinkage leads to reduced elastic recoil within the lungs.

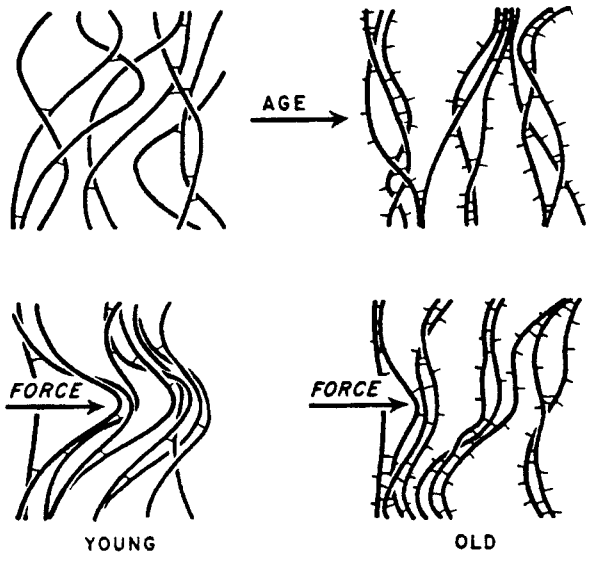


Fig. 2: Increasing crosslinkage of collagen fibrils with age produces a more rigid structure, less easily deformed by applied force than in younger subjects (Kohn 1964).

Elastic fibres are distributed in different directions within different parts of the respiratory tract. Around the airways they are found in the lamina propria following a longitudinal course. Within the respiratory portion of the lungs they are distributed spirally in association with smooth muscle and fibrocollagenous tissue around the openings of the alveolar ducts, beyond which the elastic fibres pass as fine filaments into the alveolar walls (Pierce and Ebert 1965). With ageing there is reduction in the normal elasticity of fibres due to increased crosslinkage between fibres, as seen with collagen (Starcher 1986). In addition there is a progressive increase in the total amount of elastin in the lungs with ageing, in contrast to the main arteries where elastin concentration remains unchanged. Calcification and apatite deposition occurs to a much lesser extent in pulmonary arteries than it does in the aorta and other main arteries. It has also been shown that elastin fibres damaged by overstretching are more prone to bind calcium (Blumenthal et al 1964).

The increase in elastin with age, in association with a static collagen concentration, therefore results in a reduction in the collagen/elastin ratio (Fig. 3). These changes in collagen and elastin are the same in both men and women (Pierce 1964).

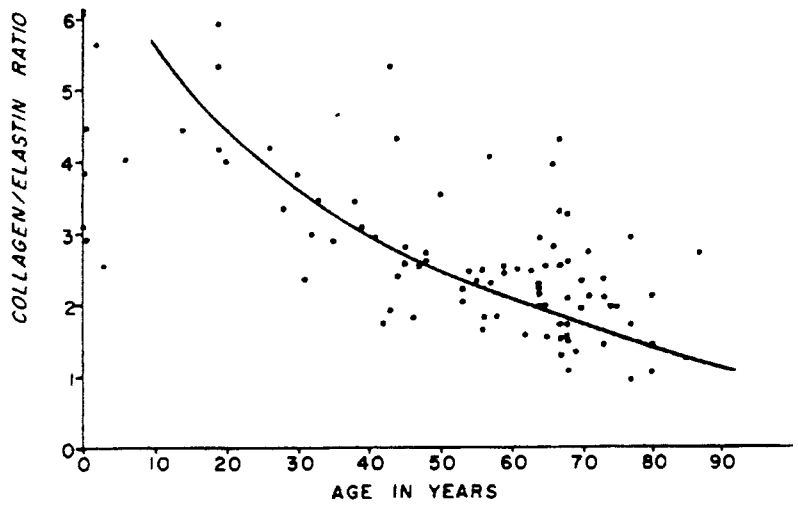


Fig. 3: Negative correlation between age and the ratio of collagen to elastin, due to increased amounts of elastin in the lungs of elderly subjects (Pierce 1964).

The changes in collagen and elastin do not completely explain the reduction in lung elastic recoil observed with ageing (Gibson and Pride 1976). More recent studies have shown that surface tension forces acting in the alveoli may be the major determinant of elastic recoil within the pulmonary parenchyma (Nunn 1977). These forces develop at the interface produced between air and blood across the vast surface area of the alveoli, which is covered by surfactant. Surface tension here is less affected by the ageing process than by the changes in lung volume that occur with ageing (Comroe 1974). Despite extensive investigation of the role of surfactant (Hills 1981; Rooney 1985) there is currently little information regarding any age-related changes in its function.

1.3 Changes within the chest wall.

The preceding section has considered some of the aspects of altered structure and function occurring within the lungs, which reduce their elastic recoil. Associated with these is an increased rigidity of the thoracic cage. Factors such as degeneration of intervertebral discs, ossification of costal cartilages and arthrosis of costo-vertebral articulations all contribute towards reduced elastic recoil of the thoracic cage (Rizzato and Marazzini 1970; Cotes 1979).

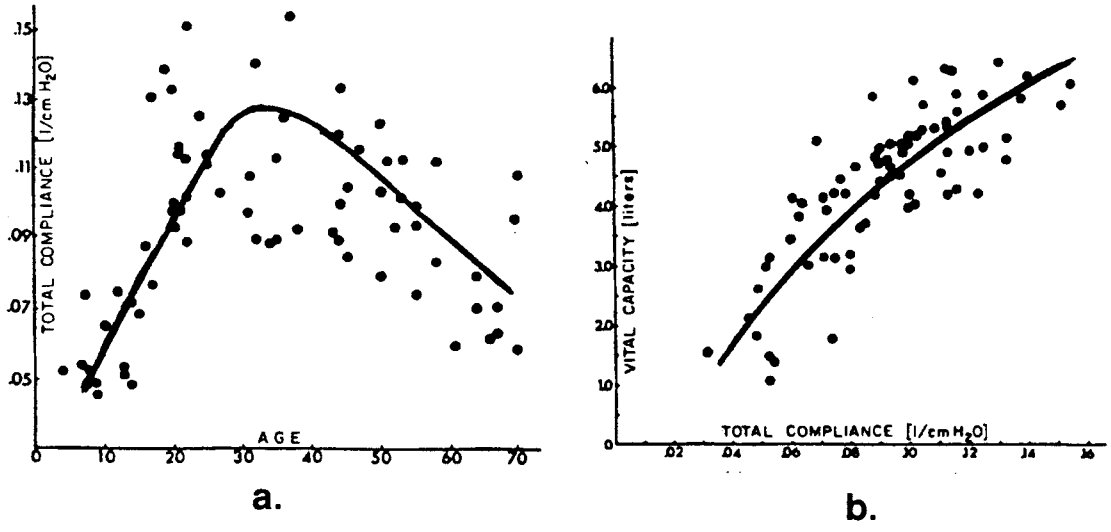


Fig. 4: Relationship between total respiratory compliance and (a) age (b) vital capacity. Results for 70 normal subjects age 4-70 yrs (Redrawn from Cherniac and Brown, 1965).

Cherniac and Brown (1965), looked at the normal range of total respiratory compliance up to age 70. During the first three decades total compliance increased, then fell steadily with advancing age (Fig. 4a). This trend correlated best with measurements of vital capacity (Fig. 4b). Body size was unrelated, and the authors suggested that the fall in total compliance observed in the later decades was due to increased resistance in the chest wall. Correcting total respiratory compliance for lung size (and so getting rid of the effect of increasing lung size in the first 20 years of life), total respiratory compliance (ie. lungs and chest wall together) is seen to decline steadily with age (Fig. 5).

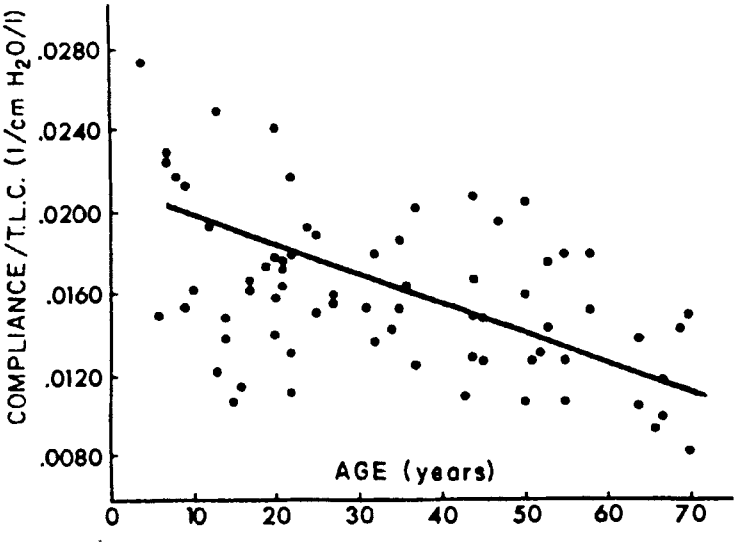


Fig. 5: Decline in total respiratory compliance with age after correcting for the effect of lung size. Results for 70 normal subjects age 4 - 70 years. (Cherniac and Brown 1965).

A relative fixation of the thoracic cage with advancing years could explain both the fall in total respiratory compliance (which contrasts with increased lung compliance noted with age - sections 1.1, 1.6) and the other alterations in lung volumes (section 1.6) observed with ageing (Permutt and Martin 1960). In view of the close relationship between VC and total respiratory compliance (Fig. 4b) the VC can be used as an index of the elastic resistance of the lungs and chest wall - principally those structures outside the lung which move on respiration (Naimark and Cherniac 1960; Cherniac and Hodson 1963).

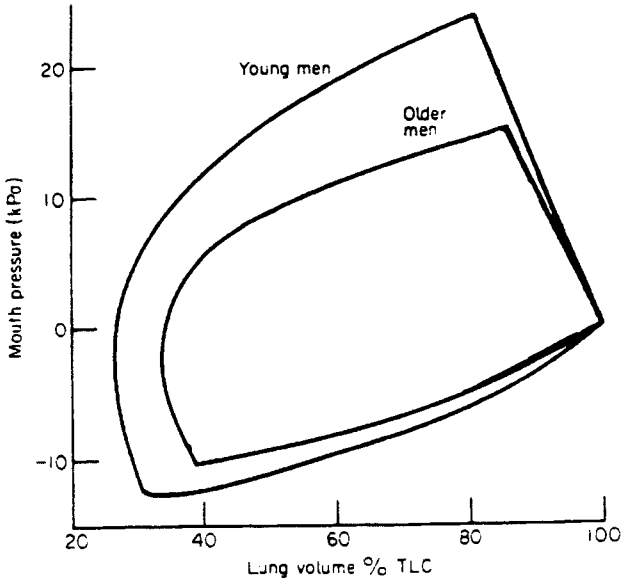


Fig. 6: Maximal pressure volume loops constructed to compare older and younger male subjects. These represent a dynamic combination of the effects of ageing in the chest wall musculature, thoracic cage and lungs at different lung volumes throughout the respiratory cycle (breathing with maximal effort in and out of airtight containers of capacity 1.5 l - 200 l). (Cotes 1979a, using data from Cook et al 1964).

It is evident from figure 6 that elderly subjects are not able to generate the same magnitude of dynamic pressure changes, measured at the mouth, as younger subjects. This is due to the combination of musculo-skeletal and lung tissue changes occuring with ageing, further limited by thoracic kyphosis, and any previous lung or chest wall surgery or injuries. Static lung volume measurements are also affected by changes in the chest wall, progressive kyphosis, for example leading to reduction in vital capacity (Cotes 1979). Increasing rigidity of the thoracic cage, however, has greatest influence during activity (as shown during dynamic measurements of lung function), where it is a major factor contributing to the reduction in compliance of the respiratory system observed with age - and thus increases the work of breathing (Turner et al 1968). This was similarly demonstrated in the earlier work of DuBois, summarised at the Tenth Hahneman Symposium (DuBois and Alcala 1964).

1.4 Functional assessment

Dynamic measurements of lung function are more complicated to record than static lung volume measurements and have inherent limitations (Gibson and Pride 1976). However it is important to remember that the patient is principally concerned about his symptoms and anything that can be done to relieve them. Thus a careful functionally orientated history to assess how he is **actually** limited by the symptoms before embarking on detailed assessment is important.

The simplest dynamic test is an assessment of the severity of breathlessness or respiratory symptoms that develop with graded exercise. This is not a pure measurement of lung function, factors such as cardiac disease (eg. ischaemic heart disease, congestive cardiac failure) or arthritis in the hip or leg joints also being important influences in determining how breathless an individual gets on exercise. The "walking time" between two fixed points (Cooper 1968; Mahler et al 1984) does provide a useful and simple, non-invasive guide to screen out individuals who require more detailed investigation and can also be used as a simple way to assess response to treatment.

Within anaesthetic practice the functional ability of the subject is recognised as being more important than the chronological age in pre-operative assessments and in prediction of likely postoperative respiratory complications. This has recently been reviewed by Shaw and Evans (1988), offering guidance to general practitioners on how to assess their patients regarding suitability for surgery and is further discussed in Chapter 2.1.

The smoking history is also important, since smoking has been shown to hasten the rate of decline in lung function (Milne and Williamson 1972b). It is significant that fewer of the very elderly age-group smoke (Milne and Williamson 1972a; Horsley et al 1987) - a trend particularly noticed amongst the females studied in both these reports. This reflects both the changing social attitudes towards smoking between different generations as well as earlier death from smoking-related diseases of many of the contemporaries of our present elderly members of society, leading to a selective reduction in smokers within the retirement population (Baylis et al 1986). Smoking history will also be considered further in Chapter 2.

1.5 Limitation of predictive "normal" values

When interpreting predictive "normal" values for age-related changes in lung volumes, it is important to bare in mind this data has all come from cross-sectional studies - comparing groups of subjects of different ages with each other at one particular time. This is clearly simpler than undertaking longitudinal population studies, where it is necessary to follow large groups of people over many years, testing them repeatedly as they age.

The major limitation of the cross-sectional study is that we do not know what the 80 or 90 year old subject was like in their 20's and 30's, nor that subjects being studied in their 20's will live to their 80's. Thus extrapolation of data to predict changes in lung function at a given age must be interpreted with caution, since it is possible that those subjects now in their 80's and 90's represent a distinct subgroup of "survivors" who had different (better than "normal") parameters when they were younger (as compared to their shorter living contemporaries). When a longitudinal study was undertaken in Baltimore (Beaty et al 1984) to assess the association between the rate of decline in lung function and various potential risk factors; the results were inconclusive. Only age and smoking were consistently associated with loss of FEV_1 in both men and women, the other factors assessed (ABO blood group, protease inhibitor type, ABH secretor status, alcohol, coffee, family history) being poorly and inconsistently related to lung function changes. This was, however, only a study over a 4.7 year period (mean interval of follow up) with a high drop-out rate at second review, so its conclusions were inevitably limited, highlighting the problems of longitudinal population surveys.

It is also important to ensure that adequate numbers of elderly subjects were included in the initial population sample studied, so that predictions for the elderly can be made with reasonable certainty. Few studies have included many elderly subjects, many only going up to age 70 yrs (for example, Berglund et al 1963), the studies of Milne and Williamson (1972 a,b,c) and, more recently, Burr et al (1985) being noteable exceptions.

1.6 Changes in lung volumes

With "normal" ageing the reduction in elastic recoil of the lungs (section 1.2) leads to an increased static compliance of the lung tissue, as first measured by Pierce and Ebert (1958), so that the lungs become more easily distensible - ie. less pressure for expansion is required. After inflation the ageing lungs would not recoil back to the same resting position as for younger subjects (hence the floppy, collapsible lungs observed by Laennec with the chest open

at post mortem - section 1.1) if it were not for the increased "stiffness" of the chest wall. Thus changes in lung volumes reflect a balance between the increase in lung compliance (a tendency for the lungs to become hyperinflated) and the restricting forces exerted by a more rigid, less distensible thoracic cage (Kent 1978). (Fig. 7).

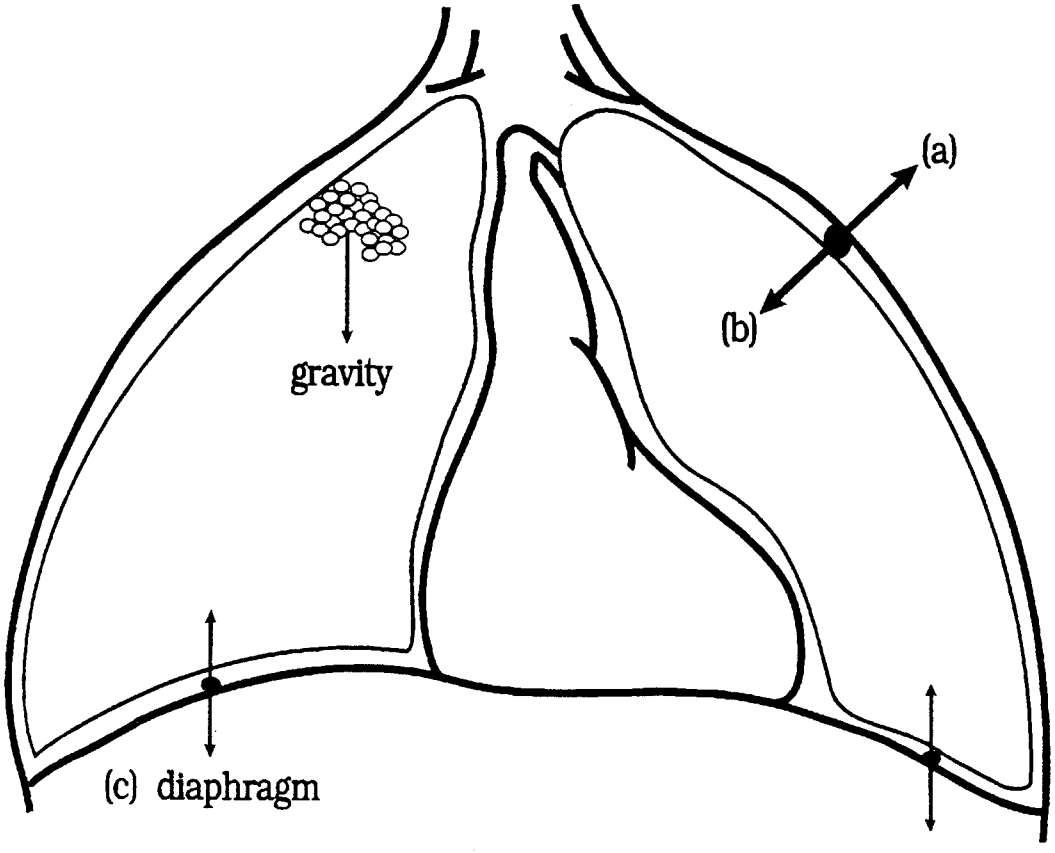


Fig. 7: Balance of forces which determine lung volumes:
(a) Increased lung compliance, tending to hyperinflate lungs due to increased lung elastic recoil;
(b) Decreased elasticity of chest wall, due to reduced muscle strength and increased "stiffness" due to arthrosis of costo-vertebral articulations;
(c) Diaphragm.

1.6.1 Static lung volume

Boren et al (1966) showed in a large cross-sectional study that measurements of total lung capacity reduced with age. However, there is progressive decrease in height with ageing, partly due to decreasing size of the intervertebral spaces, and partly because of the effect of better nutrition complicating the cross-sectional data analysis - ie. younger subjects tend to be taller than those from different generations were at the same age (Goldman and

Becklake 1959). Normalising TLC measurements for height, it was found that TLC remained constant with age (Boren et al 1966).

The volume of gas remaining within the lungs after a maximal expiration (RV) is determined by the strength of the expiratory muscles, which have to work in opposition to the tendency for the chest wall to recoil outwards at low volume (Cotes 1979), and also by trapping of air through earlier airways closure, which also occurs with ageing (discussed below). Measurements of RV increase from an average of 1.5 *l* at age 20 to around 2.29 *l* by age 60 in men (Cotes 1979) (Fig. 8). Associated thoracic deformities, such as the thoracic kyphosis which often develops with ageing, may further increase RV. As a consequence of the increased RV and reduced chest expansion, vital capacity falls (Boren et al 1966).

Rahn et al (1946) showed that at the end of a normal respiratory cycle during tidal breathing all the muscles of respiration are relaxed. They showed that at this point, termed functional residual capacity, the inward elastic recoil of the lungs balanced the outward elastic recoil force of the chest wall. This "balance point" has been shown to increase with age (Masoro 1981), as does the ratio of FRC to TLC. This has the effect of reducing the inspiratory reserve volume, as tidal breathing now occurs at a higher volume (Fig. 8).

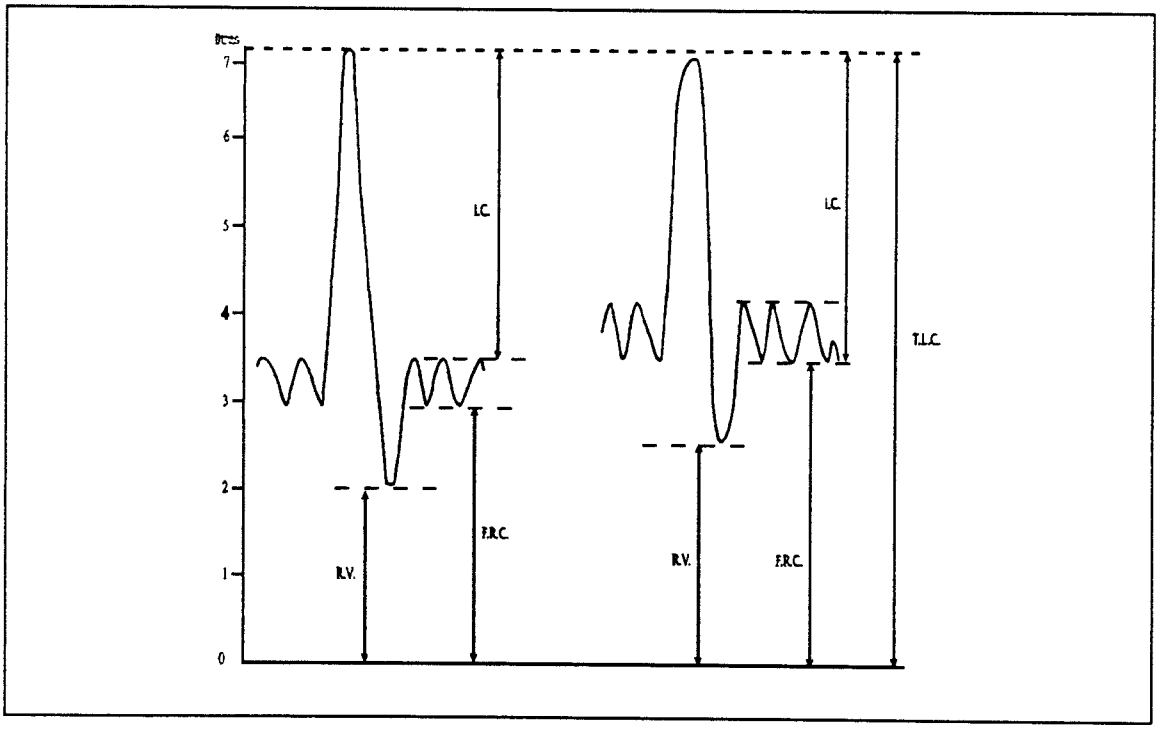


Fig. 8: Changes in respiratory pattern with age, comparing lung volumes for a 6 ft. tall male at ages (a) 20 years and (b) 70 years. Normal values from Cotes (1979).
TLC - Total lung capacity *IC - Inspiratory capacity*
FRC - Functional residual capacity *RV - Residual volume*

Some lung function measurements change by greater proportions with age than others, as is evident in figure 9 which summarises changes in several lung volume measurements occuring between the ages of 20 and 70 years. Changes were particularly marked in closing volume (discussed below), expressed in figure 9 as a percentage of TLC and termed the closing capacity (CC).

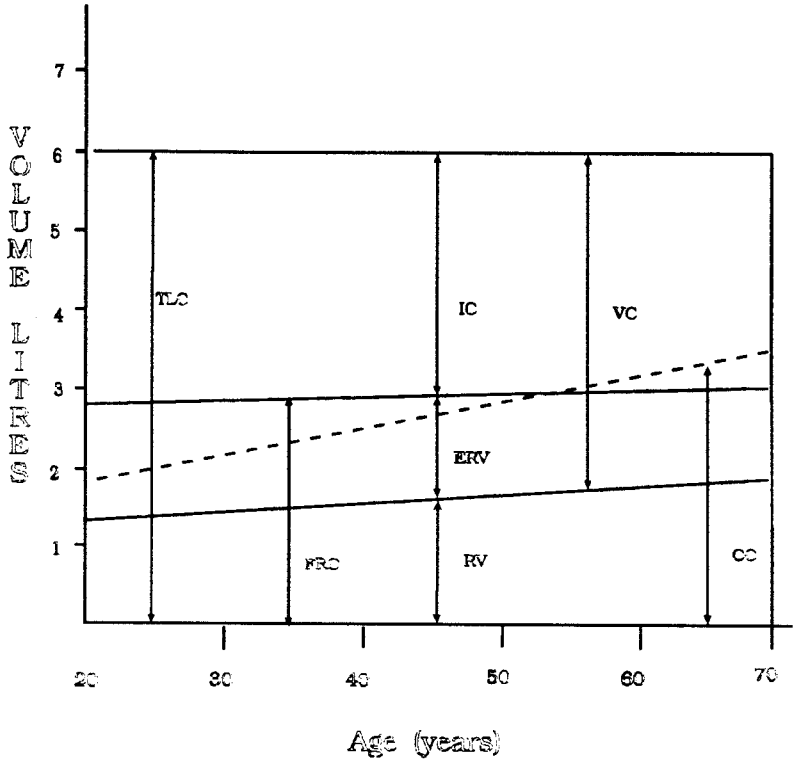


Fig 9: Changes in static lung volumes with age (Levitzky 1984)
VC - Vital capacity *ERV - Expiratory volume*
CC - Closing capacity

1.6.2 Dynamic tests of lung function - FEV_1,FVC,PEFR, Airway resist ance

Several studies have looked at airway resistance and shown no change with age (Briscoe and Dubois 1958; Wahba 1983), therefore this does not account for the reduction in forced expiratory flow rates demonstrated with ageing (Boren et al 1966; Milne and Williamson 1972 b, c; Burr et al 1985). The increased compliance of the small airways makes them more susceptible to the effects of dynamic compression during the forced expiratory manoeuvre.

During respiration, air flows along the airways according to the pressure gradient between the mouth (at atmospheric pressure) and the alveoli, the direction of flow reversing at the mid-point of each respiratory cycle. During tidal breathing the mid-thoracic pleural pressure does not usually rise above zero, but on forced expiration this becomes positive (Pride 1971). The significance of this positive intrapleural pressure is greatest towards the end of forced expiration when the gas flow rate within the airways (which contributes to the maintainance of airway patency on expiration) begins to fall. The smaller peripheral airways are more susceptible to compression by this positive intrathoracic pressure because they have less rigid walls, and with age-related changes become even more easily compressible. Therefore, once the pleural pressure (P_{pl}) exceeds the static elastic recoil pressure (P_{stat}) of the airway, airway compression will occur with air trapping distal to this point (Pride 1971). This is shown diagramatically in Fig. 10.

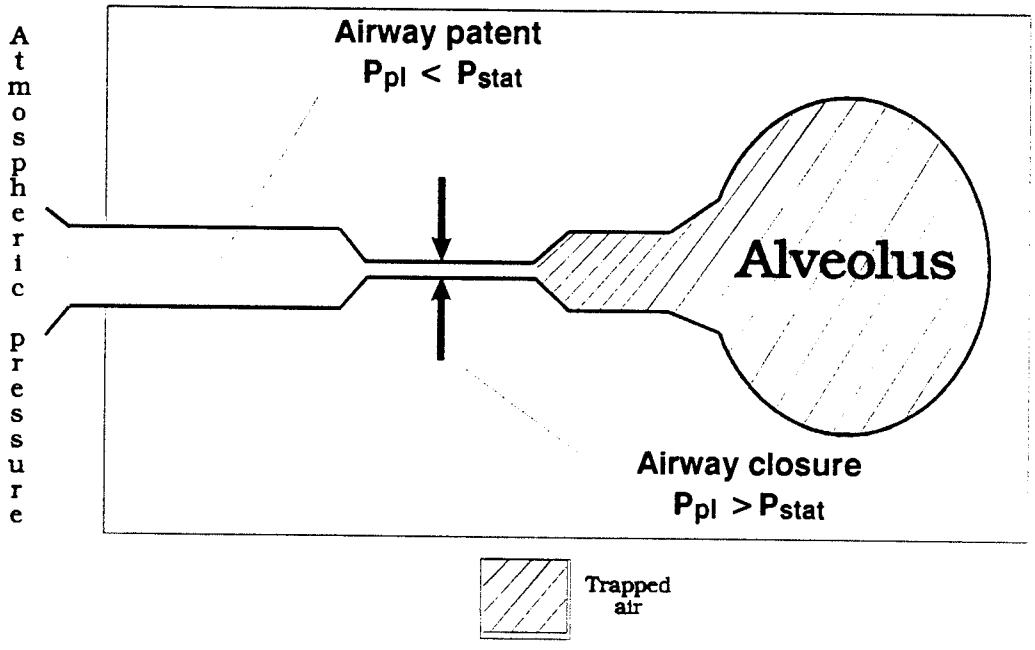


Fig. 10: Diagramatic representation of the mechanism of dynamic airway compression during forced expiration.

The intrapleural pressure increases from approximately -10 cm H_2O at the apices, to 2.5 cm H_2O at the lung base (West 1979) in the upright posture. Alveoli at the apices are therefore more widely distended than those at the lung bases. Using Xenon studies, Saunders (1977) has shown that, at lung volumes above FRC, ventilation per unit lung volume is higher at the bases than in the apical regions. However the lower airways close more readily then those in the apices, since a lesser increase in intrapleural pressure is needed on expiration to initiate airways closure. Therefore, as lung volumes

approach RV during expiration, the pleural pressure becomes less negative which, together with decreasing alveolar volumes and reduced airways diameter, results in airway closure. The basal airways close first, but at RV there are closed airways in all lung regions, although the greatest percentage of closed airways are at the bases. The volume at which closure first occurs is termed the closing volume (when expressed as %VC) or closing capacity (expressed as %TLC).

To estimate closing volume , the subject inhales a maximal breath from RV to TLC of 100% oxygen. This is preferentially distributed first to the apical zones and then progressively to the lower lung regions (Fowler 1952). Then, during a slow steady expiration, the concentration of nitrogen is continuously monitored and plotted against lung volume . When airway closure starts to occur the nitrogen composition of the exhaled gas is seen to start increasing as air is exhaled from the upper zones - ie the airways and alveoli that were fully distended and patent at RV, and had therefore received least oxygen (McCarthy et al 1972; Buist and Ross 1973). This simplified technique to assess airways closure has confirmed the age-related trend to earlier airways closure demonstrated by Anthonisen et at (1969) using a Xenon technique.

Although RV/TLC ratios had been shown to increase with age, due to increasing RV, it was not clear whether this was due to focal or generalised changes within the lung. Jones et al (1978) studies this using a multiprobe detector system and inhaled Xenon - 133 in seated subjects, measuring the ratio of RV to TLC in five vertically separated lung regions of each lung (RV_r/TLC_r). This study demonstrated uniform increase in RV_r/TLC_r throughout the lungs with increasing age (Fig. 11) and no significant change in the ratio of upper zone to lower zone RV_r/TLC_r measurements (Fig. 12). These findings are in keeping with a generalised reduction in lung elastic recoil with ageing, leading to premature airways closure at higher lung volume than during youth. A similar explanation has been offered to explain why closing capacity approaches FRC with increasing age (Anthonsen et al 1969; Leblanc et al 1970).

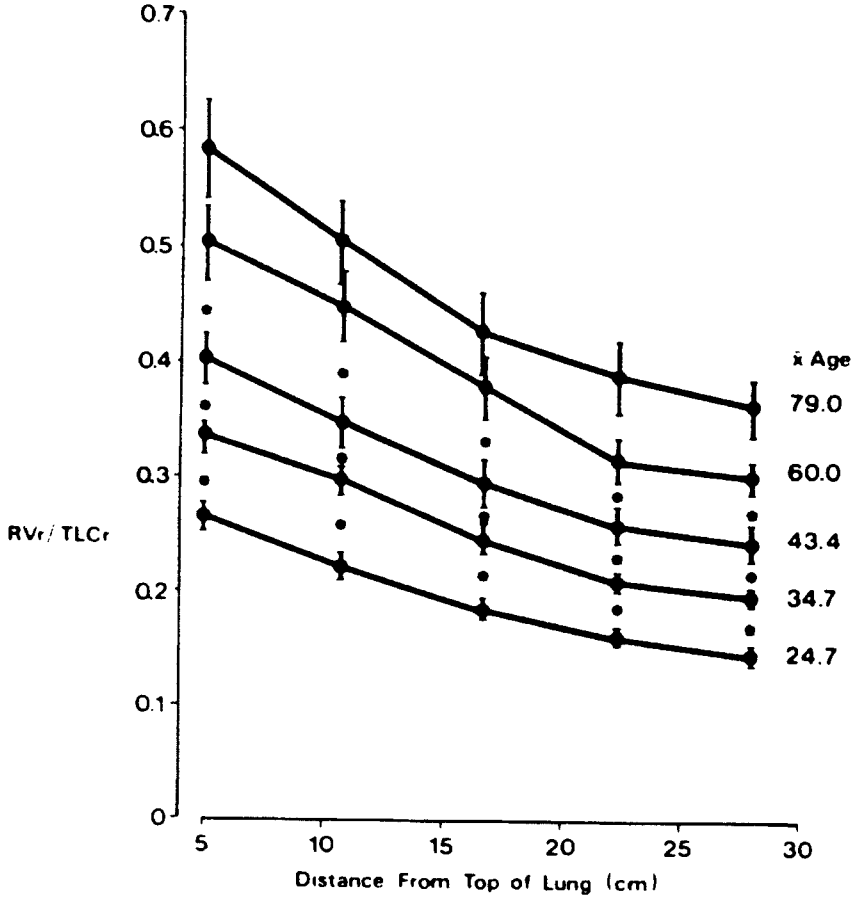


Fig. 11: Variation in RV_r/TLC_r with age. Results shown as mean ± 1 S.E.M. for five vertically separated lung regions in seated subjects, with mean age of subgroups shown. Significant differences ($p < 0.05$) exists between specified regions (*) of adjacent age groups. (Jones et al 1978).

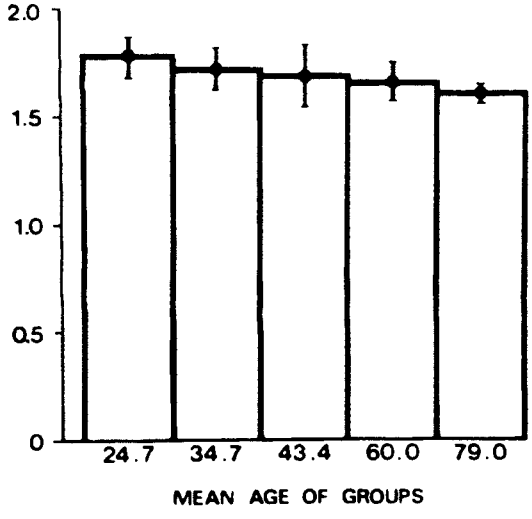


Fig. 12: Ratio of apical RV_r/TLC_r to basal RV_r/TLC_r for different age groups expressed as mean ± 1 S.E.M. No statistically significant difference existed between age groups. (Jones et al 1978)

Maximum expiratory flow rates are shown to decline progressively with age, due to reduced lung elastic recoil, this deterioration being accelerated by smoking (Fletcher and Peto 1977; Oldham 1987). The presence of airflow obstruction also affects regional lung function, although the changes in RV_r/TLC_r are patchy, as demonstrated by Horsley et al (1985) when acute bronchospasm was induced by methacholine inhalation. Regional lung ventilation also becomes impaired on exercise, if there is airways obstruction, and at higher respiratory frequencies the contribution of airways resistance to the homogeneity of lung ventilation becomes increasingly important. In one study, again using Xenon-133 and a multiprobe detector system, significant impairment of regional ventilation was shown at 60 breaths per minute compared with measurements at 10 breaths per minute; normals showed no change at the higher respiratory frequencies (Jones et al 1977). Although airway resistance does not increase significantly with age in the healthy non-smoker (Briscoe and DuBois 1958), changes in resistance with smoking are found and result in the elderly smoker becoming increasingly symptomatic (Milne and Williamson 1972a,b), and in particular symptomatic at higher respiratory frequencies (Jones et al 1977).

CHAPTER 2

VARIOUS RESPIRATORY PROBLEMS IN RELATION TO AGEING

2.1 Response to infection and anaesthesia

The first chapter has concentrated principally on how structural and functional changes interrelate to produce alterations in lung mechanics and altered respiratory reserves. Despite progressive changes in lung function with age, accelerated by smoking (Milne and Williamson 1972 a, b), most elderly subjects only become symptomatic when stressed, whether by exertion, illness or infection. In particular with regard to respiratory infections, the ability to handle new infections is impaired due to several factors. Respiratory reserves are reduced due to a combination of changes in the mechanics of the thoracic cage, changes in the bronchi and lung parenchymal tissues and also by the scars of previous diseases - for example, pulmonary tuberculosis, which was still relatively common when the current cohort of 'elderly' were young.

The ability to mount an immune response to invading organisms becomes impaired with age, as does the rate at which infected secretions can be cleared from the lungs, putting the elderly at increased risk from serious chest infections. Fewer cilia are present in the lining epithelium of the airways, leading to decreased efficiency of muco-ciliary transport (Wanner 1977; Levitzky 1984) and retention of secretions, a situation further worsened by smoking since this also has a deleterious effect on ciliary numbers and function (Greenstone and Cole 1985). Additionally with age the protective cough reflex becomes impaired in terms of the volume, force and flow rate exhaled (Wahba 1983). This may lead to problems even for the healthy elderly subject after a prolonged anaesthetic. This is particularly significant if abdominal surgery is involved, where diaphragmatic function will also be affected in the post-operative period (Vickers 1982; Shaw and Evans 1988). A thorough pre-operation assessment of respiratory function by both physician and physiotherapist can reduce the pulmonary risks of anaesthesia and enable earlier identification of those likely to develop problems, to whom more intensive pre- and post-operative physiotherapy can then be directed.

Other predisposing causes to respiratory infection and bronchopneumonia are well documented, such as the presence of diabetes mellitus, excessive alcohol consumption or ischaemic heart disease, chronic bronchitis and malignancy (Bartlett 1980; Emerson and Knowles 1984). In the elderly decreased mobility, dental sepsis and dehydration (often from over-enthusiastic diuretic therapy) all increase risks of respiratory infections. For the post-operative patient the risks of chest infection are increased by the type of anaesthesia (ie general anaesthetic, sedative or narcotic drugs used) and the presence of a nasogastric tube further increases risks.

With nasogastric tubes the increased risk is largely due to interference caused by the tube in laryngeal function, increasing the risks of reflux and subsequent aspiration of gastric contents (Bartlett 1980). A similar situation may also occur in a number of patients with chronic airways disease, since theophylline drugs have been shown to reduce gastro-oesophageal sphincter tone and therefore predispose to gastro-oesophageal reflux (Mays 1976). Mansfield and Stein (1978) suggested that it was not necessary for actual overspill into the lungs to occur for bronchospasm to be produced, suggesting that the presence of refluxed acid within the oesophagus could produce vagally mediated bronchospasm in certain individuals. Wilson et al (1987) have, however, concluded that simple vagal mediation does not explain this reflex bronchospasm which follows oesophageal stimulation. Although in some such patients definite overspill into the lungs has been demonstrated (Greyson et al 1982), this is difficult to conclusively demonstrate even when there are strong clinical indications suggesting that recurrent nocturnal aspiration is taking place (Horsley and Sproule 1986).

When bronchopneumonia does develop in an elderly patient the mortality is considerably higher than for younger subjects (Woodford-Williams 1966; McKeown 1965; Harris 1974). Some studies have shown as high as 35% mortality in patients aged greater than 65 years with pneumonia and several risk factors can be identified (Allen 1986), any combination of which increases mortality (Table 1).

Table 1 - Factors adversely affecting survival from bronchopneumonia in the elderly (derived from McKeown 1965; Exton-Smith, Corless 1965; Woodford-Williams 1966; Allan 1986; Howard 1987; Woodhead 1988).

Age
Hypothermia
Dehydration (Blood urea > 7 mmol//)
Persisting hypotension)diastolic b.p. <60 mmHg)
Leukopaenia (< $1x10^9$//)
Confusion
Hypoxia (P_aO_2 < 6.6kPa on room air)
Multiple lobe involvement
Radiographic progression
Bacteraemia
Associated diseases
- malignancy
- pre-existent lung disease
- congestive cardiac failure
- diabetes mellitus
- renal failure
- neuro-muscular diseases (eg. stroke, Parkinsons disease, motor neurone disease)

It is important to remember that chest infections and pneumonia do not always present with fever (Jones and Fairweather 1987) or the usual symptoms found in younger patients. Often confusion, falls or incontinence are the only presenting features - as they can be with many other conditions in elderly patients, hence the description of these symptoms as the 'geriatric giants' (Isaacs 1981). Whilst treating the pneumonia it is therefore also important to search for the precipitating event, remembering that multiple factors may be contributing to the final presentation (Fig. 13, next page).

The chest radiograph is often helpful and as a 'routine' investigation has a much higher pick-up rate than for younger patients. Puxty and Andrews (1986) found 44% of routine chest radiographs were abnormal out of 308 consecutive admissions to their geriatric unit, with a particularly high yield when investigating the 'geriatric giant' type admissions. Blood cultures are also helpful, since sputum is often hard to obtain and has a low diagnostic yield. Approximately 25% of blood cultures are positive in patients with pneumonia if they have not already been started on antibiotics prior to hospital admission (Allen 1986). Recording the respiratory rate can also be

very helpful, although this is a measurement which is often made inaccurately by junior nursing staff. McFadden et al (1982) showed that there was seldom significant respiratory disability if the respiratory rate was less than 26 per minute in an unsedated conscious patient.

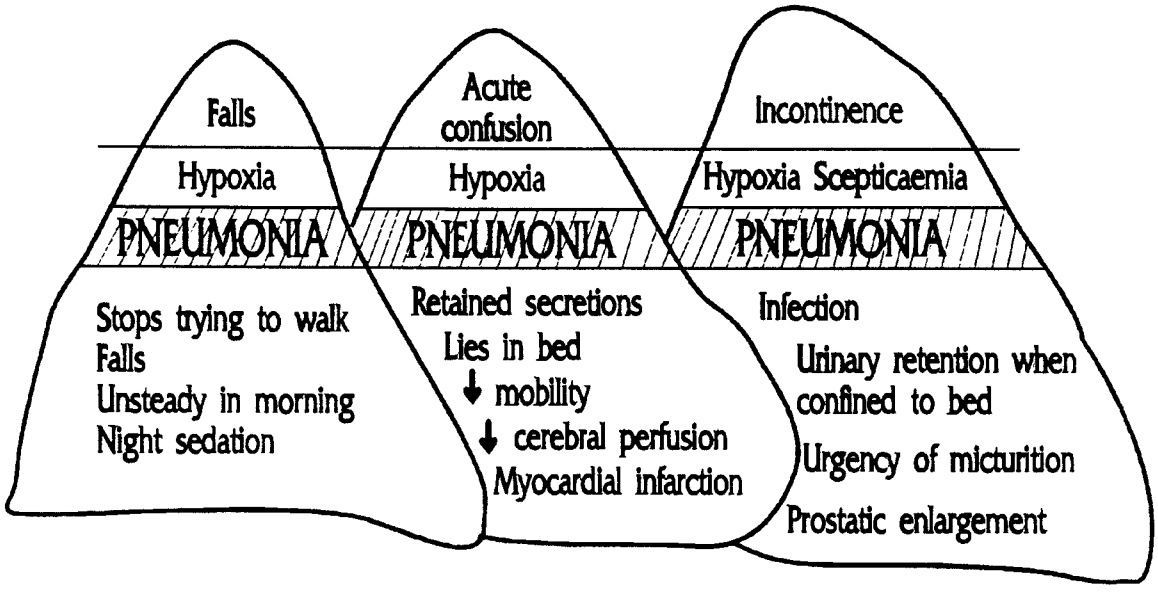


Fig. 13: An example of the multifactorial sequence of events that may result in the development of pneumonia in an elderly patient, leading to a "geriatric giants" type presentation (falls, confusion, incontinence). As with an iceberg, the real cause lies beneath the surface.

2.2 Breathlessness

Breathlessness is a common symptom, affecting 43% of elderly men in one study in Edinburgh (Williamson et al 1964). A further study using the MRC symptoms questionnaire (MRC 1965) found breathlessness of grade 2 or worse in 20% of the sample, although the severity varied for individuals over a 5 years study period (Milne 1978) - improving in some, deteriorating in others. Breathlessness was more likely to worsen if the individual smoked more than 15 cigarettes per day. It is interesting to note that those in whom breathlessness improved over the study period were almost all female and that, in this study, stopping smoking made no appreciable difference to symptoms or lung function - mainly because those who had stopped smoking had few symptoms at the commencement of the study. A greater proportion of those who died during the 5 year study period had breathlessness greater than grade 2 - 36.4% of those dying compared with 16.8% of survivors (Milne 1978). This confirms the earlier study of Oswald et al (1967) who, in a 10 year review of subjects in the Civil Service with chronic bronchitis, also found the severity of dyspnoea correlated strongly with survival, which decreased with increasing grades of dyspnoea.

The symptom 'breathlessness' implies a subjective awareness of increased frequency of respiration or increasing difficulty in breathing and, particularly amongst the elderly, is multifactored in origin (Lye 1975). Anxiety states are commonly associated with increased respiratory rates and breathlessness, but it is important to bear in mind that anxiety may be the result of the breathlessness and not the cause. Lung paranchymal and musculo-skeletal changes occurring with ageing have beeen discussed in chapter 1. These may lead to breathlessness by increasing the work of breathing, so that the subject becomes aware of a change in the respiratory pattern or rate. Other factors causing exertional breathlessness are summarised in table 2, including non-respiratory factors which must be considered - for example, mobility disorders and obesity, which also increase the work of breathing or effort expended during physical activity.

Psychological	
	- anxiety states
	- depression
Lung parenchymal	
	- pulmonary fibrosis
	- obstructive airways disease
	- pneumonia
	- lung resection (eg. for TB, cancer)
Cardio-vascular	
	- anaemia
	- congestive cardiac failure
	- peripheral vascular disease
Musculo-skeletal	
	- age-related changes in throracic cage and spine
	- arthritis
Neurological	
	- motor neurone disease
	- stroke
	- Parkinsons disease
Obesity	

Table 2 - Factors associated with shortness of breath on exertion in elderly subjects.

Studies have been undertaken to assess how the central control of respiration is affected by ageing, to see if changes in the respiratory centre of the medulla may account for the increased frequency of breathlessness where other factors (table 1) do not appear to be involved. Although the metabolic rate decreases with advancing age (Aub and Dubois 1917), there are generally less demands made on the respiratory and other systems by the older person. Respiratory frequencies increase slightly with age (McFadden et al 1982). However, the basic need for intake of oxygen and excretion of carbon dioxide means that alveolar ventilation relative to metabolism remains constant with age. Thus the arterial CO_2 partial pressure remains essentially constant throughout life in the absence of disease (Tenney 1964).

Ventilatory drive and respiratory centre function can be assessed by measuring the ventilatory response to hypercapnoea (Read 1967; Rebuck 1976) or hypoxia (Severinghaus et al 1976). This may be further supplemented by the measurement of mouth occlusive pressures generated when a shutter is closed momentarily (0.1 seconds after onset of inspiration) at different levels of hypoxia or hypercapnoea (Whitelaw et al 1975; Cherniak et al 1976). These measurements are affected in chronic lung disease where diminution of respiratory drive has been demonstrated in chronically hypercapnoeic individuals (Goldring and Turino 1976; Meili et al 1980). This contrasted with the demonstration of increased drive associated with acute hypercapnoea occuring with airways occulsion occuring in an asthmatic attack (Gelb et al 1977; Zackon et al 1976). Reduced inspiratory muscle force also diminishes the ability of the respiratory system to respond to hypercapnoea or hypoxia (Mead 1976), in particular affecting the measurement of mouth occlusive pressures.

Within the central nervous sytem increased thresholds and poorer discrimination has been noted in higher sensory phenomena with advancing age (Mahler et al 1986), associated with morphologic decrease in the number of cells in the cortex. Cells in the medulla are the last to undergo ageing change and therefore the integrity of the vital centres are preserved even in extreme old age (Tenney 1964). It has been shown, however, that with ageing the responsiveness to both hypoxia and hypercapnoea decreases (Hirshman et al 1975). Levitzky (1984) suggests that this may be due to decreased sensitivity of arterial and central chemoreceptors, compounded by reduced respiratory muscle strength and altered lung and chest wall mechanics (chapter 1). For smokers respiration may be further impaired, possibly due to an effect of nicotine on the respiratory centre, even in subjects with no significant airways obstruction (Chadha et al 1985).

No significant change in ventilatory response to CO_2 is detected in the normal elderly subject until the maximum breathing capacity (M.B.C.) has fallen to about 40% of that achieved by a normal young adult, which does not occur until around the age of 70 years, and even then showing no more than a 50% reduction (Tenney 1964; Kronenberg and Drage 1973). This is clearly illustrated in figure 14. Although alveolar partial pressures of CO_2 (P_ACO_2) remain unchanged with increasing work loads in the elderly, the decreases in maximum breathing capacity leads to reduced P_ACO_2 on exercise. The degree of depression of the respiratory centre following narcotic analgesics is only slightly greater than in younger adults, but a striking difference is the tendency for morphine to produce Cheyne-Stokes type periodic breathing in the elderly (Mahler et al 1986).

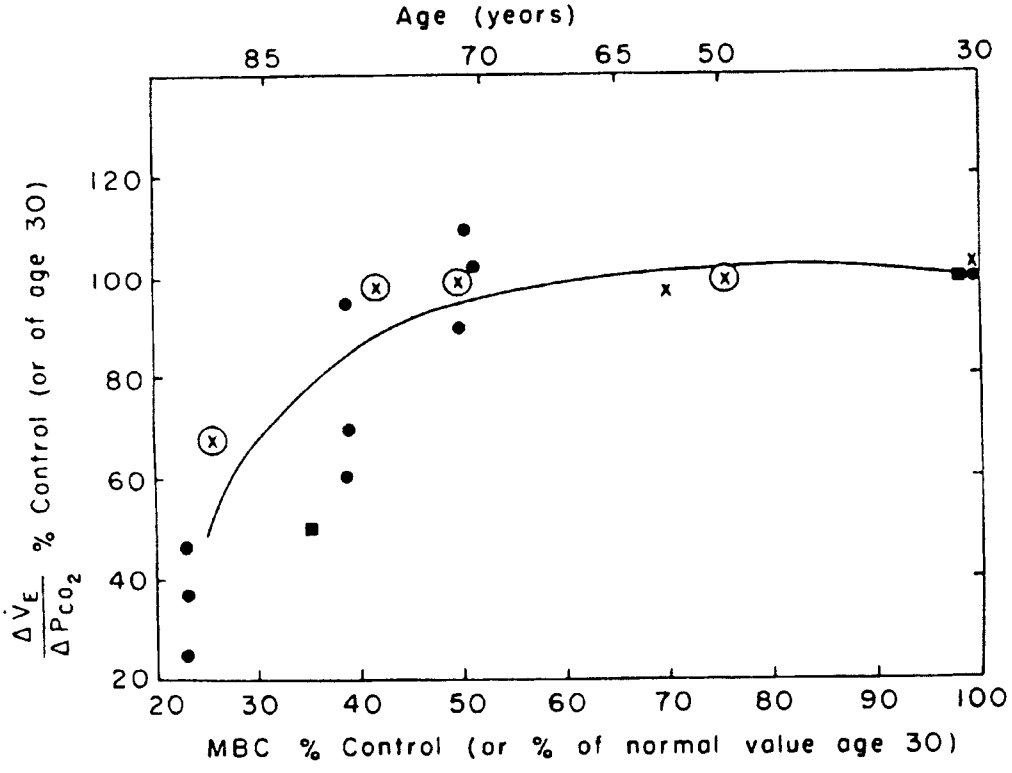


Fig. 14: Change in ventilatory response ("sensitivity") to CO_2 ($\Delta V_E / P_ACO_2$) in relation to reduction in maximum breathing capacity (M.B.C.) produced by obstructed breathing at different ages. Control values used are as for a normal subject aged 30 yrs. (Tenney 1964)

2.3 Smoking and chronic lung disease

Since the 1950's it has been well demonstrated by extensive research that smoking is directly related to the incidence of lung cancer, chronic bronchitis and emphysema. Pulmonary fibrosis may also be produced as a result of cigarette smoking (Weiss 1984). Smokers have also been shown to suffer from chronic and acute illness in proportion to the amount smoked (Balarajan

1985). Many smokers stop because of deteriorating health hence recent ex-smokers consult their doctor most often with symptoms (Horsley et al 1986), but smokers continue to grossly underestimate or deny the risks to themselves of continued smoking (Marsh 1985). Motivation to stop smoking is unrelated to age (Horsley et al 1987), although many elderly smokers take the attitude that, having smoked for most of their lives, there is little point stopping in their 70's and 80's unless forced to do so by financial constraints. This may, in fact, be true for some smokers who have so far escaped respiratory complications, since there is some evidence that the smoking pattern (depth of inhalation, 'puffing' pattern, puff-inhalation time) may relate to whether lung disease develops or not (Medici et al 1985). Even for the elderly, however, there is considerable benefit to be gained from stopping smoking (Beck 1981; Pounsford 1987). A greater proportion of elderly people are lifelong non-smokers, and the General Household Survey in 1982 (OPCS 1984) showed a significant decline in smoking amongst the elderly over the preceding 10 years.

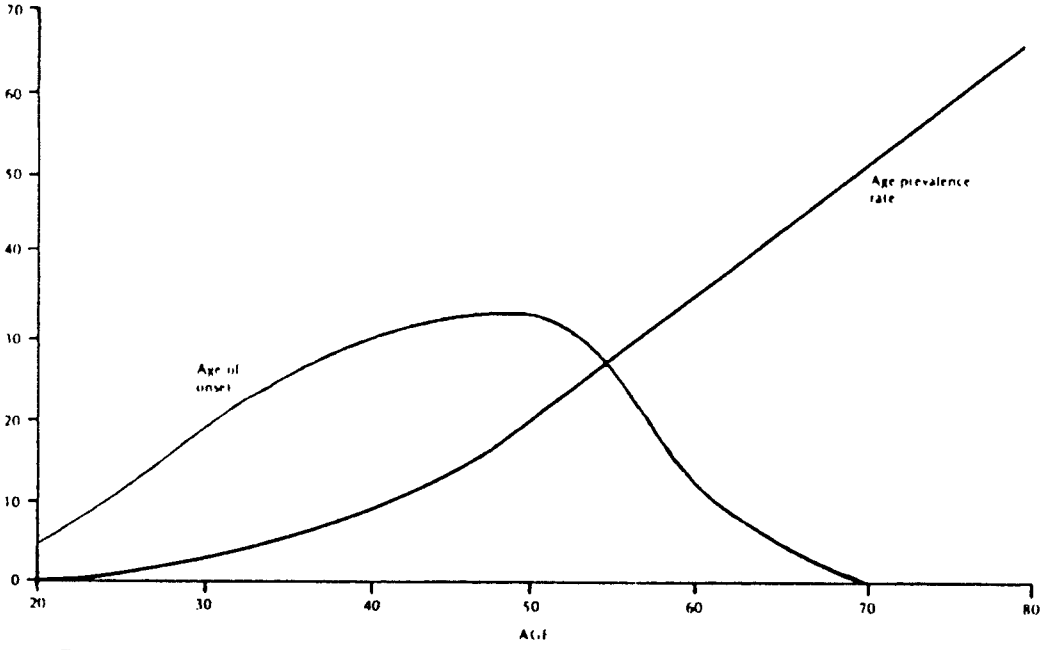


Fig. 15: Prevalence of chronic bronchitis in males (Lye 1986, using data from Fry, 1960 and the College of General Practioners, 1961).

A survey conducted by the College of General Practioners in 1961 demonstrated that the peak age of onset for chronic bronchitis for men was in the 4th and 5th decades, with the prevalence increasing rapidly with advancing age (Fig. 15). It is unusual, however, for chronic bronchitis to begin once

over the age of 60 yrs, (Lye 1986). The lower prevalence of chronic bronchitis for elderly women reflects the lower prevalence of smoking amongst women (OPCS 1984) and may also be influenced by a difference in smoking patterns as described by Medici et al (1985).

Milne and Williamson (1972b), using the FEV% as an index of airway obstruction, showed that the FEV% was significantly lower in elderly cigarette smokers than non-smokers. They found 32.4% of male cigarette smokers (including ex-smokers) had an FEV% of less than 60%, as compared to 6.7% of male non-smokers and 11.5% pipe smokers. The chance of having airflow obstruction (FEV% < 60%) correlated closely with the number of years smoked in elderly men:

40 year + smoking history	- 33% had FEV% < 60%
20 - 39 yrs smoking history	- 7.4% " "
Never smoked cigarettes (but includes pipe smokers)	- 9.8% " "

Although a similar correlation between reduced FEV% and cigarette smoking was seen for women, it was not as striking as for men and was not so clearly related to the numbers of years smoked.

Respiratory symptoms were significantly worse, and reported more frequently, by subjects with FEV% < 60%, as shown in table 3. Wheeze was a common symptom, particularly amongst those with airflow obstruction (Milne and Williamson 1972b), and was also shown to be related to cigarette smoking (Milne and Williamson 1972a). A history of asthma was given by 9.3% (42/450 in table 3), commonest amongst those with airflow obstruction. More severe breathlessness (graded according to the MRC criteria, 1965) was found amongst male cigarette smokers, only 5.1% non-smokers having grade 3 or 4 dyspnoea as compared to 18.1% of current and ex-smokers (Milne and Williamson 1972a). Interestingly, there was no difference in the prevalence of severe dyspnoea according to smoking status amongst the females studied.

Caird and Akhtar (1972) also showed a high prevalence of chronic bronchitis, affecting 26% of elderly men and 13% women, in an age-stratified random sample in Glasgow. Unfortunately 30% of those approached refused to participate, therefore introducing an unavoidable bias into the prevalence based on the 300 who agreed to participate. Nevertheless the prevalence is close to that found in Edinburgh where 31.8% men and 9.2% women had chronic bronchitis, with an overall prevalence of 23.7% (Milne and Williamson

1972a). Clearly, with chronic chest disease being so common amongst the elderly, a positive approach to its management is essential (Paine and Make 1986). Although chronic bronchitis seldom starts in old age (Lye 1986), the problems resulting from it certainly increase with age (Howard 1987).

	Percentage symptomatic			
	Men		Women	
FEV%	<60%	>60%	<60%	>60%
(n)	(51)	(156)	(13)	(230)
Persistent cough + phlegm	55.0	25.6	46.0	7.4
Hospital admission with respiratory illness	29.4	14.7	38.0	7.0
Wheeze	74.5	41.0	69.0	33.0
Asthma	25.5	7.1	38.0	5.7
Severe dyspnoea (grades 3 & 4)	34.0	8.8	41.7	17.4

Table 3 - Relationship between FEV% and respiratory symptoms in 450 elderly people (age range 62 - 90yrs). (Milne and Williamson 1972b).

A multidisciplinary approach is particularly beneficial for the elderly with chest disease and can achieve a worthwhile improvement in quality of life (Morris 1987). The Day Hospital can provide a useful venue for treatment, but requires local general practitioners to be fully aware of the type of services available for proper patient selection (George and Young 1989). Much can be done without recourse to polypharmacy, since multiple drug regimens can cause considerable morbidity amongst the elderly. There is significant benefit to be gained from simple daily exercise routines, for example, which can achieve as much as 25-30% improvement in exercise tolerance (Howard 1987) as well as immeasurable improvement in morale.

CHAPTER 3

ASTHMA

3.1 Introduction

Progress in epidemiologic studies of asthma has been hampered by a lack of uniformity in the diagnostic criteria applied. This is further complicated by the variability of symptoms with which the patient may present. Laennec (1834) described the spasmodic nature of asthmatic attacks and also noted that, in severe attacks, wheezing was often absent. This was similarly described by Farr et al (1973) who highlighted the importance of thorough pulmonary function assessment, including bronchodilator response, in a patient complaining of episodic tightness in the chest, even if physical signs are absent on examination.

An interesting historical review by Sakula (1988) traced descriptions of treatment for symptoms suggesting asthma to ancient Chinese writings dating from at least 1000 B.C. In the works of Aretaeus, who lived from 81-131 AD, comes a vivid description of asthma:

> *"The symptoms of its approach are a heaviness of the chest, sluggishness to one's accustomed work and to every other exertion, difficulty breathing on a steep road.... But if the evil gradually gets worse, a wheeze during the waking state, but the evil much worse in sleep, a desire of much and of cold air ... they breathe standing as if desiring to draw all the air which they can possibly inhale and they also open the mouth... During the remissions, though they may walk erect, they bear the traces of the affliction." (Aretaeus: TrAdams 1856)*

Although "asthma" has been a well-recognised disease since ancient times, it's diagnosis can still present a problem - especially in the inactive phase between attacks. The difficulties in defining "asthma" were considered recently by Scadding (1987), relating observed symptoms and recorded abnormalities to variable airflow obstruction. Although pathogenesis must be taken into account in the definition, "asthma" is generally accepted as a clinical condition with multiple aetiologic factors involved and several different presentations.

3.2 Definition of asthma

In 1958 a Ciba Foundation symposium was convened to consider the "Definiton and Classification of Pulmonary Emphysema" (Ciba 1958). A definiton of asthma was produced that recognised variability in airways obstruction as the principle feature of asthma:

> *"Asthma refers to the condition of subjects with widespread narrowing of the bronchial airways which changes in severity over short periods of time either spontaneously or under treatment, and is not due to cardiovascular disease."*

Subsequently Scadding (1983), discussing the variable clinical manifestations of "asthma", offered a definition in physiologic terms:

> *"Asthma is a disease characterised by wide variations over short periods of time in resistance to flow in intrapulmonary airways."*

Both these definitions go beyond the purely symptomatic descriptions given by Aretaeus (1856) and Laennec (1834), and identify the need to relate symptoms to measureable abnormalities in lung function. However, since medicine is principally a clinical speciality, a physiologically based definition does not help the general practitioner to recognise the condition earlier.

An attempt to offer a collection of symptoms which related to the clinical entity recognised as "asthma" was reported by Mortagy et al (1986). In particular, his study set out to identify those people likely to benefit from bronchodilator therapy, since respiratory symptoms alone are little value in predicting increased bronchial reactivity (Howell and Waters 1987). Limitations in the use of bronchial reactivity measurements for the diagnosis of asthma are further discussed in chapter 4. It is generally agreed however, that bronchial hyperreactivity to a variety of inhaled substances is commonly, but not exclusively, a feature of the asthmatic subject (Chung 1986).

Pathologic definitions of asthmatic characteristics are largely based on post mortem findings, but have also been supplemented by data from broncho-alveolar lavage and endo-bronchial biopsies (Hogg et al 1977). In view of the marked inflammatory reaction demonstrated in the airways, the term "chronic desquamating eosinophilic bronchitis" has been suggested to describe the pathologic features, differentiating the asthmatic response from airway changes associated with chronic bronchitis or smoking (Reed 1988).

A comprehensive definition for asthma is therefore difficult to attain since it must take account of four different aspects of the condition:

(i) symptoms
(ii) physiologic changes in lung function
(iii) provocative factors/aetiology
(iv) pathologic changes

The American Thoracic Society (1962) endeavoured to do this in a statement aimed at achieving agreement on terminology "to facilitate communication and to promote understanding" amongst physicians dealing with chest diseases:

> *"Asthma is a disease characterised by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy."*

Unfortunately this statement still does not adequately describe the disease, omitting any reference to specific aetiology, leaving out detail on specific clinical and pathologic features, and with no reference to specific immunologic features - all points which Scadding (1971, 1983) considers essential to the definition of a disease. A second Ciba Foundation symposium on asthma also failed to reach agreement on a universally acceptable definition. They felt that more research was needed to study the variability of different measurements in asthma. A working group was set up after the symposium and, although still unable to offer a comprehensive definition for asthma suggested that:

> *"In the meantime, confusion would be reduced if all those who use the word 'asthma' in publications would provide as much detailed information as possible on symptoms and clinical signs (including characteristics of the sputum), on tests of lung function (including blood gases), on precipitating factors, on evidence of immunological abnormalities, on bronchial hyper- reactivity and, where appropriate, on anatomical changes." (Fletcher et al 1971)*

Controversy still exists over the classification of asthma proposed at the Ciba Foundation Symposium (1971) in view of the difficulty separating asthmatic subjects from those with bronchitis, many of whom also have increased bronchial responsiveness to other stimuli (Pride 1984), this being a particular problem amongst children (McNichol and Williams 1973). A further problem is that the airways of asthmatics are not consistently responsive to stimuli, so that the absence of increased bronchial reactivity does not exclude the diagnosis. This is discussed further in chapter 4.

3.3 The prevalence of asthma

Estimates of asthma prevalence in the community have varied considerably, affected both by the survey methods used and the criteria accepted for the definition of "asthma". A history of episodic wheezing is frequently reported - affecting 22% of male and 20% of female subjects over 18 yrs of age in one study conducted in a rural area of Conneticut (Schachter et al 1985). Although this was a cross-sectional survey, there were relatively few subjects aged over 45 years so that the data cannot be reliably applied to a population with a different age profile. On review after 6 years they discovered that 77% of those reporting wheezing when first interviewed were now asymptomatic. A history of asthma was elicited in 7% of males and 5% of females, of whom 68% (50 subjects) were in remission when reviewed after 6 years. A history of wheezing correlated strongly with both cigarette smoking and chronic bronchitis, but there was considerable overlap with the asthmatic group.

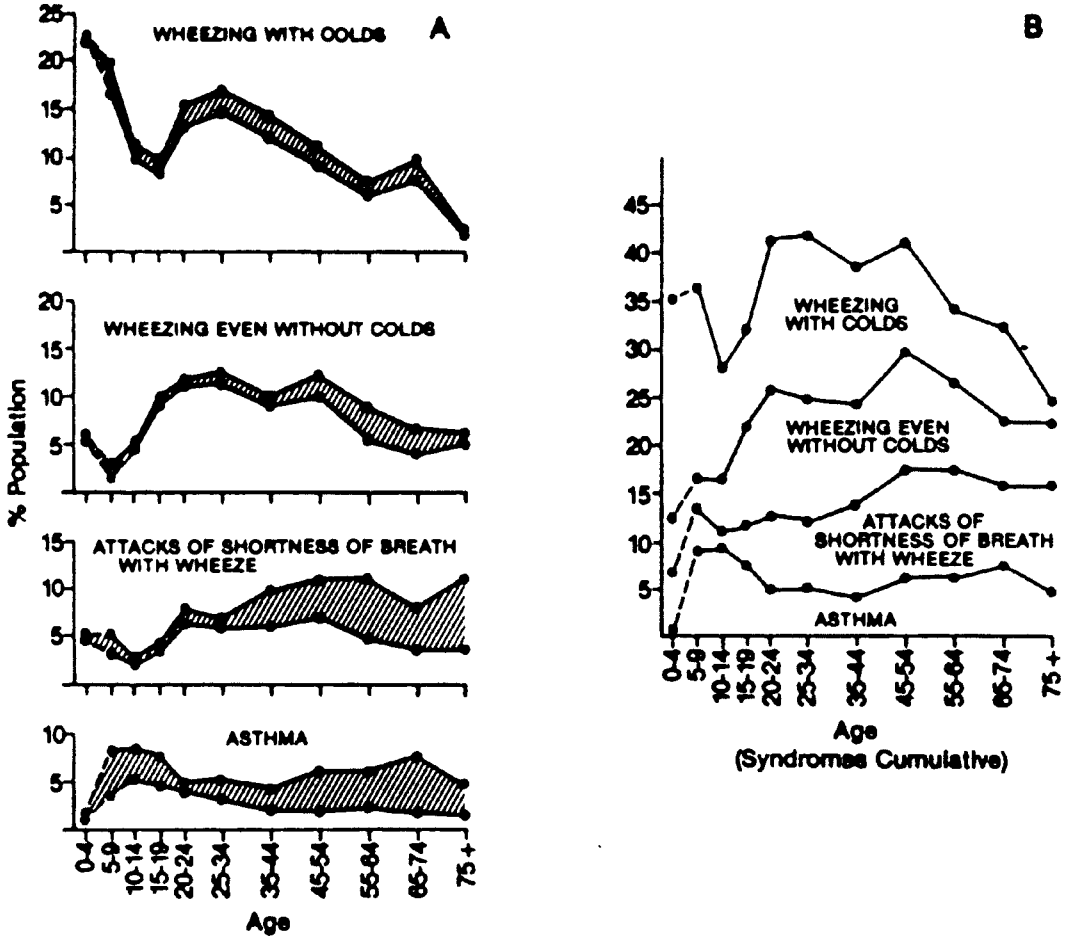


Fig. 16: Prevalence of various "wheezing syndromes" identified within a general population sample in Arizona by age-group.
a. Point prevelance of each of the "wheezing syndromes". The shaded area indicates subjects diagnosed as having both "chronic bronchitis and/or emphysema" and specified "wheezing syndrome".
b. Shows the contribution of each of the "wheezing syndromes" to the total prevalence of wheezing episodes within the population studied.
(Dodge and Burrows 1980)

Dodge and Burrows (1980) carried out one of the most detailed analyses of asthmatic symptoms in a large (3860 subjects) random stratified sample. An 83.4% response rate was obtained and from this they were able to construct point prevalence figures for the population (Fig 16) showing striking variations in the prevalence of asthma at different ages, from less than 2% in infants aged under 5 years to a peak of 9.5% in men aged 50-59 years. Above age 50 yrs the prevalence of asthma was greater in men, in whom there was also a greater prevalence of chronic bronchitis and emphysema - often diagnosed concomitantly with asthma. Wheezing was again found to be nonspecific, associated with asthma, chronic airways disease and upper respiratory tract infections, and reaching a prevalence in excess of 40% in some age groups.

However, this was not a true representation of the total population, since only non-Mexican white American households were surveyed. This is further complicated by the trend for patients with established chest diseases to move to Arizona due to its favourable climate, adding to the prevalence of symptoms in the older age groups, around 75% of asthmatics having had their disease before moving to Arizona (Burrows 1981). Nevertheless it is clear that, even if a history of shortness of breath is also taken into account as well as wheezing, using symptoms alone to diagnose asthma would have given an enormously high prevalence (over 40% in some age groups) compared to the prevalence of known asthma (6.6%). In fact the true prevalence of asthma is likely to be in between these figures, since such a dramatic overlap between bronchitic and asthmatic symptoms was demonstrated by this study: of 97 asthmatics aged over 50 years, 75% of men and 67% of women had also been diagnosed as having "chronic bronchitis and emphysema" using accepted criteria (A.T.S. 1962). Dodge and Burrows (1980) therefore concluded that in older subjects it was not possible to clearly distinguish between "asthma" and "chronic bronchitis", suggesting the term "asthmatic bronchitis". This does not appear helpful, however, since by lumping the two conditions together it diverts attention from the importance of distinguishing those with reversible airflow obstruction from those with less remediable disease.

The prevalence of asthma does appear to be rising (Fleming and Crombie 1987) and there is growing concern about the possibility of environmental factors, in particular pollution, being responsible for this increase (Editorial 1986). Sulphur dioxide can provoke asthmatic attacks (Bethel et al 1983), but a Swedish study did not show any relationship between sulphur dioxide exposure and asthma. It did, however, indicate correlation between cigarette smoking, male sex, occupational sulphur dioxide exposure and the development of chronic bronchitis (Stjernberg et al 1985). Hodgkin et al (1984)

showed atmospheric pollution (smog) definitely increased the risk of developing chronic airways disease in non-smokers, but this did not appear to affect the prevalence of asthma - 6.4% prevalence of diagnosed asthma in low pollution areas compared with 6.7% in areas of high atmospheric pollution. Table 4 summarises various recent estimates of the prevalence of asthma in general population ranging from 2.7 - 11.1% in children and 1.0 - 9.9% in adults. Higher prevalences were noted for adults in Scandinavia and Norway, and some of the highest figures from the United States. This topic is also considered in greater detail by Gregg (1983).

Author	Area	Age group (yrs)	Prevalence (%)		
			Male	Female	Overall
Children					
Williams 1969	Melbourne, Australia	7 - 10			19.1
Morrison-Smith 1976	Birmingham, UK	5 - 16			2.7
General adult					
Irnell 1968	Sweden	30 - 64	2.3	2.3	2.3
Burr 1975	South Wales	20 - 44	1.7 Current asthma		
			3.4 current + past asthma		
Higgins 1977	Michigan, USA	20 - 74	3.0	4.0	
Dodge 1980	Arizona, USA	All	6.9	6.2	6.6 (1.5 - 9.5 according to age)
Mikaelsson 1982	North Sweden	20 - 64	3.0	3.2	
Hodgkin 1984	California, USA	25 +			6.5
Schachter 1985	Conneticut, USA	7 +	7.0	5.0	
Fleming 1987	England & Wales	5 +	2.8	2.6	
Elderly					
Broder 1962		60 +			5.3
Higgins 1977	Michigan, USA	65 - 74	5.3	9.9 Asthma ever	
			3.1	3.5 Current asthma	
Burr 1979	South Wales	70 +	5.1	1.8	6.5 asthma ever 2.9 current asthma
Dodge 1980	Arizona, USA	60 +	7.1	6.4	
Bannerjee 1987	North Wales	55 - 97			41.2 broncho-dilator responsive

Table 4 - Various estimates of asthma prevelence in different communities

3.4 Asthma in the elderly

Most studies of asthma have either excluded the elderly or included too few elderly subjects to provide accurate data on the prevalence of asthma in the elderly. Lee and Stretton (1972) have pointed out that asthma may occur for the first time in the elderly, in whom it is frequently misdiagnosed as chronic bronchitis or obstructive airways disease. Also asthma that persists in adults, whatever the age of onset, tends to worsen as the subject gets older and more deaths from asthma occur over the age of 55 years. Burr et al (1979) found that, of his elderly subjects with asthma, 37% had developed symptoms only after age 55 years and 22% first developed symptoms after age 65 years. Moreover, asthma in the elderly is just as life threatening as in the young adult.

Burr et al (1979) surveyed a 1:8 sample of subjects aged over 70 years in a South Wales town. Of 485 subjects, 12 (2.9%) were found to have current asthma - 3 of these had not been previously diagnosed as asthmatic and 4 were unaware of their diagnosis, despite being on treatment for asthma. Another 15 (3.6%) had either mild asthma or a history of past asthma, giving a total prevalence of 6.5% for any history of asthma (past or present). They noted that the disease might start or remit at any age and that a history of asthma was more common amongst elderly men (5.1%) than women (1.8%). Spirometric abnormalities were shown to be more severe than for younger asthmatics. In addition, 29.7% (41) of the men surveyed and 13.9% (39) women had chronic bronchitis.

Late onset asthma is generally intrinsic, frequently with a history of chronic bronchial irritation and seldom with positive skin tests (Ford 1969; Dodge and Burrows 1980). This has contributed to the misdiagnosis of elderly asthmatics as "bronchitic" and a tendency to "therapeutic nihilism" (Scadding 1971).

In the study by Burr et al (1979) residents of residential homes (social service or private) were excluded. Bannerjee et al (1987) therefore surveyed patients aged 55-97 years attending the Wrexham Geriatric Day Hospital or in local authority residential homes. Respiratory symptoms were compared to bronchodilator responsiveness, measuring FEV_1, PEFR and FVC before and after salbutamol inhalation. They found that 41.2% showed significant improvement in PEFR (larger than 15% increase) after salbutamol, described as "reversible" subjects in table 5. Sputum and cough were a little more common amongst the "non-reversible" subjects, although wheezing was equally common in both groups. Although 61% of all their study patients had a significant degree of airflow obstruction and 41.2% responded to bronchodilator, only 6% were receiving any respiratory medication or antibiotic therapy. A similar problem with gross under diagnosis and undertreatment of asthma has also

been reported in children (Speight et al 1983), suggesting unnecessary respiratory mobidity at both ends of the age spectrum.

(n)	"Non-reversible" (113)	"Reversible" (82)
Mean age, years	79	78
% male	58	60
% smoker	45	50
% wheeze		
none	70	71
moderate	27	26
severe	4	4
% sputum		
none	64	73
moderate	35	21
severe	1	6
% S O B		
none	69	66
moderate	29	31
severe	2	2
% cough		
none	50	59
moderate	39	38
severe	12	4
Pre-test PEFR (% predicted)	69.0	53.5

Table 5. - Relationship of bronchodilator responsiveness to respiratory symptoms in 195 randomly selected elderly patients. Reversibility defined as > 15% increase in PEFR after salbutamol (Bannerjee et al 1987) S.O.B. = Short of breath

3.5 Asthma mortality

There has been a disturbing increase in asthma deaths in recent years, both in England (Eason and Markowe 1987) and overseas (Keating et al 1984). As shown by the latter study, this is despite increased prescribing of bronchodilator drugs and does not appear to be due to adverse effects of the drugs, in contrast to the strong association between over the counter sales of isoprenaline inhalers in the 1960's (Speitzer et al 1968; Fraser et al 1971). An inquiry by the British Thoracic Society (1987) found that respiratory infections were the commonest event to trigger the fatal asthmatic attack, and that appropriate and potentially life-saving measures were often not given, or commenced too late, because patients, relatives and doctors had failed to recognise the warning signs of acute severe asthma. Atopic asthmatics were shown to be at greatest risk of acute severe attacks.

The elderly, who are generally non-atopic, are equally at risk (Lee and Stretton 1972), and frequently tend to underestimate their symptoms and delay reporting them to their doctor (Williamson et al 1964). Recent O.P.C.S. data (1987) has shown that almost half the asthma deaths occur in patients aged over 65 years. A major concern is that the increased availability of home nebulisers may lead to delay in hospital admission for acute severe asthma by giving the patient and doctor a greater sense of (false) security in the home (Cochrane et al 1985; Sears et al 1987).

Eason and Markowe (1987) found 45% of patients dying from asthma had done so before hospital admission; other studies have shown up to 86% dead on arrival (BTS 1982). Clearly, patients are not necessarily "safe" once they have reached hospital, since positive pressure ventilation may be incorrectly delayed in someone who appears "comfortable" after bronchodilator nebulisation (Eason 1988). The British Thoracic Society (1982) concluded that 82% of asthma deaths investigated in their study were potentially avoidable, identifying major areas of mismanagement in many of these.

Acute severe asthma and asthma deaths occur commonly at night (Barnes 1984), associated with the well-documented circadian rhythm in asthma which results in increased airways obstruction occuring at around 0300-0400 hrs (Clark 1985). Horn et al (1987) established that nocturnal deaths in their study were related to the variability of airflow obstruction and not due to lack of available domiciliary medical (general practitioner) care.

Rea et al (1986) demonstrated that patients dying from asthma were likely to have had a previous life-threatening asthmatic attack and most had also had a recent hospital admission with their asthma. This would suggest that recognition of a high-risk group should be relatively easy and intensive education about their asthma could be directed to these patients. Unfortunately Ellis and Friend (1985) found that even patients attending a specialised Asthma Clinic had a poor understanding of their disease and were unable to judge the severity of their asthma or what to do in the event of an acute attack. Lack of awareness of danger signs, leading to delay in seeking medical help until desparately ill, was also found, with evidence of inadequate patient education. This is an even greater problem for the immigrant population, for whom language barriers lead to even greater difficulties in patient education (Ayres 1986). A similar problem with comprehension of instructions may also contribute to asthma deaths amongst the elderly, with the misconception that they should "try not to bother the doctor until the morning".

3.6 Treating asthma in the elderly

The previous section underlines the importance of proper patient education, irrespective of age, if respiratory mortality is to be reduced. Instructions must be clear, but if there appears to be any difficulty in comprehension a short assessment of mental function (Quereshi and Hodkinson 1974) is advisable before deciding on the method of treatment. Allen and Prior (1986) found that if the mental function test score was less than 7/10 it was unlikely that the patient would cope with a self-administered metered dose inhaler.

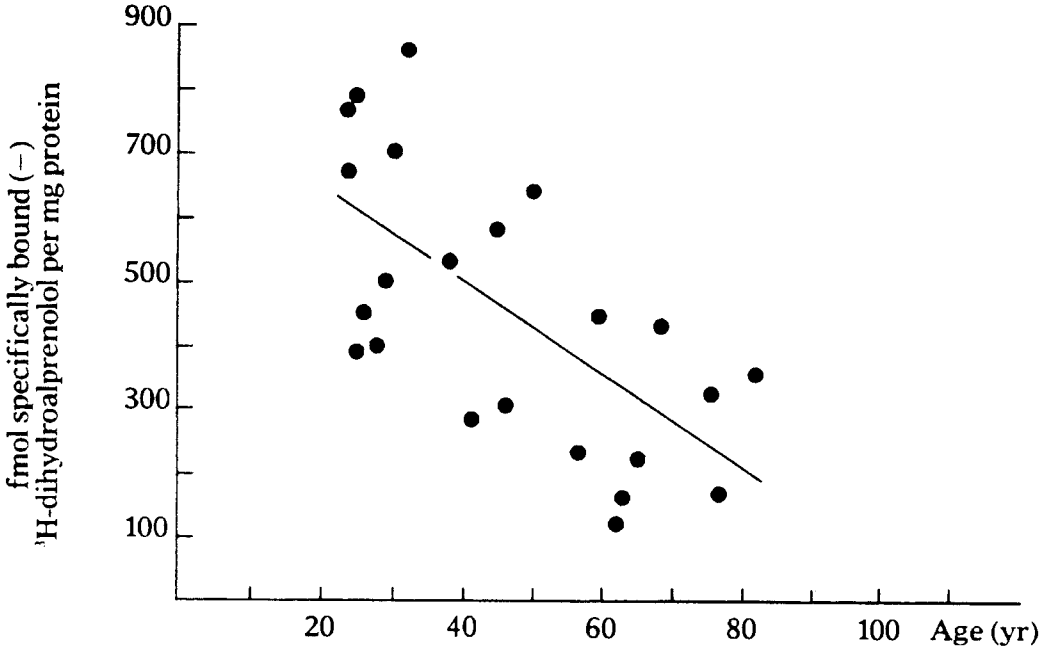
Assessing 30 elderly patients who had been prescribed a metered dose inhaler, Allen and Prior (1986) found 40% were totally unable to use the inhaler and only 10% had an ideal inhaler technique. Incoordination between inhaler activation and inhalation was the commonest problem, unrelated to age, and this could not be overcome for several patients even with intensive coaching. Problems with inhaler therapy can therefore be anticipated in the following situations:

Impaired cognitive function (mental test score $< 7/10$)
Dyspraxia
Weak or deformed hands
Poor instruction

Armitage and Williams (1988) found that decreased ability to squeeze the inhaler was a common problem, due to weak hands, but could be overcome by using a simple squeezing device (Haleraid, Allen and Hanbury). Once this problem was overcome, the majority of elderly patients in their series were able to properly coordinate inhaler activation with inhalation. If after several attempts at instruction, the patient remains unable to use the inhaler, an alternative delivery system should be tried. Several are now available, some using dry powder delivery systems (eg. Ventodisc, Allen and Hanbury) and others dispensing a single dose of the drug into a chamber which can then be inhaled (eg. Turbohaler, Astra). Recently a breath activated metered dose inhaler has also become available (Aerolin Autohaler, 3M Riker). Other devices such as the Volumatic delivery system (Allen and Hanbury) permit activation of the inhaler into a conical flask, from which the dispersed medication can be inhaled readily via a low resistence one-way valve at the mouth piece.

Only around 10% of the administered dose of a bronchodilator reaches the lower airways, whether it is given by nebuliser or a correctly used metered dose inhaler (Newman et al 1981). Thus it is important to ensure proper inhaler technique to optimise delivery before considering the use of domicil-

iary nebulisers, which carry with them considerable risks if improperly used or inadequately supervised (Laroche et al 1985). Inhaler technique is not the only cause for decreased effectiveness of bronchodilators in the elderly, however, since several studies have shown that the number of beta-receptors in the airways declines with age, (Fig. 17, Schocken and Roth 1977).



Maximal specific binding of (−) ³H-dihydroalprenolol
to crude mononuclear cell membranes of subjects aged 24-81 yr.

Fig. 17: Decline in beta-adrenergic receptors with age, as measured by maximal specific binding of (-)3H-dihydro-alprenolol to crude mononuclear cell membranes of subjects aged 24-81 years. (Schocken and Roth 1977).

Reduction in beta receptor numbers is suggested as the reason why elderly subjects are less responsive to salbutamol and similar drugs (Vestal et al 1979). Alternative inhaled medication, such as ipratropium, may therefore be more effective than salbutamol in the elderly, as no age-related decline in ipratropium-responsiveness has been demonstrated (Ullah et al 1981). Connolly (1984) found oral beta-agonists and theophyllines were used more frequently in older subjects attending his asthma clinic. He also noted more elderly on oral cortico-steroids, due to a combination of difficulty using inhalers and increased cortico-steroid resistance in older subjects. The synergy between inhaled and oral medication is also considered by Flenley (1987), but he also warns of the dangers of polypharmacy producing more adverse effects than benefit. Accurate diagnosis is essential and chapter 4 reviews methods of assessing bronchial hyperreactivity as a means of supplementing the clinical interview and examination in establishing the diagnosis of asthma.

CHAPTER 4

BRONCHIAL HYPERREACTIVITY - CLINICAL SIGNIFICANCE AND ASSESSMENT

4.1 Introduction and Historical Review

Bronchial asthma is characterised by the presence of increased bronchial reactivity and reversible airflow obstruction (chapter 3.2). In remission, however, the degree of airways obstruction may be minimal and lung function test results entirely normal (Parker et al 1965; Horsley et al 1985). Airways hyperreactivity to inhaled bronchoconstrictor agents, both naturally occurring or when administered during iatrogenic provocation testing, remains elevated whilst the asthmatic is in remission (Juniper et al 1982), the degree of airways responsiveness correlating closely with the presence and severity of asthma (Hargreave et al 1981). Thus a major benefit of bronchial provocation challenge testing is the identification of increased airways reactivity in subjects without other features of active asthma. This is important since it enables a proper diagnosis to be obtained in a patient presenting with episodic "tightness in the chest" which is not necessarily a psychologic overlay manifesting itself between more obvious asthmatic attacks (Farr et al 1973).

Considerable research has been undertaken using bronchial provocation testing, stimulated by awareness of the deficiencies in knowledge relating to the pathogenesis of airways reactivity (Holgate 1987). However this is not a new technique, Barker and Sladen (1912) reporting the contrasting effects of subcutaneous pilocarpine and atropine in asthmatic subjects. A few years later Alexander and Paddock (1921), again using subcutaneous pilocarpine, showed that symptoms and signs similar to an asthmatic attack could be induced in 20 asthmatics who were clinically in remission at the time of study. Starr et al (1933a) inadvertently produced acute bronchospasm following subcutaneous acetyl-beta-metyl choline administration to a young patient who had not had any asthmatic symptoms over 7 years. This led him to further studies which demonstrated that orally administered methacholine could also precipitate mild bronchospasm in asthmatics as well as various non-respiratory effects such as tachycardia and gastro-intestinal upsets (Abbott 1933; Starr 1933b).

These studies led Moll (1940) to review the literature on the action of parasympathometic drugs in asthma. This led on to studies of the response to subcutaneous methacholine in subjects with other respiratory diseases, including a group of healthy medical students as 'controls' - who did not react. He was able to differentiate by the response obtained following injection between subjects with bronchiectasis associated with asthma (who developed major chest symptoms) and those with bronchiectasis from other causes such as pulmonary tuberculosis (few chest symptoms, but considerable generalised reaction - flushing, lachrymation, salivation, sweating). Atropine was then demonstrated to block the response when given prior to subcutaneous methacholine. He considered that lung damage was an essential factor in determining the abnormal response to methacholine in asthmatics, leading to enhanced local sensitivity in the lungs. This suggestion was supported by the demonstration that the non-respiratory symptoms produced by methacholine were the same for asthmatics and non-asthmatics, the only difference being in respiratory response. Moll concluded that this test was valuable in the differentiation of true asthma from respiratory neurosis, particularly hysterical hyperventilation. No matter how mild or infrequent asthmatic attacks were, he had found increased sensitivity to subcutaneous methacholine in most asthmatics.

The following year, after preliminary studies in dogs, Dautrebande and Philippot (1941) reported the effects of aerosolised carbaminocholine inducing breathlessness and bronchospasm, as well as increased respiratory frequency with altered alveolar gas composition. An aerosol of phenylaminopropane was shown to reverse the effects completely, for the first time demonstrating that drugs could be administered into the respiratory tract for the diagnosis and control of asthma.

The next major contribution towards the use of nebulised bronchoconstrictors in the diagnosis of asthma was from Curry (1947). He demonstrated that a 1:40,000 dilution of methacholine nebulised into the lungs could produce a much greater reduction in vital capacity than when administered by other routes - even though the doses given intravenously or intramuscularly were considerably greater. The pattern of response to nebulised methacholine was similar for his asthmatic subjects although the magnitude of response varied, a 76% fall in vital capacity occurring in one subject - fortunately responding to intramuscular epinephrine after intravenous atropine, which had been recommended by Moll (1940) for use following iatrogenic bronchoconstriction, had failed to work. He had clearly shown that the tracheo-bronchial tree was particularly sensitive to bronchoconstric-

tors administered by nebulisation and that the magnitude of response was affected by the degree of asthmatic control.

Aerosol bronchoprovocation testing became more practical when the apparatus required and technique was simplified by Parker et al (1965). In addition to providing a method for further study of the mechanisms affecting control of bronchial reactivity (Boushey et al 1980), some authors consider the assessment of the level of bronchial hyperreativity to be essential in the complete assessment of an asthmatic. Woolcock (1980), for example, states that measurement of non specific airway reactivity

".....should be as essential to the diagnosis of and management of asthma as the glucose tolerance test is to diabetes".

4.2 Nonspecific bronchial reactivity

The airways of asthmatics have been shown to be markedly more sensitive than non-asthmatic controls to a variety of nonspecific agents. These include chemicals such as methacholine (Curry 1947; Fish et al 1976), histamine (Curry 1947; Ryan et al 1982), carbachol (Dautrebande and Phillipot 1941; Orehek et al 1977) and suphur dioxide (Sheppard et al 1980; Bethel et al 1983). Physical agents may also provoke bronchoconstruction. Cold air (Latimer et al 1983; Heaton et al 1984), nebulised sterile water or hypotonic solutions (Schoeffel et al 1981; Black et al 1985) and exercise (McFadden and Ingram 1979) have all been used as means of assessing broncial hyperreactivity. It is therefore unlikely that a single mechanism is responsible for mediation of bronchoconstruction in all these situations.

Moll (1940) suggested that pre-existent lung damage was fundamental to the increased bronchial reactivity of asthmatics. Laboratory studies have since supported the hypothesis that damage to the airway epithelium is an important factor, with bronchial biopsies adding further evidence. Laitinen et al (1985) showed that epithelial cell destruction, particularly ciliated cell damage, was evident in asthmatics with varying degrees of bronchial hyperreactivity. Although the degree of bronchial hyperreactivity could not be directly correlated to the extent of lung damage demonstrated, they concluded that exposure of mucosal afferent nerves to released stimuli or inhaled irritants could explain bronchial hyperresponsiveness in asthma. Other studies have suggested that opening of the epithelial tight junctions also plays an important role, exposing intraepithelial nerves and producing increased mucosal permeability to mediators of bronchoconstriction (Boucher et al 1978; Hogg 1982).

Recent viral infections enhance airway reactivity (Minor et al 1976), an effect which may be blocked by atropine inhalation prior to nonspecific challenge

(Empey et al 1976). Temporary epithelial damage was shown to result from the viral infection, leading to increased bronchial hyperreactivity by viral sensitisation of the airways receptors to inhaled irritants. This bronchoconstriction is considered to be mediated via the vagus nerve, in view of the protection afforded by pre-challenge atropine aerosol administration. Britten et al (1987) also demonstrated a strong association between early childhood respiratory infection and adult respiratory disease, as suggested by Pullen and Hey (1982), following infection with respiratory syncytial virus, in the first year of life, although other workers have not found this (Mok and Simpson 1984; Jenkins and Breslin 1984).

Cigarette smoking has been shown to damage the airway epithelium, producing increased mucosal permeability to irritant substances as a result of mucosal inflammation (Hulbert et al 1981; Hogg 1982). This does not necessarily lead to increased nonspecific bronchial reactivity (Kennedy et al 1984) unless there is co-existent allergic rhinitis (Buczko and Zamel 1984a), or a history of heavy cigarette smoking (Buczko et al 1984b). Although cessation of smoking in the latter study produced improvement in respiratory symptoms, it did not alter the level of airway reactivity. However, Taylor et al (1985), in a much larger study group, found a definite relationship between cigarette smoking and increased bronchial reactivity in smokers aged over 35 years: 30% of smokers, 24% of ex-smokers and only 5% non-smokers were reactors to inhaled histamine (up to a maximum dose of 16 mg/ml). Posession of increased bronchial reactivity in smokers was associated with an accelerated annual rate of decline in FEV_1. This supports the findings of Kanner (1984), who also showed a close relationship between bronchial reactivity and deterioration in FEV_1 for subjects with chronic airways disease. Unfortunately this latter study omitted detail of atopy and smoking history, although commenting that smoking was also "significantly associated" with decline in lung function, as was age. Further prospective longitudinal studies are needed since it remains unclear whether it is the bronchial hyperreactivity leading to the decline in the lung function, or cigarette smoking through other mechanisms (Weiss and Speizer 1984). Assessment of reactivity does appear to offer a means to detect a "high risk" group of smokers, to whom intensive anti-smoking health education and bronchodilators could then be targeted.

Increased levels of airway reactivity have been shown in close (non-asthmatic) relatives of patients with asthma, especially if they themselves are atopic (Townley et al 1974). Twin studies have been intriguing, in that one member of a monozygotic pair may be asymptomatic with normal airway reactivity whilst the other has severe asthma with grossly hyperreactive

airways (Fallier et al 1971). Thus perhaps one may inherit a predisposition to developing asthma given an appropriate environmental trigger (eg. viral infection, occupational exposure, medication) rather than directly inheriting hyperreactive airways. This suggestion is supported by the results from Clifford et al (1987) who studied a group of asthmatic adults and their children. Increased reactivity to inhaled methacholine was demonstrated in 93% of parents and 43% of their children. This contrasts sharply with the estimated 14% prevalence of bronchial hyperreactivity in adults (Burney et al 1987) and 17% (Salome et al 1987) to 25% (Sears et al 1986) for school children.

Reviewing the extensive research on bronchial hyperresponsiveness, Holgate et al (1987b) concluded that the most likely mechanism determining reactivity involves the activation of cells (probably mast cells) within the airways with release of active mediators. Several such bronchoconstrictor mediators have been identified (histamine, leukotrienes, platelet activating factor, slow releasing substance [SRS-A]) so that it is clear that bronchoconstriction is multifactorial in origin (Benson 1975; Boushey et al 1980). These mediators regulate airway smooth muscle tone either directly or indirectly via vagal fibres in the airway (Leff 1982).

Other factors are also important in some individuals and are summarised in table 6. Suggestion can either increase or decrease the level of airways responsiveness (Spector and Kinsman 1979). Unfortunately, this is complicated by the observation that those subjects in whom the greatest bronchoconstriction or bronchodilation can be induced in this way are also those with most reactive airways. Measurements of airways resistance are particularly susceptible to the effects of suggestion, the FEV_1 much less so. Lewis et al (1984) concluded that the temperature of the test solutions used in bronchial challenge was more important than suggestion in the production of bronchoconstriction following diluent (saline) administration. This statement has been challenged by Neild and Cameron (1985) who, despite ensuring cold solutions were not administered, still found suggestion could induce bronchoconstruction in certain asthmatic subjects.

Increased reactivity	Decreased reactivity
Acute recent viral infection	Inhaled bronchodilators
Recent influenza vaccination	Oral theophyllines
Recent rubeola vaccination	Antihistamines
Air pollution	Inhaled sodium cromoglycate
Suggestion	Inhaled steroids
Genetic predisposition	Atropine
Cigarette smoking	Suggestions
Chronic lung disease	Natural rubeola infection
Atopic status	
Allergic rhinitis	

Table 6. - Factors affecting nonspecific bronchial reactivity

Medication also affects airways responsiveness. In particular, inhaled bronchodilators acutely reduce airway reactivity and should therefore be withheld prior to challenge testing (Townley et al 1979; American Thoracic Society 1980). Oral theophyllines in therapeutic doses reduce the level of bronchial reactivity, but sub-therapeutic blood levels did not give any protective effect against histamine challenge (Cockcroft et al 1977a). Inhaled beclomethasone diproprionate and sodium cromoglycate have both been shown to reduce bronchial hyperreactivity (Dahl and Johansson 1982; Brogden 1983). Oral corticosteroids, however, do not have a consistent effect on nonspecific reactivity assessed by methacholine inhalation. In one study of 37 asthmatics, Spector and Farr (1975) found 27 had unaltered or even increased levels of bronchial reactivity as compared to levels prior to commencing oral steroid therapy. It is therefore recommended that inhaled bronchodilators are not used for 12 hours prior to challenge testing; theophyllines, inhaled sodium cromoglycate, inhaled beclomethasone diproprionate and antihistamines should be withheld for 48 hours prior to testing (American Thoracic Society 1980).

The above guidelines apply when airway reactivity is being assessed for diagnostic purposes, which is the principle reason for undertaking challenge studies. Juniper et al (1982) demonstrated that the level of bronchial responsiveness is constant in stable asthmatic subjects, so long as exacerbating factors (eg. infection) remain absent. This therefore provides an opportunity to assess the effects of medication in controlling bronchial hyperreactivity (Juniper et al 1981; Cade and Pain 1981). The therapeutic benefit of this is

that it is well recognised that severe attacks of asthma are more likely in poorly controlled asthma (Hetzel and Clark 1983). Staudenmayer et al (1979) demonstrated that asthmatics with most highly reacitive airways are hospitalised most frequently, in particular those who disregard or deny their breathing difficulties, delaying reporting symptoms until extremely ill. Thus assessment of bronchial reactivity, both on and off therapy, can help identify those most at risk from their asthma and also offers objective measures of therapeutic success.

4.3 Epidemiologic Studies of Bronchial Hyperreactivity.

Bronchial hyperreactivity is not always found in subjects with asthma, nor does the presence of hyperreactivity necessarily mean a subject has got asthma (Orehek 1982; Griffon et al 1987). Clinical assessment on the basis of history and physical examination is unfortunately often unreliable in the diagnosis of asthma (Pratter et al 1983). Thus Adelroth et al (1986), finding a diagnosis of asthma on clinical grounds alone incorrect in 26% of their study group even after assessment by chest specialists, concluded objective measurements were important to obtain a correct diagnosis of asthma. A normal methacholine challenge study despite the presence of symptoms highly suggestive of asthma, although not totally excluding the diagnosis, makes a correct diagnosis of asthma less likely. This helps identify subjects in need of further investigation since recurrent pulmonary emboli and endobronchial tumours may also mimic asthma in their presentation (Poe et al 1982).

Critical assessment of the reliability of any test is important, this being particularly so when used for a condition exhibiting such variability as asthma. Britton and Tattersfield (1986a), discussing the validity of assessing nonspecific reactivity as an aid to the diagnosis of asthma, found variations in methodology to be major limiting factors when comparing studies reported by different research workers. Measurement techniques are discussed further in section 4.5.

In epidemiologic studies a precise definiton of asthma is essential if accurate prevalence figures are to be obtained. Since bronchial hyperreactivity is readily demonstrated in a large proportion of asthmatics (Boushey et al 1980), assessment of nonspecific reactivity provides a useful objective basis for population studies despite the limitations discussed in the previous paragraph. The use of bronchial hyperreactivity as a marker of asthma is supported by the observation that asthma prevalence , as defined by other

conventional means, closely matches the prevalence of increased bronchial reactivity (Woolcock et al 1988). Thus Woolcock et al (1987) state:

> *"Until a definition for asthma is universally accepted we suggest that useful comparisons between populations may be made by measuring the prevalence of bronchial hyperresponsiveness and of symptoms consistent with asthma and determining the relation between them. In the future if provoking agents that are more specific for asthma are found, the prevalence and distribution of bronchial hyperresponsiveness may be sufficient to estimate the prevalence of asthma".*

Van der Lende et al (1973) produced some of the first data on the prevalence of histamine-induced reactivity, but took their end-point as a 10% fall in FEV_1 at up to 32 mg/ml histamine solutions using a tidal breathing technique. By this dose, 41.5% of adults tested had reacted, but this is a higher dose than is now generally considered appropriate and a 20% fall in FEV_1 is usually required before accepting a "positive" response (ATS 1962). Subsequently Cockcroft et al (1977b) showed only 3% of the "normal" population had a positive challenge (up to 8 mg/ml maximum dose of histamine and 20% fall in FEV_1). However, in subjects with currently active asthma, 100% reacted to histamine and 69% of those with asymptomatic (quiescent) asthma also had a positive challenge. Interestingly 47% of those with cough, but no other chest symptoms, also had a positive challenge test.

Woolcock et al (1978) contrasted civilian and military groups in Papua New Guinea, where asthma is rare, with groups in Australia where the prevalence of asthma is approximately 4%. Bronchial hyperreactivity was demonstrated in 6% of the groups studied in both countries, but known asthmatics were first excluded so that the overall prevalence of bronchial hyperreactivity could not be calculated. Atopy, based on positive skin tests, was found in a surprisingly high percentage of subjects (27-49% in the subgroups), but did not appear to correlate with bronchial hyperreactivity in this study. They concluded that factors other than atopy were necessary before bronchial hyperreactivity developed.

A similar prevalence of hyperreactivity was found in the non-atopic population (as assessed by skin testing) by Witt et al (1986), where 5.8% of adults with negative skin testing had negative challenge; if skin tests were strongly positive, however, 35.3% of children and 22.2% adults had increased bronchial reactivity. Unfortunately, as in the previous study by Woolcock et al (1978), the skin test results could not be used to predict bronchial reactivity, since 68.3% of those with hyperreactive airways had one or more positive skin tests, as did 43.8% of those without hyperreactive airways. This contrasts with the findings of Britton et al (1986b), who found that, although 22%

of children with bronchial hyperreactivity were asymptomatic, symptomatic bronchial hyperreactivity was more likely amongst atopic children.

A further study by Cockcroft et al (1983) found 36% of young adults had hyperreactive airways, although the prevalence of known asthma was only 9.3% (current asthma 2.7%). This was in a randomly selected study group of 300 subjects, achieving an 83.3% response, and of whom 63% had neither asthma nor rhinitis; the prevalence of atopy (skin prick tests positive) was 32.1%. All currently asthmatics had moderate to severe bronchial hyperreactivity. Similarly Weiss et al (1984), using a different technique which involved hyperventilation with subfreezing air, found 92% of asthmatics had bronchial hyperreactivity compared to 19% of non asthmatic children and 6.7% of adults. Children and young adults had a higher prevalence of increased reactivity. However, since many of the young adults were actually included in the "childhood" population (age range 7-28 yrs) because of the way in which the study groups were chosen, the prevalence of hyperreactivity in both subgroups is artificially reduced in the adult sample by the exclusion of young adults with hyperreactivity and correspondingly artificially increased in the "childhood" group.

Most studies have concentrated on general population samples of different ages. The data from Weiler et al (1986) is interesting in that it concentrates on young, physically fit adults who might have been expected to represent an exceptionally healthy subgroup of the population. Surprisingly 19% of football players had significant chest symptoms (cough, wheeze, chest tightness, prolonged breathlessness after exercise) and 12% had asthma. No basketball players had asthma but 12% had chest symptoms, as compared to 37% of medical students experiencing respiratory symptoms (7% had asthma). A high prevalence of bronchial hyperreactivity was shown, affecting half of the football players and a quarter of basketball players, as well as 41% of students. The presence of chest symptoms correlated poorly with bronchial reactivity since, although 76% of the symptomatic football players had a positive challenge, 47% of those with minimal or no symptoms also reacted to methacholine.

For children the relationship between chest symptoms (wheezing within the past 12 months) and bronchial hyperreactivity appears stronger. Sears et al (1986) reported their data negatively as showing 35% of children with a history of wheeze did not have bronchial hyperreactivity. The corollary of this is that, in the majority (65%) of those who were symptomatic, airways hyperreactivity was demonstrated. They correctly pointed out that a single negative challenge test does not completely rule out the diagnosis of asthma.

Equally they showed that bronchial hyperreactivity may be present in 8% of asymptomatic children. This is not surprising, since, in the measurement of any naturally occuring variable, in all grades of the parameter under investigation (in this case hyperreactivity) are likely to co-exist as part of a continuous spectrum between health and disease. Cockcroft et al (1983) have produced data to support this, finding a unimodal log normal distribution of bronchial responsiveness within a random population sample (Fig. 18).

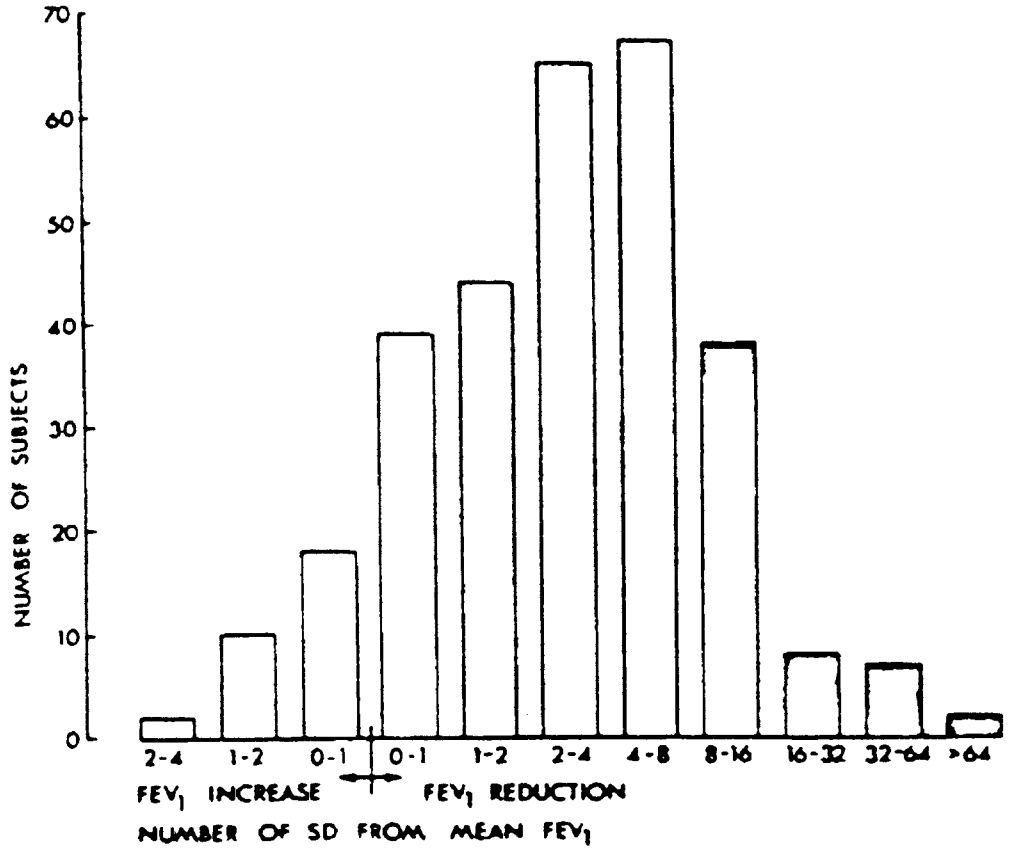


Fig. 18: Distribution of change in FEV_1 at 8 mg/ml histamine in a sample of 300 randomly selected students (age 20-29 yrs) in whom there was a 9.3% prevalence of asthma (2.7% current asthma). The change in FEV_1 is expressed as the number of standard deviations increased or decreased from the mean pre-histamine FEV_1 value. (Cockcroft et al 1983).

The preceeding studies appear to give widely varying estimates of bronchial hyperreactivity, using varying challenge techniques and, in several studies, very selective population samples. The data is summarised in table 7, although the differing methods of presenting the results makes direct comparisons difficult. Two recent independant studies (Woolcock et al 1987; Burney et al 1987), using the same techniques and end points (Yan et al 1983), have produced much more compatible results. Unfortunately both are limited by their high non-response rates (40%), particularly affecting responses from smokers, young and elderly subjects in the study by Burney et al (1987) - only 47% of those aged under 25 years and 53% aged over 54 years responded.

TABLE 7 - Summary of published data regarding prevalence of bronchial hyperreactivity (BHR). Methods of assessment are abbreviated as below:-

H	*Histamine*	*1*	*Tidal breathing*
M	*Methacholine*	*2*	*Dosimeter*
S	*Sub-freezing air hyperventilation*	*3*	*Hand-held DeVilbiss 40*

Author	Method	Age group (yrs).	n	Findings
Van der Lende et al 1973 (Holland)	H1	Adults	359	41.5% BHR (High max. dose 32 mg/ml used; 10% fall FEV1 positive)
Cockcroft et al 1977 (Canada)	H1	Young Adults	307	Normals 3% BHR; Active asthma 100% BHR Asymptomatic asthma 69% BHR; Rhinitis alone 22% BHR, Rhinitis + chest symptoms (not asthma) 40% BHR; Cough alone 47% BHR;
Woolcock et al 1978	M3	Adults (military and civilian)	505	Papua New Guinea 6% BHR Australia 6% BHR
Ramsdell et al 1982 (USA)	M2	53 - 75	22	100% BHR in patients with chronic obstruction bronchitis
Cockcroft et al 1983 (Canada)	H1	20 - 29	300	Overall 36% BHR (0.3% highly reactive). Current asthmatics 100% BHR
Weiss et al 1984 (USA)	S	Adults (mean 38 years) Children (mean 12 years	134 213	Adults 6.7% BHR Non asthmatic children 19% BHR; Asthmatic children 42.9% BHR (past and current asthma); Current asthma 92% BHR
Hopp et al 1986 (USA)	M1	5 - 21	400	Current asthmatics 100% BHR (82% strongly positive); Non asthmatics 5.2% BHR; Non-allergic 47% BHR.
Weiler et al 1986 (USA)	M2	Young athletes	334	Football players: (151) 50% BHR (12% known asthmatics, 19% chest symptoms); Basketball players : (16) 25% BHR (0% asthmatics, 12% chest symptoms); Medical students: (167) 41% BHR (7% asthmatics, 37% chest symptoms).
Witt et al 1986 (Australia).	H3	18 - 88	891	Overall 9.2% BHR BHR related to atopic status assessed by number of positive skin prick tests: Non atopic 5.8%BHR; Atopic 13.8% BHR (1 or more positive); Strongly atopic 22.2% BHR (all 5 positive). 68.3% with BHR atopic; 43.8% without BHR atopic.

continued overleaf . . . .

Author	Method	Age group (yrs).	n	Findings
Witt et al 1986 (Australia)	H3	6 - 19	1293	Overall 7.9% BHR BHR related to atopic states (as above): Non-atopic 3.5% BHR; Atopic 10.8% BHR; Strongly atopic 35.3% BHR. 82.4% with BHR atopic; 32.5% without BHR atopic.
Sears et al 1986 (New Zealand)	M1	Children	815	Overall 25% BHR History of wheeze in 220/815 (27%) If wheeze within past year 65% BHR Asymptomatic children 8% BHR.
Britton et al 1986 (Australia)	H3	Children	1487	Inland: 19% BHR (12% moderate - severe BHR) 13% asthma; 38% atopic (skin tests) 35% symptomatic (wheeze, breathlessness, nocturnal cough). Coastal: 15% BHR (9% moderate - severe BHR). 10% asthma; 38% atopic; 29% symptomatic.
Mortagy et al 1986 (England)	H1	Adults	4143	Bronchial irritability syndrome: 6.7% Southampton; 4.6% New Forest.
Clifford et al 1987 (England)	M3	Asthmatic adults + their children.	64	Parents 93% BHR Children 43% BHR
Burney et al 1987 (England)	H3	18 - 64	511	Overall 14% BHR; Current smokers 23% BHR; Atopic subjects 19% BHR; Men 16% BHR
Woolcock et al 1987 (Australia)	H3	Adults (31.6% age > 60)	916	Overall 11.4% BHR Prevalence current asthma 5.9%; 68.2% (71/104) subjects with BHR had asthma Prevalence BHR + symptoms of asthma 7.8%
Connolly et al 1988	M2	Elderly asthmatics 65 - 88	20	100% BHR with asthma

Woolcock et al (1987) studied rural Australian adults on two separate days, confirming the reproducibility of their method by independant observers. Bronchial hyperreactivity at or below 3.9 μmol histamine was found in 10.5% of 876 challenged. In addition, of 40 who were unfit for challenge, 12 had a significant improvement following bronchodilator administration, indicating increased bronchomotor tone (Jenne and Tashkin 1983). This gave a cumulative prevalence of hyperreactivity of 11.4% in this study population, 68.2% (71/104) of those with hyperreactive airways also having symptoms of asthma. Most of those with highly reactive airways also had respiratory symptoms and impaired lung function. No association between airway reactivity and age or sex was shown, but strong correlation was found with cigarette smoking, atopy, respiratory symptoms and abnormal lung function.

Burney et al (1987) took a 20% random population sample of Dorset and Hampshire adults, taken from the electoral register in 3 towns. Bronchial hyperreactivity was demonstrated in 14% of those tested, frequently associated with a smoking history or atopic status (assessed by skin prick testing). The prevalence appeared bimodal, with the lowest prevalence in the 35-44 yrs age group, but the lower response rates at both ends of the age spectrum may have distorted the prevalence figures. This prevalence figure is higher than that obtained by Mortagy et al (1986) in the same geographic area (Southampton and New Forest), also sampling from the electoral registers, because of the different diagnostic criteria applied. Mortagy et al (1986) had tried to directly relate bronchial hyperreactivity to specific respiratory symptoms, rather than just report the prevalence of hyperreactivity. Clearly, if close correlation between easily recognisable symptoms and airways reactivity exists, and all such people also fulfill the accepted criteria for asthma, this is of great clinical benefit in recognising undiagnosed asthmatics - in particular those with intermittent symptoms for whom challenge testing is often otherwise required (Horsley et al 1985).

Mortagy et al (1986) found a close association between bronchial responsiveness to histamine and the posession of one or more of the following symptoms:

(i) Nocturnal breathlessness
(ii) Prolonged morning chest tightness (more than 1 hour)
(iii) Symptoms of bronchial irritability (wheeze, breathlessness) with certain environmental stimuli - entering a smokey room; going from a warm room to a cold room; traffic fumes; chemical irritant smells(eg hairspray).

Cough was also noted by a significant number of respondents in response to the environmental stimuli, but was considered non-specific and therefore not included in the criteria for the Bronchial Irritability Syndrome. The prevalence of these symptoms appeared to increase with age, although relatively few elderly were included in the population sample and none were selected for challenge studies. As Connolly et al (1988) have demonstrated, there is no reason to exclude subjects because of age, thus assessment of bronchial reactivity and relationship to symptoms in a representative elderly population is essential if Mortagy's findings are to be confirmed.

4.4 Assessment of Bronchial Reactivity

4.4.1 Techniques

Although various methods for assessing bronchial reactivity are presently in use, they can be broadly grouped as follows:

a) techniques involving continuous aerosol generation during tidal breathing.
b) techniques with intermittent aerosol generation during controlled inspiration.
c) techniques involving airway cooling
d) bronchodilator challenge

a) Continuous aerosol generation

This method was first suggested by Dautrebande and Philippot (1941), but the early technique was too cumbersome for widespread application until simplified by Parker et al (1965). Subsequently, Cockcroft et al (1977) refined the technique so that a simple reproducible dose-response assessment became possible. Different strengths of solutions of bronchoconstor agents are continuously nebulised using a Wright nebuliser, the aerosol being delivered via a face mask to the subject during tidal breathing (Hargreave et al 1981). Although highly reproducible, this is a slow method and therefore not readily suited for large scale epidemiologic studies. Mortagy (1984) therefore tried to abbreviate the technique using a Pulmasonic ultrasonic nebuliser. Unfortunately the output from this nebuliser proved difficult to standardise, so offered no advantage over Cockcroft's method (Britton et al 1986c).

b) Intermittent aerosol generation

Because continuous nebulisation is relatively wasteful of aerosol, requiring constant aerosol production despite inhalation only during a tidal breath at a normal rate of quiet respiration, Rosenthal (1979) developed a dosimeter technique. This delivered a consistent amount of aerosol at a pre-determined point during inspiration, timing of nebulisation being regulated by an automatic breath-activated valve. Variations on this apparatus are simple to construct (Horsley et al 1985), but there is greater variability of aerosol particle size with this method due to sudden onset of nebulisation when the valve opens, although this does not appear to adversely affect the airway response or reproducibility of the technique (Ryan et al 1981a). Bennett and Davies (1987) have emphasised the importance of recording results in terms of the actual dose of drug producing a specified fall (usually 20%) in FEV_1 (PD_{20}), since the concentration of solution producing this fall (PC_{20}) varies between techniques according to actual dose delivered to the airways.

Chatham et al (1982a) demonstrated that it was possible to condense the intermittent challenge procedure and still get reproducible results. Their method involved specified numbers of deep breaths from a face mask, into which aerosol was delivered with a manually controlled nebuliser without a dosimeter. Even though good reproducibility was obtained, a compressed air source was still required to power the nebuliser, limiting its application in field studies. The method developed by Yan et al (1983) only requires a hand held nebuliser and produces equally reproducible results when compared with other standard challenge techniques (Britton et al 1986c). Because of its simplicity this method has been widely used in recent epidemiologic studies assessing bronchial reactivity (Table 7) and was therefore chosen for use in the survey described in the experimental section of this thesis, where operational characteristics are discussed further.

c) Airway cooling.

Airway cooling is considered the basic mechanism of exercise induced asthma (Souhrada and Kivity 1983) and has also been used in studies of asthma (Weiss et al 1984) to assess bronchoconstriction during hyperventilation whilst breathing sub-freezing air. Although exercise induced bronchoconstriction is reproducible and compares closely with histamine or methacholine-induced bronchoconstriction in sensitive subjects (Kiviloog 1975; Eggleston 1979; Anderton et al 1979), it is a laboratory-based procedure and therefore not suitable for epidemiologic field studies. However many asthmatics do not develop bronchoconstriction on exercise (Chatham et al 1982b), so that exercise does not always provide an adequate challenge to the airway.

d) Bronchodilator challenge

Some individuals are unfit for challenge testing with histamine or methacholine, others may not consent to provocative challenge studies. Individuals with a significant degree of airlow obstruction should not be challenged (ATS 1980), in view of the risk of inducing major bronchoconstriction in an already functionally impaired individual - although this seldom actually occurs (Townley et al 1979). Bronchodilator challenge may safely be applied as an assessment of increased bronchomotor tone, which closely relates to bronchial sensitivity to inhaled bronchoconstrictor agents (Jenne and Tashkin 1983), hence its use in routine pulmonary function testing to assess objective reversibility in airflow obstrucion.

4.4.2 Agents used in challenge studies.

Specific challenge with antigens or by measurement of lung function parameters during monitored occupational exposure can prove invaluable in establishing direct causal relationship for respiratory symptoms - particularly valuable in the assessment of occupational asthma (Chan-Yeung 1987). Lam et al (1979) found significantly increased nonspecific bronchial reactivity in patients with occupational asthma. However Hargreave et al (1984) have shown isocyanate induced asthma may occur when methacholine bronchial responsiveness is normal, concluding that it is the strength of the stimulus (ie. intensity of exposure) which determines whether or not an asthmatic reaction occurs. It has been suggested that posession of increased nonspecific bronchial responsiveness may predispose workers to developing occupational asthma given the appropriate stimulus (Malo 1985), but no prospective studies have yet been undertaken with pre-employment assessments to support this (Yeung and Grzybowski 1985; Burge 1987).

Nonspecific airway reactivity is most frequently measured following challenge with either histamine or methacholine aerosols. Provided that standardised protocols are followed the response to either agent is reproducible and directly comparable for both normals and asthmatics (Juniper et al 1978). In this study the cumulative dose effect was shown to be greater with methacholine than histamine. These observations have been confirmed in several other studies using different aerosol inhalation techniques (Hargreave et al 1981; Bahous et al 1984).

4.4.3 Factors affecting response to challenge studies.

General factors affecting bronchial reactivity have been considered in section 4.2 and are summarised in table 6. All aerosol studies are also affected by variations in the mode of aerosol generation and inhalation technique, both affecting the pattern of aerosol deposition within the airways (Brain and Valberg 1979; Ryan et al 1981b) - hence the need for adherence to a standardised protocol and the avoidance of inter-observer variation in interpretation of results from large studies. Careful assessment of nebuliser output is important, especially if more than one nebuliser is being used, since considerable variability is often demonstrated and can be altered by changes in operating characteristics eg. the volume of liquid in the nebuliser, temperature of solution, altered pressures applied to the nebuliser for generation of the aerosol (Mercer 1973, 1981).

Particle sizes vary from any nebuliser, but if the droplet size is too large they will not reach the respiratory portions of the airway. Larger particles in the 5-10 μm AMMD range (aerodynamic mass median diameter) are predominantly deposited by inertial impaction in the central airways. Most challenge studies employ mouth breathing techniques, so that the major site of deposition of large particles is in the pharynx and larynx, some also reaching the initial 5-6 bronchial bifucations (Newhouse and Ruffin 1978). This is the likely reason for the sore or dry throat often noted by subjects after challenge procedures. Most nebulisers are therefore designed to produce particles in the 1-5 μm AMMD range (Mercer 1981), so that these smaller particles can penetrate further into the respiratory tract, where they settle principally by gravitational sedimentation in the 15th-17th bronchial divisions (Landahl et al 1951; Sanchis et al 1972). Nevertheless, around 15-20% of 3 μm particles are still deposited in the central airways by impaction, even with perfect inhalation technique (Sanchis et al 1972). The effect of particle size for therapeutic aerosols and different delivery systems is considered in greater detail by Newman (1982, 1983).

Newhouse and Ruffin (1978) demonstrated that by adjusting the aerosol particle size and mode of delivery to give mainly central airway deposition, much less inhaled histamine was required to produce a significant (20%) fall in FEV_1 than when a more diffuse intrapulmonary deposition pattern was produced. This was also shown by Wanner et al (1985) in normal subjects, finding that variations in airways responsiveness to histamine in normals was significantly affected by the total dose deposited within the airway, in turn related to the mode of delivery.

Dolovich et al (1981) showed that maximum penetration of small particles (>1 μm AMMD) was obtained when inhaled with inspiratory capacity breaths followed by a 10 second breath-hold at total lung capacity before exhalation. Maximum peripheral deposition of aerosol particles can be obtained when the aerosol is delivered in the latter half of inspiration, when inspiratory flow rates are lower and less deposition by impaction in the central airways consequently occurs (Rosenthal 1979; ATS 1980).

Presence of airway obstruction reduces peripheral penetration of aerosols, as demonstrated by Agnew et al (1981) and Clague et al (1983). Peripheral deposition may be impaired in both smokers and those with obstructive airways disease, in addition to reduction in those who are dyspnoeic through disease and unable to perform a controlled inspiration and breath-hold (Chamberlain et al 1983). Similar patchy changes in deposition are also

shown on conventional ventilation lung scanning (Ramanna et al 1975) in patients with obstructive airways disease.

It is evident that it is possible to regulate the site of aerosol depositon by applying knowledge of aerosol kinetics to therapeutic benefit. Factors affecting aerosol deposition within the respiratory tract during inhalation challenge testing are summarised in table 8.

(i) Determined by nebuliser:	
	Nebuliser output volume
	Aerosol particle size
	Temperature of test solution
	Correct concentration of test solution
(ii) Determined by subject	
	Respiratory rate
	Depth of inspiration
	Inspiratory flow rate
	Timing of aerosol delivery during inspiration
	Duration of breath hold pause at end of inspiration
	Airway obstruction or disease

TABLE 8 - Factors affecting the deposition of aerosols within the respiratory tract during broncial inhalation challenge studies.

PART 2:
EXPERIMENTAL

CHAPTER 5

POPULATION DEMOGRAPHY AND POSTAL SURVEY

5.1 Introduction

The preceding chapters have considered the effect of ageing on the respiratory system and demonstrated the shortage of published data relating to asthma in the elderly. Burr et al (1979) studied the prevalence of asthma in a South Wales town, reporting detailed assessment of 485 subjects. Unfortunately, their study excluded individuals who were living in any kind of residential care, so does not reflect the true burden of disease with which general practitioners have to deal in the community. Furthermore, it is reasonable to suggest that there may be considerable local variations in disease prevalence throughout the country, affected by environmental factors such as different employment (especially significant in mining areas) or atmospheric pollution.

The prevalence of different symptoms or diseases within the community can be estimated by cross-sectional population analysis, adequate numbers being essential if the findings are to be a reliable guide to true prevalence. Data may be obtained in a number of different ways:

(i) personal interview
(ii) self-administered postal questionnaire
(iii) hospital admission statistics
(iv) death statistics

To use a personal interview is effective, provided interviewers are adequately trained, but is time-consuming and the possibility of inter-observer bias introduced by slight variations in interview technique must always be considered. Computer administered questionnaires have been used to try and avoid bias in history taking, but were found to be of limited value in distinguishing between patients with asthma and chronic airways disease (Bennett et al 1988).

Self-administered postal questionnaires allow a larger number of subjects to be screened, but the wording of the questionnaire must be unambiguous (Samet 1978). The M.R.C. respiratory symptoms questionnaire (M.R.C. 1960) has been widely used in medical research, translated into many languages, and is regarded as the "gold standard" against which other surveys should be compared. Unfortunately, it is too elaborate for self-administration, unsuitable for all but the most capable and well motivated (and potentially self-selected) subjects. Modifications of the M.R.C. questionnaire are similarly restricted by the need to be brief enough to ensure good response rates from the study group, but clear enough to avoid misinterpretations, if the replies are to be of any value. The application of such questionnaires to elderly subjects might therefore be expected to be difficult, but in fact response rates as good (and sometimes better) as those obtained in younger age groups are often found (Ebrahim et al 1987).

There has been criticism recently (Bowling and Jacobson 1989) of population registers, such as those held by general practitioners, Family Practitioner Committees and the Electoral Roll which represent the major scources of names for community epidemiologic studies. These lists are slow to include new residents in an area and equally slow to delete those who have moved away or died. Using hospital admission statistics is equally limited, since only the principal diagnosis stated is coded for hospital activities analysis. Death certificate data is notoriously inaccurate for respiratory disease, "bronchopneumonia", for example, being recorded as the terminal event in a disproportionately large number of elderly deaths. However, specifically recorded asthma deaths have been very useful in studies comparing inter-regional variations, as discussed in chapter 3.

In this study it was decided to use a well tested short respiratory symptoms questionnaire so that data obtained could be compared with that obtained in a younger study group drawn previously from the same geographic area (Mortagy 1984, 1986). This chapter considers the methods of subject selection and the overall response to the questionnaire. The prevalence of various respiratory symptoms found in the survey are given in chapter 6.

5.2 Subjects and Method

5.2.1 General organisation

The study was based in the Geriatric Day Hospital at Lymington Infirmary, covering the Western (New Forest) sector of the area served by the Department of Geriatric Medicine in Southampton General Hospital. Full support of all general practitioners in the area (4 group practices: 3 in Lymington and 1 with surgeries in Brockenhurst and Sway) was obtained following personal explanation of the objectives of the project prior to commencement of the study, as was approval of the Ethical Committee of the Southampton and South West Hampshire Health Authority. The study was registered under Section PO16 of the 1984 Data Protection Act.

5.2.2 Determination of sample size

The required sample size was calculated by assuming 5% prevalence of asthma in the New Forest area, based on Mortagy's estimate of the prevalence of the Bronchial Irritability Syndrome (Mortagy 1984), and expecting an 80% response to the postal questionnaire. It was then also assumed that only about half the subjects contacted would agree to attend for subsequent challenge studies and that it would be possible to study approximately 40 subjects with symptoms suggestive of asthma (symptoms of the Bronchial Irritability Syndrome; see chapter 4.3), with similar numbers of subjects who were either

1) entirely free from respiratory symptoms
2) had exertional breathlessness only
3) had wheezing, bronchitis or other respiratory symptoms (but not symptoms of the Bronchial Irritability Syndrome)

Therefore to obtain 40 subjects with suspected asthma for study would require an initial sample size of 2000:

2000 subjects with 80% response	=	1600 replies
5% prevalence of asthma / B.I.S.	=	80 / 1600
If only half of these agree to challenge studies	=	40 subjects with suspected asthma available for study

5.2.3 Sample selection

From the age-sex registers of each practice a population profile was obtained of all patients registered and compared with the quarterly statistics provided by the South West Hampshire Family Practitioner Committee. Names of equal numbers of male and female subjects were then taken directly from the

age-sex registers of each practice by random sampling (using a table of random numbers) in 10 year age-bands:

65 - 74 years
75 - 84 years
85 - oldest

Sampling was continued until 500 names had been obtained or all possible subjects within an age/sex-band had been listed within each practice. The last registered home address was then taken from the general practitioner record files and date of birth similarly verified. An index card was completed for each subject.

5.2.4 Postal survey

A two-page respiratory symptom questionnaire (appendix A1) was posted to each subject, accompanied by an explanatory letter (appendix B1) which gave details about the study and indicated the support of the relevant (named) general practitioner. Each letter was personally signed by both the research worker (JRH) and one of the Consultant Geriatricians responsible for the Geriatric Day Hospital (Dr Sterling). All envelopes used for mailing were identical; a stamped (2nd class postage), pre-addressed envelope was included for return of the questionnaire to the Day Hospital. If a reply was not received within 6 weeks a further questionnaire, stamped pre-addressed envelope and reminder letter (appendix B2) was sent. The practice health visitors were also informed of the study (appendix B3). The general practitioners and health visitors at each surgery then checked the names of any who had still not replied to exclude any who were known to them as having died or moved; prior to this stage the general practitioners had not seen the names of subjects sampled.

Names were obtained for the study during September and October 1986, with mailing being carried out from November 1986 and completed during January 1987, avoiding the week preceding and the week immediately after Christmas. Incomplete questionnaires were sent back with a covering letter (appendix B4) and a further stamped pre-addressed envelope for their return. From the respondents, 20% were randomly selected and their questionnaire replies verified, either by telephone or personal interview.

5.2.5 Data analysis

Data was coded directly on the questionnaires following a standardised code. It was then transcribed onto computer tape by a commercial firm (Data Speed, Southampton) and analysed on the University of Southampton computer under the supervision of the Faculty of Medicine Department of Medical Statistics and Computing (Mr M Mullee). Subgroup analysis is discussed further in chapter 6.

5.3 Results

5.3.1 Population demography.

Figure 19 shows the age and sex profile of all patients registered with the 4 group practices. This is summarised in table 9, which contrasts the figures derived from the age-sex registers with the average of the September and December 1986 FPC figures. There were 24.7% aged >65 years, 11.6% aged >75 years and 2.7% aged >85 years, with substantially more very elderly (aged 85+ years) females than males.

Fig 19: Age distribution of all patients listed under age/sex registers of four group practices in the New Forest (Lymington, Brockenhurst, Sway) in October 1986. There were two female subjects aged 100 years and two aged 102 years, included in the final column.

Age, years	Listed		F. P. C.	% F. P. C.
	Male	Female		
0 - 64	9,835	10,173	18,793	106%
65 - 74	1,540	1,925	3,316	104%
75 - 84	919	1,453	)	)
			) 2,908	) 106%
85 +	197	523	)	)
	12,491	14,074		
Overall Totals	26,565		25,017	106%

Table 9 - Total number of patients listed with 4 group practices in the New Forest (Lymington, Brockenhurst, Sway), drawn from practice age-sex registers compared to Family Practitioner Committee statistics (average of September and December 1986 F.P.C. figures). The final column shows totals (age-sex) expressed as a percentage of F.P.C. figures.

Although listed figures for all the practices combined exceeded FPC figures by 4-6% within the various age groups (table 9), in one practice the FPC figures differed from the age-sex register listing by only 1 patient. Greatest discrepancy was noted in the largest practice studied. Figure 20 shows the approximate boundaries of the area served by the 4 group practices studied.

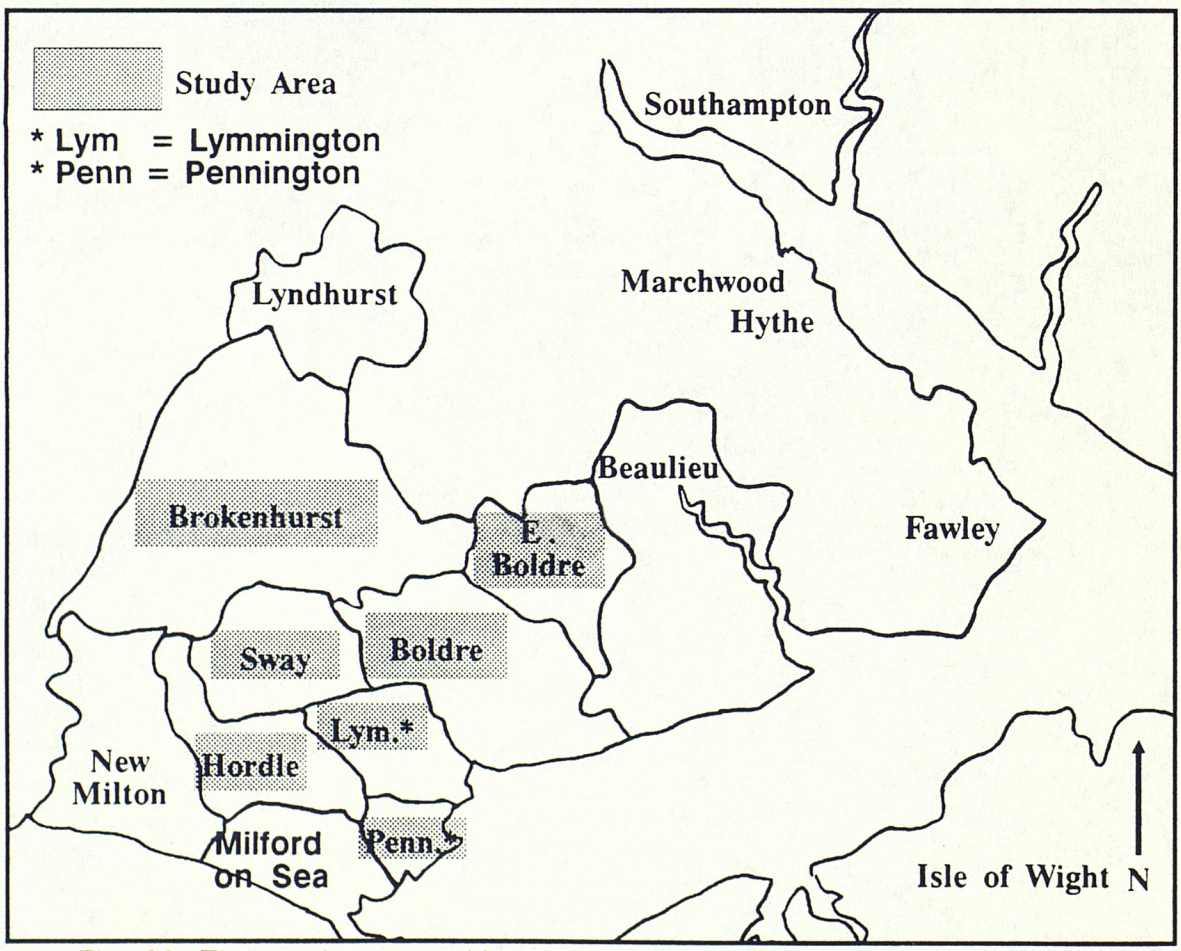


Fig. 20: The study area, with appropriate Parish boundaries, is shown in relation to the surrounding areas of the New Forest.

Table 10 shows that the parish population estimates (obtained from the New Forest District Council) are close to the number of patients registered with the 4 practices, although some patients on the edges of the study area were known to be registered with practices in New Milton, Lyndhurst and Hythe.

Parish	Population
Brockenhurst	3250
Boldre	2090
Hordle	4790
Sway	3300
Lymington and Pennington	13440
East Boldre	880
Total	27750

Table 10 - Parish population estimates given by New Forest District Council for mid 1986 in study area.

A total of 2011 subjects were selected, representing a 1:3.3 sample of all subjects listed over 65 years of age. Proportionately more of the listed men were sampled (1:2.8) than females (1:3.7), with higher sampling rates in the older age groups (table 11). Although most males age >85 years were included, it was not possible to exactly match the number of elderly females for this age group.

Age, years	Listed		Sampled		Proportion Sampled	
	M	F	M	F	M	F
65 - 74	1540	1925	438	432	1 : 3.5	1 : 4.5
75 - 84	919	1453	355	357	1 : 2.6	1 : 4.1
85 +	197	523	164	265	1 : 1.2	1 : 2.0
	2656	3901	957	1054	1 : 2.8	1 : 3.7
	6557		2011		1 : 3.3	

Table 11. - Proportionate sampling rates from listing in age-sex registers for different age-bands according to sex of subject.

5.3.2 Response to postal questionnaire

The first mailing produced 1665 (82.8%) replies from the 2011 questionnaires sent, with a further 138 (6.9%) responding to the second letter. Two elderly females replied refusing to complete their questionnaires but saying that they were "well" and the forms of three elderly females with severe dementia could

not be completed by their carers. After excluding 136 subjects who had either moved away from the area or died, an overall response rate of 96.2% was obtained for this stage of the study. Little difference in response rate was seen between the different age-bands studied (table 12); 861 of the respondents were male (mean age 76 ± 7 years) and 942 female (mean age 77 ± 8 years), with an overall mean age of 77 ± 8 years. The oldest respondents were two females, each aged 102 years, living in residential homes in Lymington.

Age, Years	Sent	Returned	Died/Moved	No reply
65 - 74	870	812 (97.1%)	34	24
75 - 84	712	637 (96.1%)	49	26
85 +	429	354 (94.2%)	53	22
Total	2011	1803 (96.2%) (957 Male)	136 (66 Male)	72* (33 Male)

Table 12 - Response to postal questionnaire for different age groups. Percentage (%) response shown after excluding those who had died or moved from the area.

** Includes 2 females who refused to complete the questionnaire and 3 females with severe dementia whose forms could not be completed even with the help of their carers*

Table 13 shows that overall 89% were still living at a private address (either their own or with relatives), but this proportion declined with age. The majority of those requiring permanent residential care (local authority, private or hospital) were in the 85+ age group. In table 27 (appendix C) there is a more detailed analysis of this data, showing that a significantly higher proportion of elderly men are cared for at home. More than three times as many females were found to be in residential care than men.

Of the respondents, 61.8% lived in Lymington or Pennington, 12.3% in Brockenhurst and 16.5% in Sway. There was very little difference in response rate for the questionnaire according to residential area or type of accommodation (assessed from registered permanent address): 96.8% of those living in Lymington replied, compared with 95.1% of those in the surrounding area (including Brockenhurst and Sway). Nine out of the 136 non-respondents (6.6%) were in private residential homes or nursing homes.

Residence	Age group (years)			
	65 - 74	75 - 84	85+	Total
Private address	97.1%	89.2%	69.7%	89.0%
Sheltered housing	2.6%	6.1%	9.6%	5.2%
Local authority (Part 3)	0.1%	1.2%	5.3%	1.5%
Residential home	0	2.2%	9.3%	2.6%
Nursing home or hospital long stay ward	0.1%	1.4%	6.1%	1.7%
Total	100	100	100	100

Table 13. - A comparison of the place of permanent residence within different age-groups for 1803 respondents to the postal questionnaire, (See Appendix C, table 27, for further details).

5.4 Discussion

It is immediately apparent from the demographic data that the New Forest area studied is atypical with regard to its elderly population. Figure 21 contrasts the age profile of the study area with national average population statistics (OPCS 1988). In England there is an estimated 15.6% aged over 65 years (including 75+ and 85+), as compared to 24.7% in the area studied. Similarly, 11.6% were aged over 75 years (including 85+) in the New Forest area, contrasting with 6.7% in the general population. Twice as many residents in the New Forest area surveyed were aged over 85 years as compared to the OPCS general population statistics.

The scenery and coastal facilities of Lymington and the surrounding areas have attracted a substantial number of affluent retired individuals, although the rural areas still have a high proportion of families with a long tradition of farming and foresting in the New Forest. The area does not particularly attract those with chest conditions, in contrast to other areas studied such as Arizona (Burrows 1981), so that no other confounding factors are evident to distort the results.

The study achieved a 96.2% response rate, with minimal difference in response shown between the age groups assessed (table 12). This exceeds the response reported by Mortagy et al (1986) for a similar study performed in the same area but with a younger population sample, which obtained 80.2% response with the same questionnaire. Even using a raffle to entice a greater response was found unhelpful by Mortagy et al (1985). Although there had been slight alterations to the wording and layout of the questionnaire used in the present study, these were so minor that it is improbable that

they would have affected the response. Possibly, in an affluent retirement area, the increased degree of literacy and familiarity with questionnaires of this type may have helped in this survey of the elderly, although there was no lower response rate observed from the "New Foresters" with a rural farming background.

Fig 21: Age profile of all subjects registered with four group practices in the New Forest (shaded area) compared with national population statistics (hatched area) obtained from the OPCS for 1987 (OPCS 1988).

The response rate differs from that reported by Rockwood et al (1989) for a survey conducted amongst the elderly in Saskatchewan. Lower response rates were obtained from the rural areas, with significant bias noted towards more healthy subjects replying. The nonrespondents in their survey tended to use hospital facilities more often than those who had replied. They concluded that health surveys amongst the elderly were unreliable as a means of assessing the extent of ill-health in the community. Also they found few very elderly subjects (over 85 years of age) had replied, contrasting with the responses from the New Forest elderly which were equally good for the

very elderly. Geographical factors, ethnic differences and major differences in the provision, and expectations of, health care in Canada as compared to Southern England may account for these differences in response, illustrating the difficulty in comparing data from dissimilar areas and populations.

Newland et al (1977) showed that the colour of envelope and class of postage used did not affect response rate to a very detailed questionnaire. The inclusion of a pre-addressed and stamped (rather than reply paid pre-printed) envelope also made no difference in Newland's study, also carried out in Southampton, and is therefore unlikely to have been a factor in the high response rate of the present study - unless a purely elderly sample reacts differently to postal mailing than a general population sample. The importance of avoiding mailing close to public holidays (in this case the Christmas period) was observed, a lower response being noted from the initial mailing in the weeks close to Christmas, (even though the week immediately before and after Christmas had been avoided), several replied to the reminder letter apologising that their questionnaire had inadvertently been discarded with the Christmas cards.

The major reason for the good response is likely to have been the degree of general practitioner support, their names being included in all correspondence. This is likely to have been further enhanced by the invitation for close relatives or other carers to assist in the completion of the questionnaire, telephoning the researcher in the event of difficulties. The willingness of the elderly to complete questionnaires must therefore not be underestimated, as many replied expressing gratitude that someone was interested in their general health. Only two subjects (both female) objected to the survey, refusing to complete the questionnaire. The accuracy of replies is considered further in chapter 6.

The value of using population registers, such as Family Practitioner Committee listings or the Electoral Roll, in epidemiologic studies has been questioned recently (Bowling and Jacobson 1989). During the preparatory phase of this study it became clear that, for the larger group practices, keeping an up-to-date age-sex register was a difficult and time-consuming task. Although newly registered patients were regularly being added to the registers, it was clear that those who had died or moved were not always deleted. Prior to starting the survey it was therefore necessary to check the practice registers carefully with the general practitioners and health visitors, to minimise this error. In the smallest practice the age-sex register was exceptionally accurate, whereas the largest practice showed 8% more patients on their

register than the Family Practitioner Committee listing - the mean error for all four practices was 6%. The delay in formal registration of new paients by the Family Practitioner Committee also affects these figures a little, but there is equally a delay in deleting those who have moved or died from the FPC central register. In reality this did not have a major effect on the study, only 6.8% (136 subjects) of those having been selected for survey being found to have died or moved - several of these deaths being during the actual study period, after patient selection had been completed.

This study included all subjects resident in the area and registered with the four practices, irrespective of the nature of accommodation. Although only 5.8% of respondents (and 6.6% of non-respondents) lived in permanent residential homes (local authority, private rest homes, nursing homes or hospital long stay ward), exclusion of these subjects would have biased the overall figures in favour of the healthier elderly who were able to live independently alone or with their relatives in the community. This is an important factor to consider when comparing these data with the figures from Burr et al (1979), where residents of local authority homes and other residential institutions were excluded.

5.5 Conclusions

This study demonstrates that the majority of elderly people are willing to support research into their general health, and capable of completing and returning a postal health questionnaire. The high (96.2%) response rate was independent of age or sex, and not significantly affected by social background, type of residential accommodation or area of residence. The general practitioner age-sex register was found to be an easily accessible means for obtaining names of elderly subjects, although delays in updating the register led to some subjects (6.8%) being included in the population sample even though they had either died or moved from the area. Active involvement of general practitioners, health visitors and other carers working with the elderly is important in epidemiologic surveys of an elderly population sample.

CHAPTER 6

THE PREVALENCE OF RESPIRATORY SYMPTOMS AMONGST THE NEW FOREST ELDERLY - RESULTS OF THE POSTAL QUESTIONNAIRE.

6.1 Introduction

Details of the background to the survey and methodology are given in chapter 5. This chapter presents detailed analysis of the symptoms reported by the 1803 respondents to the postal questionnaire (appendix A), in particular considering age- and sex-related trends.

6.2 Method: Data analysis

After data coding (chapter 5.2.5), statistical analysis of symptoms was carried out on the Southampton University computer using the SPSS-X analytical package for Social Sciences. Data are mainly presented as frequencies, with inter-group comparisons using a Chi-square test of independence where appropriate. Only differences significant at the 5% level ($p < 0.05$) are indicated. For discrete variables, such as number of years since stopping smoking, the arithmetic mean value and 1 standard deviation are shown. The Computers Rule was applied when rounding off digits.

Subjects were grouped according to respiratory symptoms, based on responses to questions 1-8 (appendix A):

1. No respiratory symptoms
2. Exertional breathlessness only (hurrying on level ground or walking up slight hill)
3. Mixed respiratory symptoms (but not bronchial irritability)
4. Symptoms of the Bronchial Irritability Syndrome
5. Unclassified (incomplete questionnaire)

Symptoms of the Bronchial Irritability Syndrome, shown by Mortagy et al (1986) to be associated with increased bronchial reactivity, are:

(i) episodes of nocturnal breathlessness;
(ii) morning chest tightness (lasting more than 1 hour)
(iii) symptoms of bronchial irritability (breathlessness, wheeze) with certain environmental stimuli - entering a smokey room; going from a warm room to a cold room; traffic fumes; chemical irritant smells (eg. hair spray, perfumes, bleach).

Any of these three symptoms may exist alone or co-exist with one or both of the other symptoms for the diagnosis of the Bronchial Irritability Syndrome.

6.3 Results

The questionnaire is shown in appendix A. Replies to the various questions are tabulated fully in appendix C, subdivided by sex (table 30), age-group (table 31) and smoking status (table 32). Subjects who had stopped smoking more than 2 years prior to the survey were included with lifelong non-smokers in comparisons involving smoking status (current smokers versus non-smokers), unless otherwise specified.

6.3.1 Completeness and verification of questionnaires

The response rate to the questionnaire (chapter 5, table 12) and the number of questionnaires returned fully completed did not show any significant variation between age groups. All 17 questions were answered by 89.5% of respondents (table 28, appendix C). Replies to questions 1-8 on the questionnaire were essential for sub-grouping by symptoms, necessary for the second stage of the study (chapters 7-9): these had been answered by 94.7% (1708) of respondents.

The accuracy of replies was verified from 355 (19.5%) randomly selected subjects: 180 by personal interview and a further 175 by telephone. No major discrepancies were evident, although some had found the question regarding symptoms associated with environmental factors (question 7, appendix A) hard to complete - although their eventual response appeared generally appropriate. Several also found question 1 about exertional breathlessness too restricting because they were housebound and marked their questionnaires accordingly.

6.3.2 Smoking status (Q9,10)

Table 14 shows that a much higher proportion of the 85+ age group were life-long nonsmokers (x^2 41.4, $p < 0.01$ comparing 'never smoked' with 'ever smoked', the latter including both current and ex-smokers). Only 19% (160) of men compared with 64% (605) of women were life-long nonsmokers (x^2 385.5, $p < 0.01$). Similarly, 21% (181) men and only 8% (76) women were current smokers (x^2 61.2, $p < 0.01$). The ex-smokers had stopped an average 21 ±14 years previously (range 2 months to 69 years).

Age, years	65 - 74	75 - 84	85 +	Total
Current smokers	125 (15.5%)	93 (14.2%)	39 (11.4%)	257
Ex smokers	392 (48.7%)	277 (42.3%)	111 (32.4%)	780
Never smoked	288 (35.8%)	284 (43.4%)	193 (56.3%)	765
Unknown	0	1	0	1
	805	655	343	1803

Table 14. - Smoking status by age-group of 1803 respondents to questionnaire. (%) Figures apply to comparisons within each age group.

6.3.3 Medical attention (Q 11)

Within the preceding 2 years 489 (27.1%) had seen their doctor with a chest complaint. Suprisingly smoking status appeared to make very little difference to the need for chest-related medical attention, 31% (80) of current smokers and 26% (409) of nonsmokers (including exsmokers of at least 2 years duration) consulting during the specified time period. Comparison between age-groups also showed no significant increase in consultation rates due to chest problems with advancing age.

6.3.4 Breathlessness (Q 1)

Exertional breathlessness when hurrying on level ground or walking up a slight hill was experienced by 38%, with similar frequency for current smokers and nonsmokers (including exsmokers). Exertional dyspnoea was seen to be slightly more common amongst females than males (40% vs 36%), although not reaching statistical significance. There was, however, an age-related trend: 31% of those aged 65-75 years, 44% aged 75-84 years and 42% aged 84 + years experienced exertional breathlessness (x^2 33.0, $p < 0.01$). Nineteen subjects indicated they were house-bound or immobile, 11 of these being aged 85 + .

6.3.5 Nocturnal breathlessness (Q 3)

Episodes of nocturnal breathlessness, waking them from sleep, had been experienced by 131 (7.3%) of respondents. Sex, smoking status and age did not significantly affect the frequency of this symptom.

6.3.6 Morning chest tightness (Q 2)

Morning chest tightness was reported by 203 (11.3%), lasting less than one hour for most (124) of these subjects. For 44 (2.4% of respondents) this symptom persisted for more than an hour. A further 16 (0.9%) wrote that they regularly used an inhaler in the morning (although not specifically asked on the questionnaire) and 32 did not complete this question.

There was an age-related trend, with morning tightness experienced by more of the 85 + age group (16.3%) than those in either the 65-74 (9.3%) or 75-84 (11.0%) age groups (x^2 11.5, $p < 0.01$). It was also a more common symptom amongst men (12.8%) than women (9.7%) (x^2 5.01, $p < 0.05$). Current smokers also reported morning chest tightness more frequently than nonsmokers (14.4% vs 10.7%), although this did not reach statistical significance.

6.3.7 Wheezing (Q 4)

Episodes of wheezing were reported by 437 (24.2%) with men wheezing more often than women (29.2% vs 19.7%; x^2 21.4, $p < 0.01$). Wheezing was much commoner amongst current smokers than nonsmokers (34.2% vs 22.6%; x^2 15.4, $p < 0.01$), and reported more frequently by subjects in the 75-84 age group.

6.3.8 Productive cough (Q 5,6)

Although 22.3% had a productive cough in the morning and 20.2% reported sputum production at other times of the day or night during the winter, only 16.4% (296) had a persistent productive cough suggesting chronic bronchitis (MRC 1965).

Significantly more current smokers than nonsmokers had a productive morning cough (35.8% vs 20.1%; x^2 32.3, $p < 0.01$) and similarly more current smokers had chronic bronchitis (28.0% vs 14.5%;x^2 30.0, $p < 0.01$). A productive cough was commoner amongst men than women, with almost twice as many male patients having chronic bronchitis (x^2 47.4, $p < 0.01$). A productive cough and chronic bronchitis were both commoner in the 75-84 year age group.

6.3.9 Asthma (Q 8)

151 subjects (8.4%) had a history of asthma, of whom half (76;4.2%) had experienced an asthmatic attack within the preceding 12 months. Although asthma was slightly more common amongst men and current smokers, neither represented statistically significant increases. Amongst the 85 + age group a history of asthma was slightly less common than in either of the other age groups.

6.3.10 Effect of airway irritants (Q 7)

This question was omitted by 54 (3%) subjects. Out of 1749 answering the question, the specific situations (a-d) listed caused either a cough, wheeze or breathlessness in 490 (28.0%); 72% were totally unaffected by any of these environmental factors. Males and females were affected with similar frequencies by each of the situations listed.

More nonsmokers than current smokers became symptomatic in the situations considered, in particular on entering a room in which someone was, or had recently been, smoking (21.3% nonsmokers vs 5.1% smokers; x^2 38.5, $p < 0.01$).

Although similar proportions of each of the three age groups remained totally asymptomatic in all four situations described, moving from a warm room to a cold room affected progressively more subjects with increasing age. In contrast, irritant chemical smells affected more of the younger (65-74 yrs) age group.

Figure 22 shows diagrams illustrating the overlap of symptoms produced in the different situations considered (a-d). Cough was the most frequent symptom for all of the airways irritants listed, and appeared relatively non-specific. Many subjects reacted to more than one of the stimuli, but not always with the same type of symptom (eg. wheezing with one situation but breathless in another).

Fig. 22: Frequency of cough, breathlessness and wheezing in 490 subjects on (a) entering a smokey room, (b) going from a warm to a cold room, and with (c) traffic fumes or (d) chemical smells (eg. bleach, perfume, hairspray). A further 1259 subjects were totally unaffected in any of these situations.

Most subjects developed symptoms in more than one of the situations (a-d); the number of those unaffected by the specified situation, but affected in one of the other situations, is shown in parenthesis.

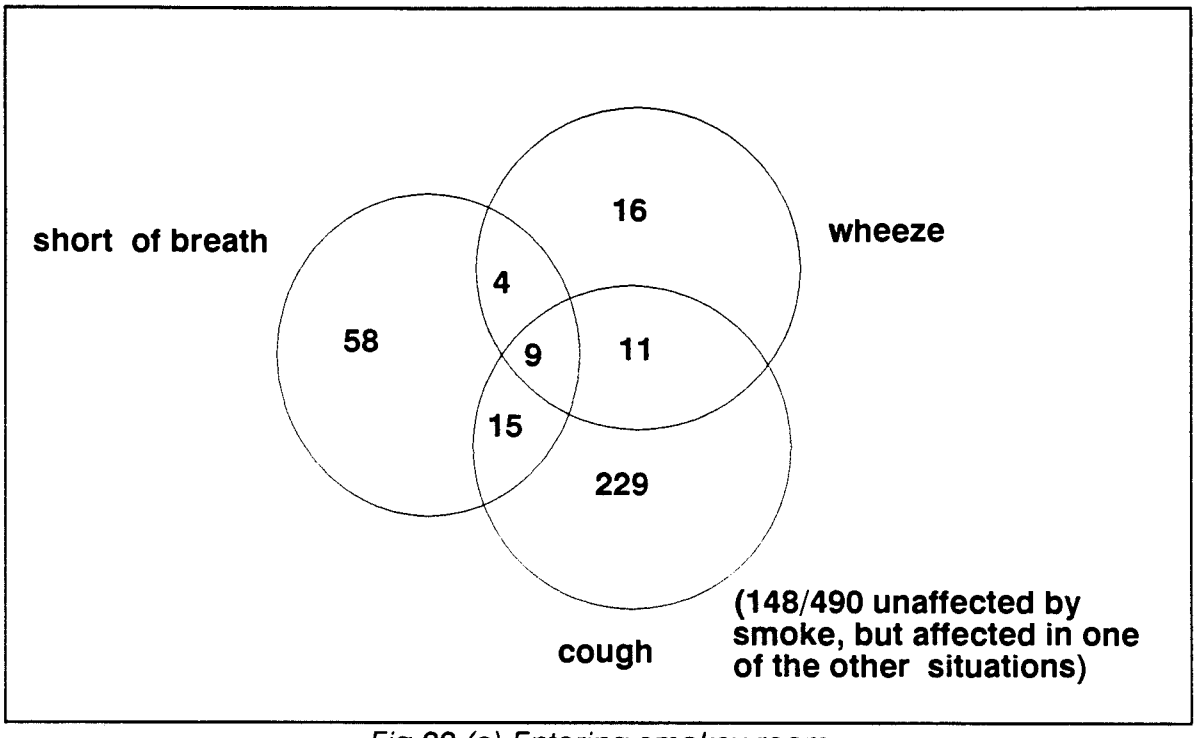


Fig 22 (a) Entering smokey room

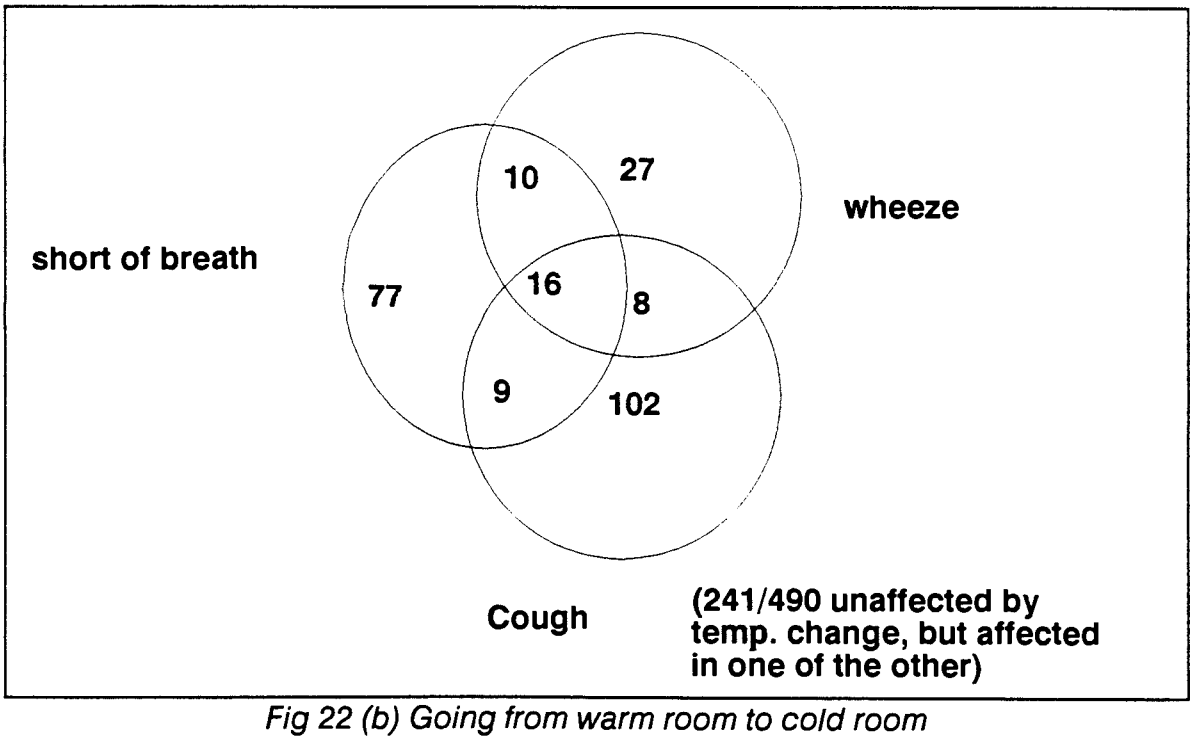


Fig 22 (b) Going from warm room to cold room

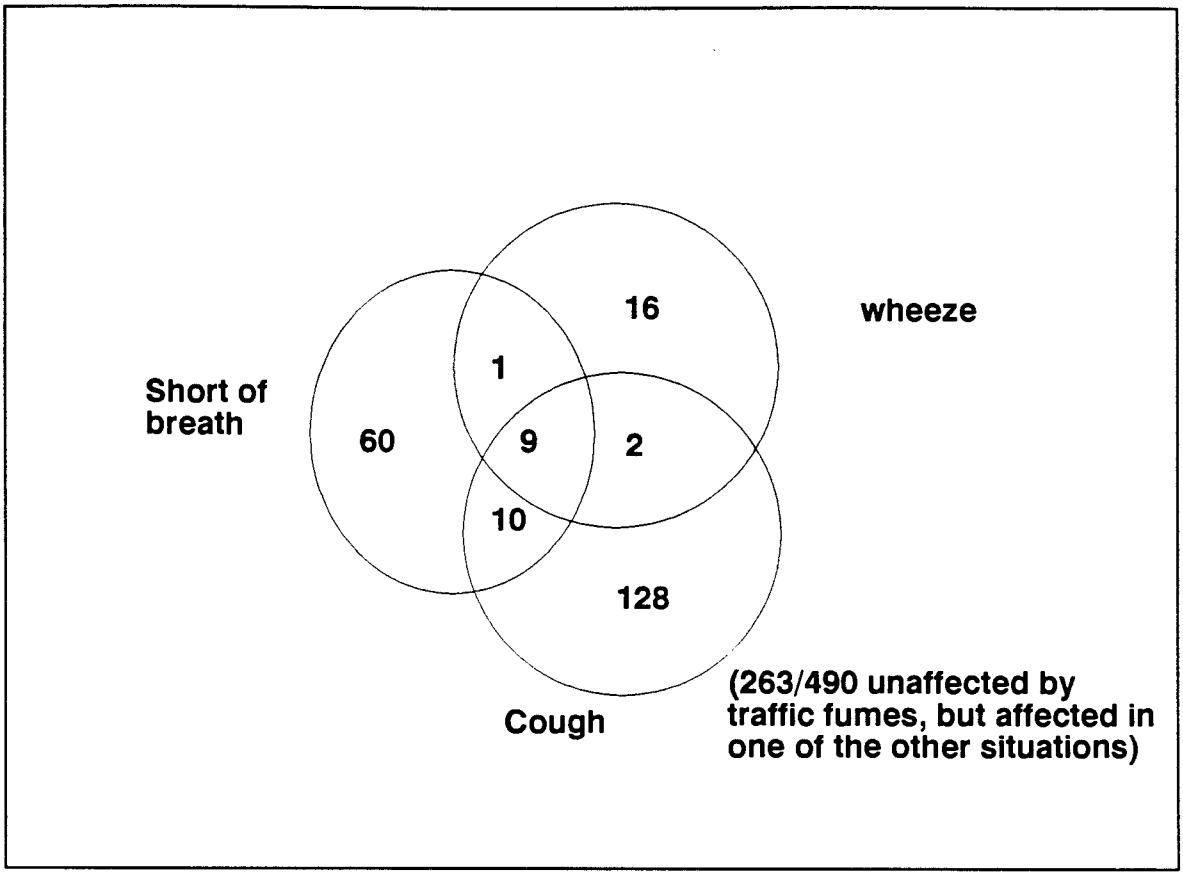


Fig 22 (c) Traffic fumes.

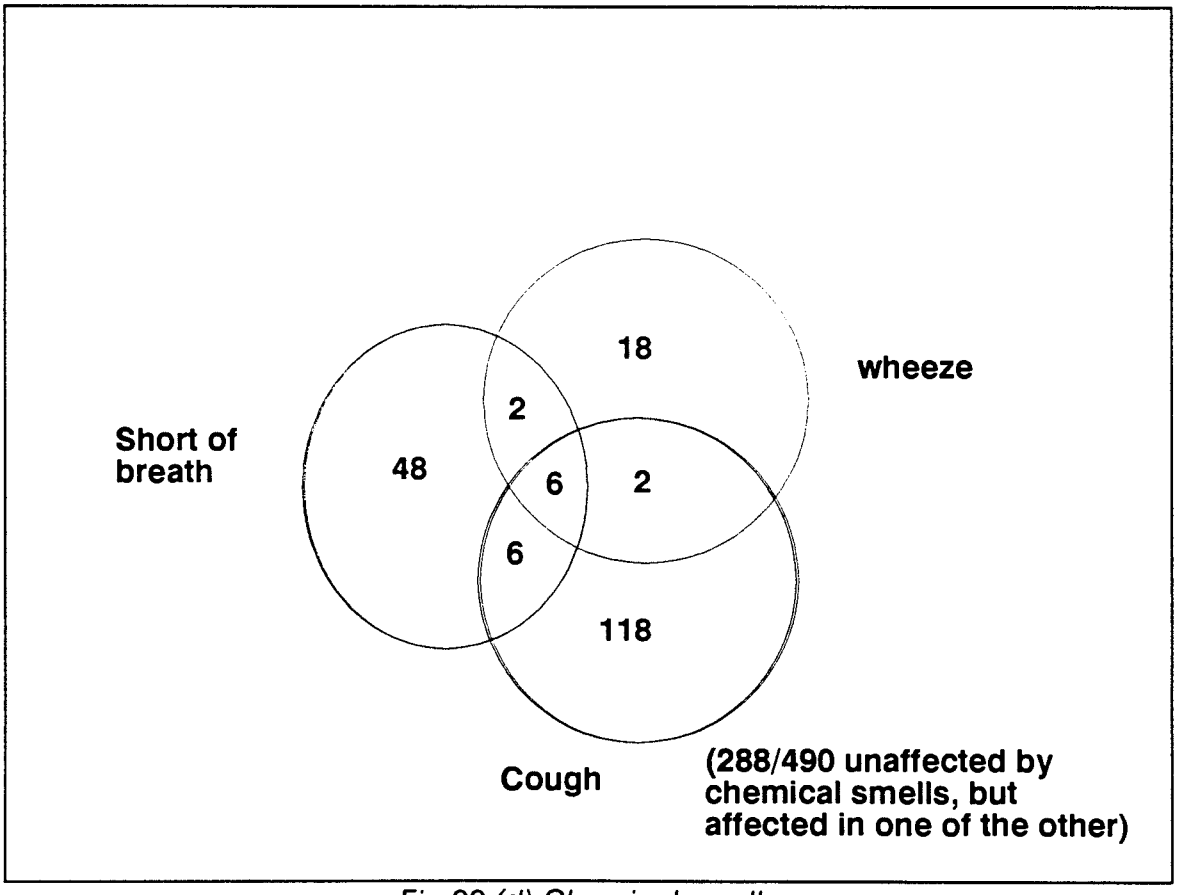


Fig 22 (d) Chemical smells

6.3.11 Symptom subgroups

Table 15 shows the subdivision of all 1803 respondents according to their symptoms given in questions 1-8 of the questionnaire; 95 (5%, group 5) had omitted one or more of these questions (see section 6.3.1). The largest group, group 1, comprised 715 subjects (40%) who were entirely free from respiratory symptoms. For a further 185 (10%, group 2) exertional breathlessness when hurrying on level ground or walking up a slight hill was their only symptom. Symptoms of the Bronchial Irritability Syndrome were described by 519 (29%; group 4). The remainder (289, 16%; group 3) had mixed respiratory symptoms, principally wheeze and productive cough, but not symptoms suggesting the Bronchial Irritability Syndrome.

	65 - 74 years	75 - 84 years	85+ years	All respondents
Group 1 - Fully healthy	359 (44.6)	233 (35.6)	123 (35.8)	715 (39.7)
Group 2 - S.O.B. only	64 (8.0)	80 (12.2)	41 (12.0)	185 (10.2)
Group 3 - Mixed symptoms	126 (15.6)	113 (17.2)	50 (14.6)	289 (16.0)
Group 4 - B.I.S. symptoms	230 (28.6)	191 (29.2)	98 (28.6)	519 (28.8)
Group 5 - Unclassified	26 (3.2)	38 (5.8)	31 (9.0)	95 (5.3)

Table 15. - Subdivision of 1803 respondents to a postal questionnaire according to respiratory symptoms. Percentages (in parentheses) show proportions of each age group in symptom subgroups.
S.O.B. - short of breath on exertion only.
B.I.S. - Bronchial Irritability Syndrome symptoms

More of those in the 65-74 years subgroup were fully healthy, and fewer of this group experienced exertional breathlessness, but table 15 shows no other major differences within age groups for the various symptom subgroups. The number submitting partially completed questionnaires did, however, increase with age, principally amongst male respondents.

A more detailed analysis by sex and age group for the symptom subgroups is given in table 29 (appendix C). More females than males were fully healthy in both the 75-84 and 85+ age groups. Within all age groups more females than males had exertional dyspnoea alone (group 2), with the converse observed in the mixed symptoms group (group 3). The prevalence of the Bronchial Irritability Syndrome symptoms was 29% in all age groups, with no difference between male and female respondents.

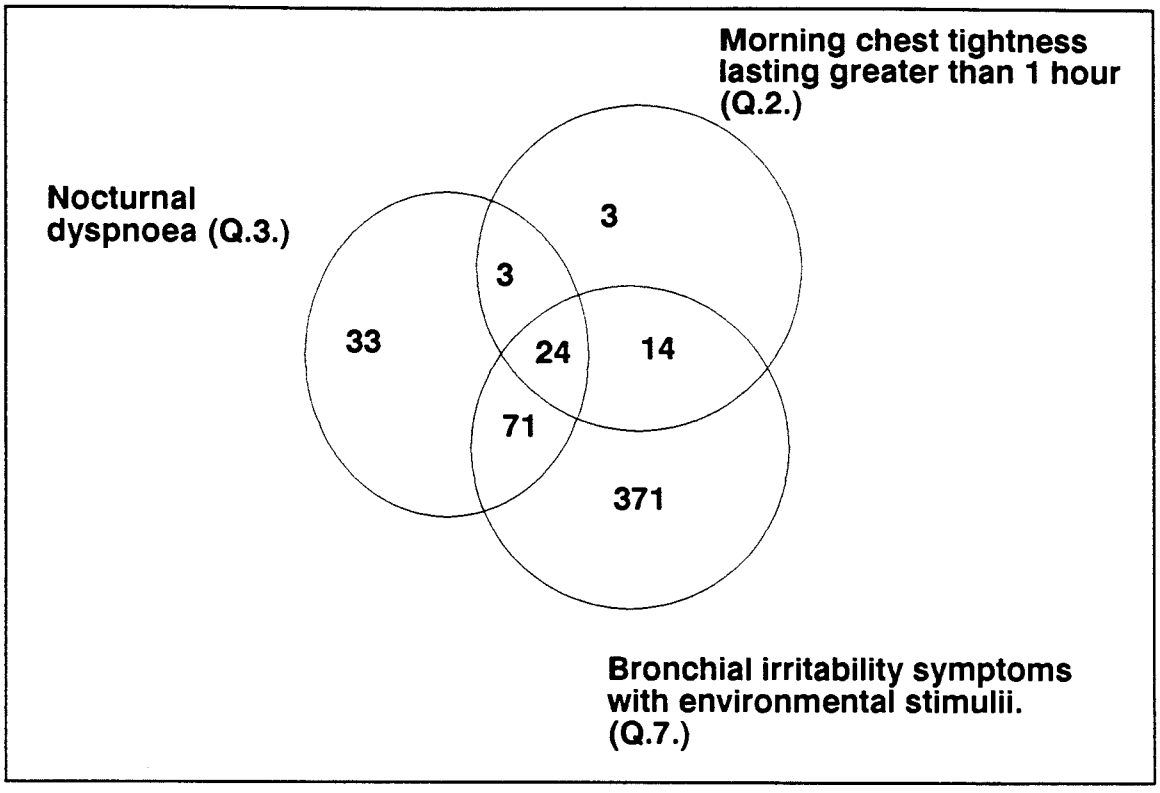


Fig. 23: Symptoms of the Bronchial Irritability Syndrome reported by 519 subjects replying to a respiratory symptoms questionnaire. These represent 29% of all respondents to the questionnaire.

Figure 23 shows the subdivision of subjects in group 4 according to their symptoms of the Bronchial Irritability Syndrome. Symptoms of bronchial irritability in response to environmental stimuli (principally cigarette smoke or cold air) were the commonest reasons for inclusion in this group. A previous diagnosis of asthma was more common amongst subjects with symptoms of the Bronchial Irritability Syndrome and most (86%) of those with currently active asthma were found to be included in group 4 (table 16).

	Asthma ever	Current asthma	Past asthma
Group 1 - Fully healthy	0	0	0
Group 2 - S.O.B. only	1	1	0
Group 3 - Mixed symptoms	40	10	30
Group 4 - B.I.S. symptoms	108	65	43
Group 5 - Unclassified	2	0	2
Total	151	76	75

Table 16. - Prevalence of previously diagnosed asthma within symptom subgroups.

S.O.B. - short of breath. *B.I.S. - Bronchial Irritability Syndrome.*

6.4 Discussion

The postal respiratory symptoms questionnaire proved effective in obtaining both a high overall response rate (96.2% of possible respondents, after excluding those who had died or moved) and an accurate response from elderly subjects surveyed in Lymington and the surrounding New Forest area. Most (94.7%) respondents had completed the eight key respiratory questions (Q1-8) fully and all except 1 subject (who had no respiratory symptoms) gave details of their smoking habits. Thus the data can be taken as a reliable assessment of respiratory symptoms in the age groups studied, no individual question having higher than a 3% non-response rate.

The higher proportion of nonsmokers, and particularly lifelong nonsmokers, observed amongst the very elderly (85+ years) agrees with the findings in several other studies. Horsley et al (1987) and Milne and Williamson (1972a, b), for example, found similar results in two different areas of the country, and the trend is confirmed by the General Household Survey findings (OPCS 1984).

The observation that smoking status did not apparently affect the frequency of chest-related medical consultations may be due to most smokers with significant respiratory morbidity having already succombed to smoking related diseases. The findings of Oswald et al (1967) and Milne (1978), discussed in chapter 2, support this suggestion. This assumes particular significance amongst men, who are much more likely to smoke than women of the same age, contributing to the striking reduction in elderly men amongst the retirement population (especially the 85+ years age group).

Respiratory symptoms were found to affect 60% of respondents, although this included 185 subjects (10% of total) for whom exertional breathlessness was their only symptom; 40% were entirely free from respiratory symptoms. Direct comparison with results from other surveys is difficult, since few have included comparable numbers of elderly subjects. The number with any degree of respiratory disability is higher than reported by Williamson et al (1964), who found 43% of elderly men surveyed experienced some degree of breathlessness or other symptoms.

In contrast to general respiratory symptoms, the prevalence of chronic bronchitis in the present survey (16.4%) is a little lower than previous reports. This study found 22.8% of men and 10.6% of women responding had features of chronic bronchitis (criteria from M.R.C. 1965). Caird and Akhtar (1972) reported 26% men and 13% women with chronic bronchitis in Glasgow, whilst

Milne and Williamson (1972a) gave an overall prevalence of 23.7% in Edinburgh (31.8% men, 9.2% women). Thus in the New Forest the principal reduction in the prevalence of chronic bronchitis is seen amongst men when compared with the two Scottish surveys.

A history of 'wheezing' is often considered to indicate underlying asthma, but this study shows that such a history is more common amongst smokers, and relates mainly to those with bronchitic symptoms. A diagnosis of 'asthma' had been made previously in 8.4% of elderly subjects (4.2% current asthma), slightly higher than the detailed survey conducted by Burr et al (1979) in South Wales, who reported a 6.5% prevalence (2.9% current asthma) of known asthma in a similar age group. This difference is likely to be due to the exclusion of residents of residential homes by Burr et al, since such residential units (Local authority, private rest homes, nursing homes) contain more of the frail elderly. Hepple et al (1989), for example, found that the principal reason for admission to nursing homes in Weston Super Mare was physical disability (42%), with physical disability also being a contributory factor in the admissions of a further 23% in their survey.

Mortagy (1984) found a close correlation between symptoms of bronchial irritability and the subsequent demonstration of increased bronchial reactivity to inhaled histamine - subsequently called the Bronchial Irritability Syndrome (Mortagy et al 1986). Discounting cough as being a nonspecific symptom with environmental irritants, unrelated to the level of bronchial reactivity, the prevalence of the Bronchial Irritability Syndrome was 6.7% in the general adult population of Southampton. Only a quarter of subjects with the Bronchial Irritability Syndrome had been previously diagnosed as having asthma.

Because of the ease of definition of bronchial irritability symptoms, prolonged morning chest tightness and nocturnal dyspnoea and the apparent close association with bronchial hyperreactivity (Mortagy et al 1986), the Bronchial Irritability Syndrome appears to offer a convenient basis for population screening. In the present study 29% of elderly subjects were found to have symptoms of the Bronchial Irritability Syndrome, the prevalence of these symptoms unrelated to age or sex. Although the validity of using this syndrome in the diagnosis of asthma has been contested by Scadding (1987), such a major increase over the prevalence of known asthma in the study group required further investigation (chapters 7-9). Underdiagnosis of asthma and underreporting of symptoms, is a well recognised feature of asthma morbidity amongst the elderly (Lee and Stretton 1972; Bannerjee et al 1987), thus the figure of 8.4% reporting asthma (past or present) is likely to underestimate the true prevalence of asthma in the study group.

It is interesting to note very little difference in most respiratory symptoms between the elderly population and the general population sample reported by Mortagy et al (1986), (Table 17, Chapter 7.1). Significantly more elderly experience exertional breathlessness and slightly more have chronic bronchitis. The response to respiratory irritants appears different, however, between the two study groups. Cough appears a much more common response amongst the general population sample, predominantly a younger subset of the population, than in the elderly. Thus most of the elderly who respond to environmental airways irritants do so by wheezing or becoming breathless (irrespective of whether they also cough or not), and are therefore included within the group with symptoms of the Bronchial Irritability Syndrome (Figure 23). Significantly fewer of the general population (11.4% c.f. 26.6% elderly) respond with wheeze or breathlessness to environmental irritants (x^2 151.3, $p < 0.01$). Therefore the subgroup of elderly subjects with symptoms of the Bronchial Irritability Syndrome (group 4, table 15) includes many more subjects with only symptoms of bronchial irritability in response to environmental respiratory irritants than seen in the considerably younger subgroup studied by Mortagy (1984,1986).

6.5 Conclusions

A postal questionnaire provides an effective and reliable means for obtaining detailed prevalence figures for various respiratory symptoms amongst the elderly. Noticeable differences in smoking habits are evident, with few elderly females smoking, and more of the very elderly (85+ years) being lifelong nonsmokers. Exertional breathlessness was commoner amongst the elderly (38% c.f. 29.0% in general population),as was chronic bronchitis (16.4% c.f. 13.5% general population) and asthma (8.4% c.f. 6.6% general population).

The response to environmental airways irritants was different for the elderly than observed in a younger general population sample. Wheeze and/or dyspnoea were more frequent responses to environmental stimuli amongst the elderly (26.6% c.f. 11.4% general population). Consequently the composition of subgroups of the population with symptoms of the Bronchial Irritability Syndrome (Mortagy et al 1986) differs with age groups.

CHAPTER 7

SUBGROUP ANALYSIS - SELECTION AND PHYSICAL EXAMINATION FINDINGS

7.1 Introduction

Dales et al (1987) found very poor correlation between responses to a respiratory symptoms questionnaire administered to 200 young men and their level of bronchial reactivity (measured during tidal breathing of nebulised methacholine solutions). The indices selected for testing against the level of airway reactivity were a history of asthma, wheeze, episodes of cough with sputum and pneumonia. They concluded that questionnaire information is not adequate for discriminating between those with and those without increased airway reactivity in population screening. Their criteria differed, however, from those developed by Mortagy et al (1986), excluding the three key questions found to be closely related to bronchial hyperreactivity in the Bronchial Irritability Syndrome (chapter 6.2).

The elderly were found in the present study to react differently to environmental respiratory irritants than a younger general population sample (Table 17, below). This results in a greater proportion of elderly subjects being included in the subgroup with symptoms of the Bronchial Irritability Syndrome (group 4, chapter 6.3.11) on the basis of response to environmental airways irritants than in a younger population sample. Consequently the reliability of the criteria proposed by Mortagy et al (1986) for the identification of the Bronchial Irritability Syndrome may not apply to the elderly, and requires reexamination amongst a sample containing adequate numbers of elderly subjects.

	General population		Elderly (65 yrs +)	
n	4143		2011	
Response	2948	(71.2%)	1803	(89.7%)
S.O.B. - short of breath	856	(29.0%)	686	(38.0%)
Wheezing	752	(25.5%)	437	(24.2%)
Morning chest tightness (any duration)	275	(9.3%)	184	(10.2%)
Nocturnal dyspnoea	153	(5.2%)	131	(7.3%)
Chronic bronchitis	397	(13.5%)	296	(16.4%)
Asthma (past or present)	194	(6.6%)	151	(8.4%)
Response to respiratory irritants:				
cough / wheeze / S.O.B.	935/2145	(43.6%)	490	(27.2%)
wheeze / S.O.B. (excluding cough)	244/2145	(11.4%)	480	(26.6%)

Table 17 - Prevalence of respiratory symptoms in a general population sample drawn from the Southampton electoral register (Mortagy et al 1986) compared to a sample from the Lymington and New Forest elderly (age 65 + years) population.

Percentage comparisons are based on those actually responding to the questionnaire, because of the lower response rate in the general population survey.

Connolly et al (1988) confirmed the usefulness of assessing bronchial hyperreactivity in a small group of elderly subjects suspected of having asthma. Bronchodilator responsiveness (measured by salbutamol administration from a standard pressurised cannister inhaler) did not reliably predict either the level of airway reactivity or the potential benefits to the patient from bronchodilator medications (inhaled steroid plus inhaled beta agonist). In contrast to bronchodilator response, the level of airway reactivity correlated extremely well with the outcome from a 6-week therapeutic trial of inhaled bronchodilators.

Formal measurement of bronchial reactivity takes longer than simple pulmonary function assessment and bronchodilator administration. However, if a standardised history, including questions from the respiratory symptoms questionnaire (appendix A), could reliably predict those requiring more detailed assessment, there would be obvious advantages in the investigation of elderly patients. Chapters 7-9 therefore look at analysis of subjects from groups 1-4 (chapter 6.3.11 and table 15), relating respiratory symptoms to objective findings on physical examination (chapter 7), spirometry (chapter 8) and measurement of bronchial reactivity (chapter 9).

7.2 Subjects and method.

Respondents to a standardised postal questionnaire were subdivided according to respiratory symptoms (described in chapter 6.3.11) into 5 subgroups:

1.	Fully healthy	715 (39.7%)
2.	Short of breath on exertion only	185 (10.2%)
3.	Mixed respiratory symptoms	289 (16.0%)
4.	B.I.S.* symptoms	519 (28.8%)
5.	Unclassified	95 (5.3%)

*Bronchial Irritability Syndrome

For each of groups 1-4 separate computer listings of subject identification numbers were obtained and re-numbered sequentially within each group. Using a table of random numbers (maximum of 3 digits used) equal numbers of male and female subjects were then selected from each group for further study. A letter (appendix B.5) was sent to these subjects inviting them to attend the Lymington Geriatric Day Hospital for interview, physical examination, spirometry and methacholine inhalation challenge. The letter invited them to contact the investigator for further information and also stated that the study had the full support of their general practitioner, to whom a copy of the results would be sent. Subjects who did not respond to the letter were contacted by telephone where possible. All appointments were arranged directly with the subjects, either in person (if they visited the Day Hospital reception) or by telephone.

On arrival the aims of the study were explained and the accuracy of responses on the initial questionnaire (appendix A.1) verified to ensure subjects were included in the correct symptoms subgroup. A supplementary questionnaire (appendix A.2) was used in verification of respiratory symptoms and to obtain a history of medication consumption and relevant past respiratory illnesses. This was followed by brief physical examination (chest and cardiovascular), recording findings on a standard form (appendix B6) and spirometry. The latter is considered in chapter 8, as is the measurement of arm span. A brief assessment of mental function was also performed if clinically appropriate using the ten questions suggested by Quereshi and Hodkinson (1974).

7.3 Results

7.3.1 Response to letter

Table 18 shows that, of 283 subjects contacted, 180 (63.6%) agreed to attend for further study. Four subjects had died in the 3 months between the postal survey and contacting them for further assessment; one female subject had become a psychiatric inpatient and was therefore also excluded from further study. Only 40% of the healthy subjects (group 1) agreed to attend for further

study, compared with 73% of group 4 subjects contacted. Less than half the asymptomatic females (group 1) contacted were willing to attend, although the overall response rate was similar for both sexes.

Group	Invited to attend		Agreed to attend	
	Male	Female	Male	Female
1. Fully healthy	36	34	22 (61%)	16 (47%)
2. Short of breath only	34*	46	20 (59%)	30 (65%)
3. Mixed symptoms	35	24+	22 (63%)	16 (67%)
4. Bronchial Irritability Syndrome Symptoms	36*	38*	25 (69%)	29 (76%)
Total	141	142	89 (63%)	91 (64%)

Table 18. Response to written invitation to attend for physical examination, respiratory function assessment and methacoline inhalation challenge.

Percentage acceptance shown in parentheses in each group for males and females separately. Twenty of those attending were subsequently excluded from challenge studies (discussed in chapters 8 and 9).

* *includes 1 recently died.*
\+ *includes 1 recently died and 1 now psychiatric in-patient*

It was clear from discussion with the subjects declining to attend that a major factor deterring them was the challenge study. Those who could be contacted by telephone shortly after receiving the letter of invitation and who had the procedure explained in detail were much more willing to attend. Several could not attend because they were housebound but many of those refusing to attend in group 1 said they were 'well' and therefore did not want any tests.

7.3.2 Interview

No significant discrepancies were found between the symptoms reported on the initial postal survey form and those at the time of interview, apart from improvement in cough and sputum production during the summer months (although this did not affect the subject groupings). Table 19 summarises the number and types of medication taken by subjects in each group, and the number with hypertension, angina, congestive cardiac failure or estab-

lished respiratory disease. The 20 subjects subsequently found unfit for challenge studies (discussed in chapters 8 and 9) are listed separately. Symptoms for each subject attending are given in table 33 (appendix C), also showing the FEV_1 and challenge test result.

Group	1. Healthy (37)	2. S.O.B. only (42)	3. Mixed Symp-toms (38)	4. B.I.S. symp-toms (43)	Not chal-lenged (20)
Medications					
Total number of medications ± S.D.	0.8 0.9	1.8 1.8	1.7 1.4	2.5 1.6	3.5 1.8
(Range)	(0 - 4)	(0 - 6)	(0 - 5)	(0 - 6)	(1 - 8)
Number of subjects on no medication	15	13	9	3	0
Principal Diagnosis					
Hypertension	5	8	9	6	3
Angina	4	5	4	6	6
Cardiac failure	1	8	5	8	7
Respiratory problem	0	0	1	11	6
Smoking History					
Lifelong non-smoker	8	20	12	15	8
Current smoker	7	5	9	6	2
Ex-smokers: yrs since stopped ± S.D.	20 13	12 8	16 9	22 15	19 12

Table 19. - Number (mean ± S.D.) medications being taken by 180 subjects, principal diagnosis and smoking history within groups according to respiratory symptoms. For ex-smokers, number of years since stopping is shown (± 1 S.D.)

No subjects in groups 1 or 2 were on respiratory medication. In group 3 only one subject was on treatment for 'bronchitis', although most (25/38) had productive coughs (11 of these had chronic bronchitis) and all except two in this group experienced episodes of wheezing. In group 4 most subjects had one or more medical problems, with a high degree of respiratory morbidity: 17 had chronic bronchitis, 8 asthma, 2 bronchiectasis and 2 had had radiotherapy for breast cancer (3 and 20 years previously). The number of

current smokers varied only slightly between groups, but the 'healthy' group contained fewest lifelong non-smokers (22% of group 1) and group 2 included most (48%).

7.3.3 Physical examination

Results of examination findings are summarised in table 20 with basic anthropomorphic measurements. One subject with a recent history of 'palpitations' that were being treated with a beta-blocker was found to be in moderately severe congestive cardiac failure associated with rapid atrial flutter. Another had severe effort limitation due to a patent ductus arteriosus. Both of these subjects were excluded from subsequent challenge studies.

Group	1. Healthy (37)	2. S.O.B. only (42)	3. Mixed Symp-toms (38)	4. B.I.S. symp-toms (43)	Not chal-lenged (20)
Age, years	74	73	76	76	71
± S.D.	7	6	6	7	23
Height, cm.	168	164	165	164	158
± S.D.	9	8	10	10	12
Arm span, cm.	176	170	172	170	165
± S.D.	10	8	10	11	13
Weight, kg.	69	72	73	67	61
± S.D.	9	12	12	15	15
Respiratory Rate, /minute	16	18	18	19	21
± S.D.	3	4	4	4	5
Systolic bp, mmHg	151	152	154	152	164
± S.D.	26	23	27	24	42
Diastolic bp, mmHg	81	82	82	82	79
± S.D.	13	11	12	14	18
Atrial fibrillation	0	4	5	5	5
Peripheral oedema or JVP ↑	0	1	1	1	1
Presence of 3rd heart sound	8	17	19	13	8
Cardiac murmers	3	6	5	10	6
Thoracic Kyphosis	3	2	4	6	7
Presence of Basal Crepitations (no. with fine crepitations)	0	4 (2)	3 (1)	3 (2)	3 (2)

Table 20. - Results of physical (chest) examination and basic anthropo morphic data. Mean values are shown ±one standard deviation(S.D.) for age, height, weight, blood pressure and respiratory rate. Remaining figures show the number of subjects with the specified finding.

Six subjects were not previously known to be in atrial fibrillation, although in only one of these (in fast atrial flutter) was introduction of medication necessary. Only one subject had significant congestive cardiac failure, although several had fine basal inspiratory crepitations on auscultation and 65 (36%) had an audible third heart sound. Mean blood pressure measurements were similar in all groups, with a diastolic pressure > 100 mmHg in 8 subjects (> 110 mmHg in 3 of these); this was untreated in 6 and inadequately controlled for 2 subjects.

Thirty subjects (17%) were found to have cardiac murmurs, associated with evidence of cardiac decompensation (left ventricular hypertrophy, cardiac failure, effort limitation) in 9 of these. Clinically detectable left ventricular hypertrophy was present in 6 subjects, associated with hypertension in one and valvular heart disease in the other five. Only 4 subjects had previously indicated on their supplementary respiratory questionnaire that they had a cardiac murmur or were aware of 'heart trouble' other than angina.

Thoracic kyphosis was present in 22 subjects, although with major deformity and effort limitation in only three of these subjects.

Cognitive impairment was found in two subjects. One subject in group 3 had a short mental function test score of 6/10 and one subject excluded from subsequent challenge studies (due to inability to perform spirometry) scored 7/10.

7.4 Discussion

The response to this part of the study was considerably lower than for the postal survey, 36% refusing to attend. It was clear that the process of randomisation contributed to this low response, since inevitably several very elderly, frail or housebound subjects were included in the number invited for further study, as were some in residential homes. Despite this the response was better than that obtained from the younger population group reported by Mortagy et al (1986), 52.5% (229/436) of whom declined to attend for challenge studies.

Subjects with greater respiratory disability (group 4) were more likely to agree to return for further study than those who were fully healthy - presumably because they felt they had more to gain from assessment. This could potentially mean that the subjects studied might represent the less healthy members of the population. However, the subject selection was obtained by random sampling from pre-determined groups with specified respiratory

symptoms based on the initial questionnaire. This is therefore unlikely to have afffected the composition of the final groups of subjects who attended for study - in contrast to the effect on an entirely random population sample, where the lower response rate would have introduced significant bias.

The interview gave an opportunity to verify the answers given on the initial postal questionnaire as well as discuss the objectives of the study and get other general health information. Underreporting of symptoms to their general practitioner was evident - "because he is so busy" being the usual reason given for this. It was clear that subjects in group 4 were less healthy than those in the other groups, with a larger number of respiratory and nonrespiratory problems.

Interview and physical examination was considered essential for all subjects prior to the challenge study to exclude any major illness. Two patients were excluded from methacholine challenge on the basis of examination findings, one being aware of her cardiac abnormality (patent ductus arteriosus) but the other being inappropriately treated with beta blockade for atrial flutter, contributing to congestive cardiac failure. Examination also showed untreated hypertension in six subjects and poor hypertensive control in a further two, as well as 26 subjects with previously undiagnosed cardiac murmurs. A third heart sound was also a frequent finding (36% of subjects), but not always associated with cardiac failure or other symptomatic heart disease.

Subsequent discussion with the local general practitioners confirmed that they had found this clinical information useful in the subjects studied. All those attending had clearly appreciated the opportunity to discuss their general health and respiratory symptoms, supporting the argument for regular health screening of the elderly.

7.5 Conclusions

All subjects replying to a postal questionnaire were grouped according to respiratory symptoms and a random sample then drawn from each symptom group. Overall a 64% response was obtained, lowest from the group with no respiratory symptoms (group 1) and highest from those with most symptoms (group 4). The interview confirmed the accuracy of data on the postal questionnaire and was found beneficial by all subjects, giving opportunity to discuss their general health. Several were found to have previously unrecognised symptomatic valvular heart disease, poorly treated hypertension and other respiratory problems. Regular health screening of elderly subjects would be beneficial and help to reduce morbidity due to delayed recognition of treatable medical conditions.

CHAPTER 8

SUBGROUP ANALYSIS - PULMONARY FUNCTION STUDIES

8.1 Introduction

The preceding chapter explains how subgroups from 1803 subjects responding to a postal respiratory symptoms questionnaire were selected for further study. This chapter gives details of lung function measurements performed on all who agreed to attend and discusses these results in comparison with other reported studies of lung function in the elderly.

8.2 Subjects and method

All 180 subjects attending in response to a written request to return for further study underwent basic physical examination (chapter 7) and spirometry to exclude any who were unfit or unsuitable for subsequent methacholine challenge studies. Height and arm span were measured.

Spirometry was performed with noseclip applied and the subject comfortably seated in front of a Vitalograph dry wedge spirometer (Vitalograph Ltd., Bucks.). Forced vital capacity (FVC) and the 1 second forced expiratory volume (FEV_1) were measured at British Standardised Temperature and Pressure (BTPS). Five forced expiratory manoevres were performed after full explanation; the lowest and highest were then disregarded in calculating the mean FVC and FEV_1. Peak expiratory flow rate (PEFR) was measured using a Mini-Wright Peak Flow Meter (Airmed: Clement Clarke International Ltd., London), again with 5 attempts and disregarding the lowest and highest measurements. All studies were supervised by the same investigator (J.R.H.) and all Vitalograph tracings retained for subsequent reference.

Subjects who, despite enthusiastic coaching, could not perform reproducible spirometry after 5 attempts were excluded from subsequent methacholine challenge, as were all subjects with $FEV_1 < 1.0$ / . Two puffs of a beta-agonist bronchodilator (salbutamol) were administered to these subjects from a standard pressurised cannister inhaler and FVC, FEV_1 and PEFR measurements repeated after 10 minutes.

Normal values for FVC and FEV_1 were calculated from the normograms from Burr et al (1985) for subjects age > 70 years and from Cotes (1979) for those age 65-69 years.

8.3 Results

Mean age, height and arm span for each group are given in table 20 (chapter 7). The groups had similar age composition. Members of group 1 (fully healthy) were on average slightly (4cm) taller than those in groups 2,3 and 4; those excluded from subsequent challenge were slightly shorter. Arm span exceeded height by an average of 6.5 cm (range 0-23 cm) in all groups.

8.3.1 Bronchodilator responsiveness of those excluded from challenge studies.

Spirometry proved difficult for 3 elderly female subjects (ages 88, 89 and 93 years), 2 of these being unable to produce an adequate seal around the mouthpiece (3 different sized mouthpieces tried). They were therefore excluded from subsequent challenge studies, although all 3 had achieved FEV_1 measurements of 1-1.5 *l*. A futher 15 subjects had FEV_1 < 1.0 *l* (2 of these had FEV_1 < 0.5 *l*) and were excluded from challenge studies; 2 of these subjects with low FEV_1 were also physically unfit for challenge (discussed in section 7.3.3). Two other subjects, both with adequate baseline lung function, are included in the group of 20 subjects not challenged because they could not complete the challenge study (discussed further in section 9.3.2).

Bronchodilator administered to the 20 subjects excluded from full challenge studies produced overall improvement in spirometry from the initial values: FVC increased by 14 ± 32%, FEV_1 9 ±10% and PEFR by 24 ± 55% (mean ± 1 SD). However in only 5 subjects was there a 20% or greater improvement in FEV_1.

8.3.2 Initial spirometry for groups 1-4 prior to challenge studies

Table 21 summarises initial spirometry for all 180 subjects according to symptom groups. Data from individual subjects are given in table 34 (appendix C).

Group	1. Healthy (37)	2. S.O.B. only (42)	3. Mixed symptoms (38)	4. B.I.S symptoms (43)	Not chal-lenged (20)
FVC, l	3.49	3.03	2.85	2.72	1.87
± S.D.	0.80	0.91	0.77	0.73	0.86
(% pred . FVC)	(119)	(112)	(103)	(104)	(87)
(± S.D.)	(21)	(21)	(24)	(24)	(32)
FEV_1, l	2.58	2.27	2.02	1.86	1.03
± S.D.	0.59	0.70	0.56	0.55	0.69
(%pred. FEV_1)	(136)	(126)	(116)	(112)	(70)
(± S.D.)	(28)	(24)	(28)	(29)	(34)
FEV/FVC %	74	74	71	70	57
± S.D.	8	6	9	12	20
PEFR, *l*/min	453	396	355	333	152
± S.D.	126	104	116	117	116

Table 21. - Initial spirometry. Expressed as mean ± 1 S.D. and, in parentheses, as percentage of the predicted values

Although subjects in groups 1 and 2 generally had better lung function than those in groups 3 and 4, most subjects achieved better than their predicted value. For measurements of FEV_1 92% in group 1, 90% in group 2, 68% in group 3 and 67% in group 4 exceeded their predicted values as compared to only 25% of those unfit for challenge testing. Only 11 subjects in groups 1-4 had an initial FEV_1 < 80% predicted (1 in group 1, 5 in group 3, 5 in group 4). For measurements of FVC the predicted value was exceeded by 84% of subjects in group 1, 64% in group 2, 55% in group 3, 58% in group 4 and 45% of those not fit for challenge studies.

8.4 Discussion

It is generally suggested that reproducible spirometry is difficult for elderly people to perform. Connolly et al (1988), for example, suggest in their paper that multiple FEV_1 measurements might be poorly tolerated in the elderly, prefering to use PEFR recordings despite the greater variability observed in these measurements. In the present study only three elderly females had to be excluded from detailed study because of difficulties performing spirometry (less than 2% of the study group).

A major advantage of FEV_1 recordings with a Vitalograph is that a permanent record is produced, unlike measurements of PEFR on a standard peak flow

meter. It is therefore possible to confirm reproducibility of spirometry and to give guidance to the subjects as to how to improve their spirometry technique. Common faults observed were not getting an adequate seal around the mouthpiece, not sustaining expiration for long enough (FVC) or inadequate initial expiratory effort (FEV_1).

Very few studies of lung function have included adequate numbers of elderly subjects, in particular in the 'very elderly' age group (age 85 + years). Milne and Williamson (1972) produced predictive equations for the elderly but, without normograms, these equations are time consuming to use in calculating predicted normal values during a clinical study. Simple linear extrapolution of the normograms produced by Cotes (1979) introduces inaccuracies, since it does not adequately allow for the reduction in respiratory muscle strength and other factors affecting the elderly (discussed in chapter 1). Thus the elderly have often appeared to have poor lung function when compared against the available predictive equations based mainly on younger population samples. Nunn and Gregg (1989) found it necessary to use a curvilinear regression equation when extending their predicted values up to age 85 years from PEFR measurements.

Using the values of Cotes (1979) up to age 70 years and those from Burr et al (1985) above age 70 years, as in this study, means that two predictive equations were used - the former representing few elderly subjects and the latter exclusively elderly subjects. The predictive FVC values were exceeded by 63% of all subjects studied (by 65% of the 160 in groups 1-4) and FEV_1 predictive values were exceeded by 73% of 180 subjects (by 79% of those in groups 1-4). Thus the newer predictive values of Burr et al (1985) seem quite modest targets for the elderly to achieve, exceeded by all but one healthy subject (group 1) aged over 70 years in this study. Even current and exsmokers compared well against these predictive values.

Despite two recent publications looking at lifelong nonsmokers (Nunn and Gregg 1989) and asymptomatic elderly smokers and exsmokers (Gregg and Nunn 1989), there are still too few elderly subjects included in their studies to confidently use PEFR predictive values for elderly subjects. The data for predicting PEFR in lifelong nonsmokers, for example, only includes 7 men and 28 women aged over 65 years and only extend up to age 75 years for men and 85 years for women (Nunn and Gregg 1989). This is, however, an improvement on the widely used predictive PEFR equation from Cotes (1979) which only included 3 men aged over 60 years.

Accurate standing height may be difficult to measure in some elderly subjects, in particular those with major dorsal kyphosis, or where stroke or arthritis limits mobility or the ability to stand erect. Height is known to decline with age due to several factors, particularly degenerative changes in the intervertebral discs and other cartilaginous structures and, in some individuals, vertebral collapse (Miall et al 1967; Friedlaender et al 1977). Fowler (1985) therefore suggested that previous maximum height should be used in predicting 'normal' values of lung function for the elderly. Full arm span is approximately equal to height at maturity (Allen 1989) and, as it does not change subsequently with age, may be used as an appropriate substitute if previous height is not known. In the present study, however, no major difficulties were encountered estimating height. The slight (on average only 6.5 cm, table 20) difference between span and height did not significantly affect the predictive lung volume estimates for most subjects. This supports the conclusion of the recent paper by Allen (1989) that measurement of arm span offers no advantage in the prediction of 'normal' values for the elderly, unless the patient is unable to stand.

Out of 180 subjects only 2 were found to have significant impairment in cognitive function (7/10 or less) when assessed by a simple test (Quereshi and Hodkinson 1974). Of these, one performed spirometry successfully and one did not. Allen and Prior (1986) have previously shown that inhaler techniques are unlikely to be learnt by subjects with a short mental function test score of 7/10 or less, stressing the need for asessment of cognitive function in elderly subjects who do not appear to understand instruction in new techniques. Close supervision and enthusiastic coaching of subjects is essential in spirometry and challenge studies. This possibly overcomes some of the potential difficulties in comprehension for subjects with mild cognitive impairment, since the patient is responding to direct instruction rather than being required to learn new information, as with instruction in inhaler technique.

8.5 Conclusions

Pulmonary function assessment of 180 elderly subjects, all aged over 65 years, showed that reproducible measurements of FVC and FEV_1 can be made in almost all subjects (only 3/180 could not perform spirometry). The predictive normal values derived by Burr et al (1985) appeared valid for subjects in this study, representing reasonable targets, achieved by all but one of the fully asymptomatic subgroup (group 1). Measurement of arm span rather than height offered no advantage for the calculation of predicted lung function values. Inadequate data is available to recommend using the currently available predictive PEFR values for elderly subjects.

CHAPTER 9

SUBGROUP ANALYSIS - MEASUREMENT OF BRONCHIAL REACTIVITY TO INHALED METHACHOLINE

9.1 Introduction

In the investigation of a breathless patient the history and simple spirometry may provide all the information necessary to reach a diagnosis (Russell et al 1986). Bronchodilator responsiveness is generally also assessed if formal pulmonary function assessment is undertaken, giving a guide as to whether bronchomotor tone is normal or increased (Jenne and Tashkin 1983). Bannerjee et al (1987) found that a large number of elderly people had respiratory symptoms, a significant number (41%) showing improvement in lung function when PEFR was measured after bronchodilator.

Salbutamol, a beta agonist, is the most widely used bronchodilator in routine pulmonary function studies in the United Kingdom. However, since beta receptor numbers decline with age (Schocken and Roth 1977), elderly subjects become less responsive to beta agonists (Vestal et al 1979; Ullah et al 1981). An alternative means of assessing reversibility of airflow obstruction may therefore be necessary, either with a different type of bronchodilator or therapeutic trial of steroids. Connolly et al (1988) demonstrated that, in a group of 20 subjects with asthmatic symptoms, the level of airway reactivity correlated better with the likely outcome from a therapeutic trial (inhaled steroid plus inhaled beta agonist) than did a single measurement of responsiveness to beta agonist (salbutamol).

Although Connolly et al (1988) demonstrated that methacholine inhalation challenge is safe and clinically useful in the elderly, little data is available on the prevalence of bronchial hyperreactivity in the elderly. Hopp et al (1985) studied 148 normal subjects aged 5-76 years, although including only 11 subjects aged over 67 years. Increased airway hyperresponsiveness to methacholine was observed in both the youngest (age under 13 years) and oldest subjects tested, suggesting age was a significant factor in the determination of bronchial reactivity. This would have important implications for genetic and epidemiologic studies of asthma prevalence and requires further study, since few subjects in their study were over 21 years of age.

The random selection of 180 subjects aged over 65 years from a larger population sample has been discussed in chapter 7 and baseline spirometric results in chapter 8. This chapter describes the assessment of airway reactivity in these subjects using the short technique described by Yan et al (1983).

9.2 Subjects and method

9.2.1 Estimation of nebuliser output.

The output from ten DeVilbiss number 40 hand held nebulisers (DeVilbiss Co. Somerset, Philadelphia) was measured. Two mls of saline were placed in the nebuliser chamber (figure 24) and the weight of the nebuliser then recorded. With the rubber bulb of the nebuliser held in the palm of one hand, the bulb was squeezed firmly ten times and the nebuliser re-weighed. The difference between the initial and second weight was noted. This procedure was repeated ten times for each nebuliser and the mean output per squeeze calculated for a single operator. The procedure was repeated again on a second day to ensure consistency in operator technique. The 5 nebulisers with the most consistent and closely matched output were then chosen for the challenge study.

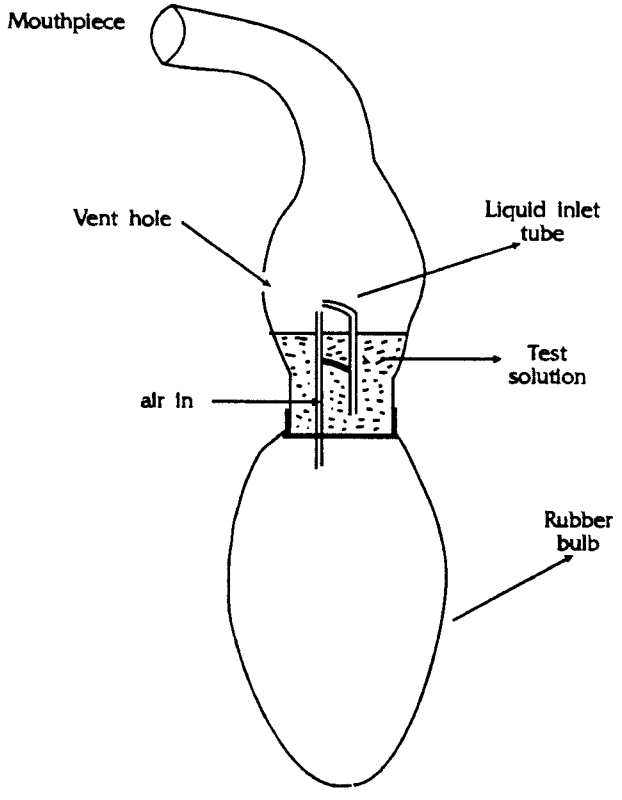


Fig. 24: DeVilbiss 40 glass nebuliser

9.2.2 Preparation of methacholine solutions

Four dilutions of methacholine solution were made. First 1.0 mg anhydrous methacholine (Sigma Pharmaceuticals, Poole) was quickly but carefully weighed and added to 20 mls of sterile 0.9% saline (Normal saline) to make a dilution of 5 mg/100 ml (5 mg%). Ten mls of this solution was stored in a sterile sealed glass container, then serial dilutions were made to obtain 10 mls of 2.5 mg%, 0.6 mg% and 0.3 mg% solutions in separate containers. To a fifth container 20 mls of 0.9% saline (diluent) were added. The five glass containers were kept sealed and refrigerated until required for use, always returned to the refrigerator immediately after dispensing the required volume (2 mls) into the nebulisers prior to challenge studies. The solutions were discarded after a maximum of two weeks and fresh solutions prepared (MacDonald 1979; Alberts et al 1983).

9.2.3 Challenge procedure

Two mls of saline (diluent) were added to one nebuliser and 2 mls of each methacholine solution (0.3, 0.6, 2.5, 5 mg%) added to 4 further labelled nebulisers. Rubber stoppers were kept in the throat tube and vent hole of the nebuliser (figure 18) until use to minimise evaporation, the nebuliser being kept upright once the test solutions had been added.

Full explanation was given to the subject before obtaining written consent for the challenge procedure (appendix B6). Baseline measurements of initial lung function (FVC, FEV_1, PEFR) were made with the subject comfortably seated in front of a Vitalograph dry wedge spirometer, as described in chapter 8.2. The challenge test was then commenced, provided that the subject was able to perform spirometry reproducibly and the initial FEV_1 was no less than 1.0 l .

Three breaths of saline (diluent) were next administered. The subject was instructed to breathe comfortably out (to FRC) and then breathe in slowly through an open mouth, taking 1-2 seconds to complete a comfortably maximum inspiration towards TLC; one puff of diluent was administered by firmly squeezing the bulb of the nebuliser as the subject breathed in. After inhalation the subject was instructed to hold his breath for 3 seconds before exhaling back to FRC. Two further breaths of diluent were then administered in the same way. One minute after inhalation, FEV_1 measurements were repeated (5 attempts, accepting the 3 closest estimates). If the FEV_1 had decreased by more than 10% from the initial (pre-challenge) value the subject was considered to be sensitive to the diluent and the test terminated and bronchodilator administered.

If the FEV_1 was not affected by saline the test proceeded, administering the sequentially increasing concentrations of methacholine solution in the same manner as diluent, measuring FEV_1 at 1 minute after each set of inhalations. The protocol (Yan et al 1983; Woolcock personal communication) permitted two different dosing schedules (appendix B8), a shorter form being used in subjects with few respiratory symptoms and the full schedule for symptomatic subjects. The exact number of breaths of each solution administered varied according to the stage in the challenge procedure and is specified in the protocol (appendix B8).

The challenge test proceeded with increasing concentrations until a 20% fall in FEV_1 from the post-saline level occurred (a positive challenge) or the final dose from the 5.0 mg% solution had been administered. Measurements of PEFR and FEV_1 were made on completing the challenge test. Two puffs of bronchodilator (salbutamol) from a standard pressurised cannister inhaler were then administered to all subjects, irrespective of whether the FEV_1 had fallen during challenge testing, and FEV_1 and PEFR measurements repeated after 10 minutes. Further bronchodilator was then administered if spirometry was not back to pre-challenge values.

As the FEV_1 had generally fallen by more than 20% in subjects with a positive challenge, it was necessary to calculate the dose that would produce a 20% fall (the PD_{20}) by linear regression based on the final and penultimate measurements of FEV_1 and methacholine doses. Subjects with a PD_{20} of less than 6.13 μmol methacholine were considered to have increased bronchial reactivity; those with a PD_{20} of less than 1.0 μmol to have highly reactive airways.

9.2.4 General precautions and reasons for exclusion from challenge studies

All patient assessment and challenge testing was performed in the Lymington Geriatric Day Hospital by a single medically qualified investigator (J.R.H.) who was experienced in both challenge studies and all resuscitation techniques. Oxygen, concentrated bronchodilator solution for nebulisation and full resuscitation facilities were immediately available in the test area, as were other members of the Day Hospital medical staff if needed.

Subjects were excluded from challenge studies if they were unwilling to procede with the study following full explanation, physically unwell or had initial (pre-challenge) FEV_1 of less than 1.0 *l* .

9.2.5 Consent and discussion of results.

All stages of the study (chapters 5-9) were approved by the Ethical Committee of Southampton and South West Hampshire Health Authority. Permission for the use of methacholine in the clinical study was obtained in writing from the Department of Health and Social Security, in accordance with the Medicines (Exemption from Licences) (Special Cases and Miscellaneous Provisions) Order 1972. Written consent for methacholine inhalation challenge was obtained (appendix B7) after full explanation of the procedure. The physical examination findings, results of spirometry and methacholine challenge were discussed with each subject at the end of the tests and a summary of these findings sent to their general practitioner (appendix B9).

9.3 Results

9.3.1 Nebuliser output

Table 22 shows mean nebuliser outputs on two separate days for 10 nebulisers, confirming reproducibility of output using a hand held method of operation. The mean output was 0.0030 ± 0.0001 mls per squeeze for the 5 nebulisers chosen for use in the challenge study.

Nebuliser	Output Day 1(ml)	Output Day 2(ml)
1. *	0.0027 (0.0001)	0.0030 (0.0001)
2. *	0.0031 (0.0002)	0.0032 (0.0002)
3.	0.0029 (0.0003)	0.0025 (0.0001)
4. *	0.0030 (0.0001)	0.0030 (0.0002)
5. *	0.0032 (0.0003)	0.0033 (0.0002)
6.	0.0033 (0.0001)	0.0034 (0.0001)
7.	0.0028 (0.0001)	0.0028 (0.0001)
8. *	0.0034 (0.0001)	0.0035 (0.0001)
9.	0.0026 (0.0001)	0.0024 (0.0001)
10.	0.0025 (0.0001)	0.0024 (0.0001)

Table 22. - Mean output from 10 DeVilbiss number 40 nebulisers per squeeze of nebuliser bulb, with one standard deviation shown in parenthesis. All measurements performed by a single operator.
*(* indicates nebulisers chosen for challenge study)*

The dose of methacholine delivered per squeeze was calculated in μmol, taking the molecular weight of anhydrous methacholine as 195.7. The maximum cumulative dose delivered was 6.13 μmol methacholine for both the full and abbreviated versions of the protocol (appendix B8).

9.3.2 Subjects excluded from challenge studies

Twenty subjects (numbers 161-180 in table 34, appendix C) were excluded from challenge studies for the following reasons:

3 unable to perform reproducible spirometry
15 initial $FEV_1 < 1.0 l$
1 unable to perform challenge study (# 166; only saline attempted)
1 withdrawn from challenge due to adverse reaction (# 163)

Thus, of 162 subjects meeting the criteria for challenge testing, only one (subject 166; female aged 87 with severe senile tremour) could not coordinate inspiration, although had performed spirometry adequately. A further subject (subject 163; male age 67) developed giddiness, nausea, wretching, throat irritation and marked sweating after a cumulative dose of 2.30 μmol methacholine despite only a slight (7%) fall in FEV_1. The challenge procedure was abandoned and he rapidly recovered after a glass of water; 2 puffs of salbutamol were also administered. These two subjects are included with the 18 who were excluded on the basis of initial spirometry in tables 19 and 20 (chapter 7) and in table 21 (chapter 8).

These 20 subjects not chalenged were from the following symptom groups:

1	group 1	Healthy (subject no. 161)
8	group 2	Short of breath only (no. 162-169)
11	group 4	Bronchial Irritability Syndrome symptoms (# 170-180)

9.3.3 Challenge Studies

Challenge studies were undertaken on 160 subjects. Spirometric data pre-challenge and during challenge is given in full for these subjects in table 34 (appendix C). Within each symptom grouping subjects have been ranked according to their measured level of airway reactivity - subjects with the lowest identification number had the most highly reactive airways within that group.

Table 23 summarises the outcome of challenge studies for each of the symptom groups. Two subjects in group 3 reacted to saline inhalation, one with a fall in FEV_1 of 17% and the other a 25% fall compared to initial values. Neither of these had a history of asthma. The subject (number 81) with the largest drop post-saline had a short mental function test score of 6/10 and

found difficulty complying with instructions regarding diluent inhalation, although she had managed spirometry successfully.

Group	1. Healthy (37)	2. S.O.B. only (42)	3. Mixed Symptoms (38)	4. B.I.S Symptoms (43)
Negative challenge	31	26	13 *	19
Positive challenge, incl highly reactive	6 (16%)	16 (38%)	23 (61%)	24 (56%)
Highly reactive	1 (3%)	1 (2%)	6 (16%)	11 (26%)
Mean PD_{20} ± S.D. of those with positive challenge	3.96 ±1.93	3.38 ±2.13	2.87 ± 2.18	2.25 ± 2.26

Table 23. - Outcome of challenge studies in 160 subjects, all aged >65 years, divided according to pre-challenge respiratory symptoms. Percentage figures indicate proportion with the specified level of reactivity within each group.

Positive challenge = PD_{20} < 6.13 μmol Methacholine
Highly reactive = PD_{20} < 1.0 μmol Methacholine

** In addition two subjects in Group 3 had >10% fall in FEV_1 following saline (diluent) inhalation.*

The frequency of a positive challenge was similar for subjects in both groups 3 and 4 (61% and 56% positive respectively) and lowest in group 1 (16%); 38% of those with only exertional breathlessness (group 2) had a positive challenge. Although more subjects in group 4 had highly reactive airways (PD_{20} < 1.0 μmol) than in group 3 (26% and 16% respectively), this was not a statistically significant difference between the groups.

Figure 25 shows the scatter of PD_{20} values obtained for the 69 subjects with positive challenge tests, divided according to reported respiratory symptoms. In view of the similarity between results in groups 3 and 4 (all subjects symptomatic), these two groups were combined and compared against the other subjects who had either no respiratory symptoms or only exertional breathlessness (groups 1 and 2). Significantly more symptomatic (groups 3 and 4) subjects had a positive challenge test (x^2 16.1, $p < 0.01$) and, similarly, significantly more had highly reactive airways (x^2 13.5, $p < 0.01$) than those in groups 1 and 2.

POSITIVE METHACHOLINE CHALLENGE

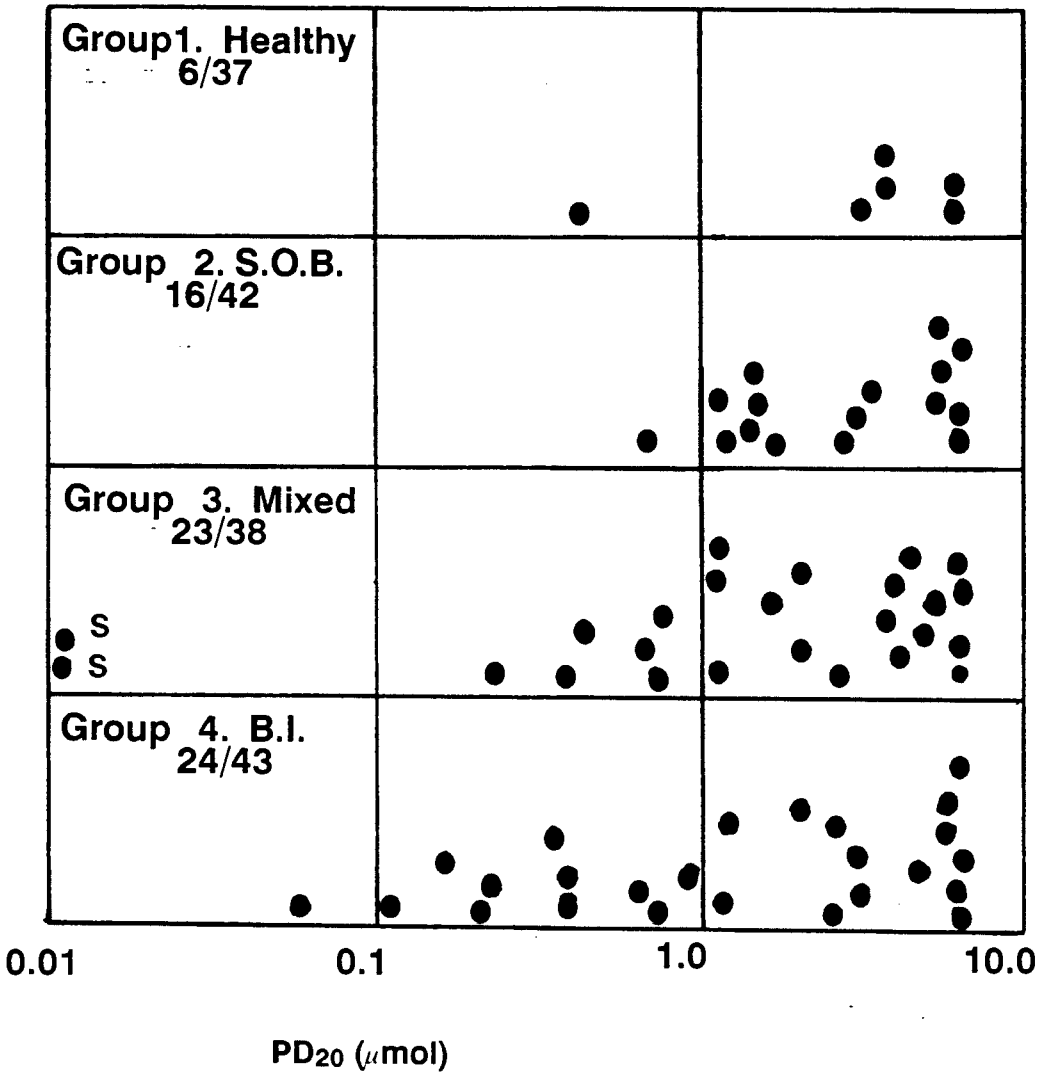


Fig 25: Cumulative dose of methacholine required to produce a 20% fall in FEV_1 (PD_{20}) for 69 subjects with positive challenge studies (PD_{20} of 6.13 μmol or less).
Two subjects in Group 3 are also shown who reacted to Saline inhalation (S); a further 89 subjects had negative challenge results at the maximum dose of methacholine used in this study (6.13 μmol).

A further 29 subjects had a fall in FEV_1 between 10-18% from control (saline) values after the maximum dose had been delivered - 7 in group 1, 7 in group 2, 5 in group 3 and 10 in group 4. No attempt at prediction of PD_{20} values was made for these subjects.

9.3.4 Relationship between low FEV_1 and airway reactivity

The outcome of challenge testing was related to the level of initial (pre challenge) FEV_1 (table 24). Subjects with a low initial FEV_1 (1-1.5 l) were more likely to have a positive challenge than subjects with FEV_1 > 1.5 l (x^2 17.7, $p < 0.01$). The prevalence of highly reactive airways was also increased amongst those with low initial FEV_1 (x^2 21.7, $p < 0.01$).

FEV_1, l	n	Positive challenge (PD_{20} < 6.13 mmol)	Highly reactive PD_{20} < 1.0 mmol)
1 - 1.5 l	28	22 (79%)	10 (36%)
>1.5 l	132	47 (36%)	9 (7%)

Table 24. - Relationship between FEV_1 and level of bronchial reactivity to inhaled methacoline.

9.3.5 Correlation between changes in FEV_1 and PEFR following cha lenge testing.

Serial measurements of PEFR were not made after administering each dose of methacholine, but PEFR was recorded prior to challenge studies and on completion of the methacholine challenge (after the final FEV_1 measurement). Comparing these two PEFR measurements, in some subjects the PEFR was actually higher after challenge despite a greater than 20% fall in FEV_1 (subjects 4, 53, 87, 129), whilst in others the PEFR had fallen dramatically in comparison to much smaller changes in FEV1. The latter pattern was observed in only one subject in groups 1 and 2 (subject 23) but noted in many of those in groups 3 and 4 (table 34, appendix C). The coefficient of corelation (r2) for percentage change in PEFR compared against change in FEV_1 after methacholine was 0.15 in both groups 1 and 2, 0.26 in group 3 and 0.34 in group 4.

9.3.6 Airway reactivity related to smoking history.

The group of 160 subjects in whom airway reactivity was measured contained 27 current smokers and 79 exsmokers, the latter having stopped on average 20 ± 14 years previously. Table 25 compares the smoking status of these subjects with their response to inhaled methacholine. Out of the 19 subjects with highly reactive airways (PD_{20} < 1.0 μmol methacholine) there was only one current smoker, but 12 (63%) of these subjects were exsmokers. However, the proportion with negative challenge studies was not significantly affected by smoking history.

	Current smokers (27)	Ex smokers (79)	Never smoked (54)
Positive challenge			
PD_{20} < 1 μmol	1 (4%)	12 (15%)	6 (11%)
PD_{20} 1 - 6.13 μmol	12 (44%)	21 (27%)	17 (31%)
Negative challenge			
	14 (52%)	45 (57%)	30 (56%)
Reacted to saline (diluent)	0	1	1

Table 25. - Relationship between smoking history and the level of airway reactivity to inhaled methacholine in 160 subjects aged > 65 years. Results shown as number and percentage with positive and negative challenge in each subgroup.

9.3.7 Airways reactivity related to respiratory symptoms.

Details of the symptoms reported by all subjects undergoing challenge studies is given in table 33 (appendix C). These are summarised in table 26, relating the level of airway reactivity (in terms of positive or negative challenge studies) to different respiratory symptoms.

Out of 19 subjects with highly reactive airways, only one was asymptomatic. However 36% of these subjects (7/19) had not told their general practitioner about their symptoms.

Symptoms	n	Positive Challenge		Negative Challenge
		PD_{20} < 1 μmol	PD_{20} 1 - 6.13 μmol	PD_{20} > 6.13 μmol
None (group 1)	37	1 (3%)	5 (13%)	31 (84%)
Exertional breathlessness only (group 2)	42	1 (2%)	15 (36%)	26 (62%)
Exertional breathlessness (including group 2)	103	18 (17%)	39 (38%)	46 (45%)
Wheeze	68	19 (28%)	25 (37%)	24 (35%)
Chronic bronchitis	28	7 (25%)	14 (50%)	7 (25%)
Morning chest tightness lasting > 1hour	8	5 (62%)	2 (25%)	1 (13%)
Any morning tightness (incl. > 1hour)	30	8 (27%)	16 (53%)	6 (20%)
Active asthma	5	3 (60%)	1 (20%)	1 (20%)
Past asthma (inactive)	3	1	1	1
Nocturnal breathlessness	15	4 (27%)	5 (33%)	6 (40%)
Symptoms with environmental irritants	36	9 (25%)	9 (25%)	18 (50%)

Table 26. - Response to methacholine inhalation challenge related to different respiratory symptoms. Unless specified the symptom may co-exist with any other symptom(s).

Number of subjects (and percentage) with stated level of reactivity is shown for each symptom listed.

Exertional breathlessness was reported by 103 subjects, of whom 18 (17%) had highly reactive airways. However, when exertional breathlessness was the sole symptom, the subjects were unlikely to have a major degree of airways hyperreactivity.

Morning chest tightness lasting more than one hour or a history of active asthma were associated with highly reactive airways more often than other symptoms. No other symptom or cluster of symptoms could be identified with close correlation to the posession of highly reactive airways. Only the

absence of respiratory symptoms (group 1 subjects) or experiencing exertional dyspnoea alone (group 2 subjects) made the demonstration of significant airway hyperreactivity unlikely.

In group 4 only 5/43 subjects reported all three of the symptoms of the Bronchial Irritability Syndrome; of these 3 (60%) had highly reactive airways and 2 (40%) had negative challenge studies. Eleven subjects reported two out of the three symptoms of the syndrome: 3 (27%) of these had highly reactive airways and 3 had a negative challenge result. When only one of the symptoms in the Bronchial Irritability Syndrome was present, 52% (14/27) had a negative challenge study and only 18% (5/27) were found to have highly reactive airways.

9.4 Discussion

The method chosen for the challenge study (Yan et al 1983) was found to be easy to explain to the elderly and simple to perform. Only one subject had to be excluded because of inability to perform the challenge procedure correctly and only one experienced a significant adverse reaction necessitating termination of the challenge procedure - even though his FEV_1 had shown no significant fall. Two other subjects were found to be sensitive to saline. A challenge procedure was therefore completed in 158 of the 162 (97.5%) subjects whose baseline spirometry was adequate for challenge.

The reproducibility of this method has not been specifically studied in this sample group. Good inter-observer correlation and consistency of measurements on different days has previously been demonstrated by both Yan et al (1983) and, independently, by Chinn et al (1986) and Britton et al (1986c). The outputs from the nebulisers used in the present study are shown to be highly reproducible when used by a single research worker (table 22), matching the nebuliser outputs used by Yan et al (1983).

The significance of a fall in FEV_1 after saline (diluent) administration is unclear. This happened in only two subjects, both in group 3. One of these subjects had evidence of cognitive impairment and the apparent fall in FEV_1 probably repreesented a combination of poor spirometric technique and fatigue after repeated measurements, rather than sensitivity to saline in this subject. The second subject (no. 80) had moderately severe airways obstruction pre-challenge (FEV_1/FVC of 49%) with improvement following bronchodilator, so that in his case the 17% fall in FEV_1 following saline may represent increased bronchial reactivity. Contamination of the nebuliser cannot be implicated

since each nebuliser was clearly labelled and only used for a single concentration of test solution throughout the study.

It is evident from figure 25 that the symptoms of the Bronchial Irritability Syndrome (Mortagy et al 1986) do not provide a means to identify elderly subjects with bronchial hyperreactivity. Marked overlap is shown between the three subgroups studied with respiratory symptoms. More subjects with symptoms of the Bronchial Irritability Syndrome (group 4) had highly reactive airways (PD_{20} < 1.0 μmol methacholine), but this did not represent a statistically significant difference from group 3 subjects who had bronchitic symptoms (breathlessness, wheezing, productive cough). This is surprising, since most subjects with a history of asthma had reported symptoms of the Bronchial Irritability Syndrome (table 16).

The overall prevalence of a positive challenge test was 43%, with highly reactive airways in 12%. This is considerably higher than previous studies in younger adults have reported (table 7), most estimating 5-10% prevalence of bronchial hyperreactivity. Burney et al (1987) found 14% of their adult (age 18-64 years) sample had increased bronchial reactivity in an area close to the present study area, but were concerned that their sample was unrepresentative because of a lower response rate at either end of their age range. Mortagy (1984) noticed a trend for more elderly subjects to report symptoms of the Bronchial Irritability Syndrome, but did not perform challenge studies on any elderly subjects to investigate this further.

The prevalence of increased bronchial reactivity shown does closely match the data for the prevalence of bronchodilator responsiveness from Bannerjee et al (1987; see table 5). Their study also concentrated exclusively on the elderly, finding 41.2% of 195 subjects tested had a greater than 15% improvement in expiratory flow rates (PEFR) following bronchodilator. Although a positive challenge test or improvement in PEFR after bronchodilator does not necessarily indicate asthma, the confirmed high prevalence of both amongst the elderly suggests considerable undetected and untreated respiratory morbidity.

At lower lung volumes the effect of even minor degrees of airway obstruction becomes more significant, due to reduced respiratory reserves. This is true even when the low lung volumes are within the 'normal' range for age, sex and height. It is therefore important to note the considerably increased prevalence of bronchial reactivity, and especially highly reactive airways, amongst subjects with an FEV_1 in the range 1-1.5 *l* (table 24). Subjects with

low baseline FEV_1 values were found to be five times more likely to have highly reactive airways than subjects with an $FEV_1 > 1.5$ *l*.

Malo et al (1983) also found a relationship between various forced expiratory flow rate measurements and responsiveness to methacholine, although their data was not conclusive. The present study confirms a strong relationship between baseline airway calibre and bronchial responsiveness, in particular to the posession of highly reactive airways. Thus those subjects with lowest respiratory reserves are also the ones most at risk from infections, drugs and other agents that cause bronchospasm. Possibly some of the deaths in the previously well elderly might be caused by this mechanism, without there necessarily being a preceding history of respiratory problems.

The relationship between airway reactivity and smoking is interesting. Although current smokers, exsmokers and lifelong nonsmokers had a similar frequency of negative challenge studies (table 25), fewer current smokers had highly reactive airways. This might be explained by suggesting that subjects with highly reactive airways become too symptomatic if they smoke - certainly slightly more of the exsmokers had highly reactive airways (although most of these had stopped smoking around 20 years earlier). The alternative, to suggest that smoking might paradoxically attenuate airways reactivity, is improbable. Many smokers stop because of the development of respiratory symptoms, no doubt contributing to the increase in the number of exsmokers amongst the 19 with highly reactive airways (63% of these subjects were exsmokers).

Amongst the group of asymptomatic elderly subjects (group 1) 16% had a positive challenge test. The posession of any respiratory symptom increased the chance of a positive challenge study, although when mild exertional breathlessness was the only symptom (group 2) this did not increase the chance of demonstrating highly reactive airways as compared to fully healthy (group 1) subjects. A history of active asthma or prolonged morning chest tightness correlated closely with the posession of highly reactive airways, although only small numbers of subjects with these specific symptoms were tested. Symptoms of bronchial irritability (wheeze, breathlessness) on exposure to environmental irritants such as cigarette smoke or moving into a cold room were commoner amongst the elderly than in younger subjects (chapter 6.4), but correlated poorly with bronchial hyperreactivity (table 26).

No cluster of symptoms could reliably identify elderly subjects with highly reactive airways, since most respiratory symptoms could be associated with

bronchial hyperreactivity. Even the total number of symptoms reported by an individual did not appear to directly relate to the level of airway reactivity (table 33, appendix C), although severity of symptoms could not be assessed from the answers to the brief questionnaire used. Therefore, although the respiratory symptoms questionnaire was extremely useful in providing data on a large sample of elderly subjects, it was not sufficiently sensitive to be used as an alternative to formal interview and pulmonary function testing for the diagnosis of significant airways disease. The questionnaire did, however, prove useful in separating out those with a low risk of bronchial hyperreactivity and with good lung function (groups 1 and 2) from those in whom abnormal lung function and bronchial hyperreactivity were more common (groups 3 and 4).

9.5 Conclusions

Using a hand-held DeVilbiss 40 nebuliser, methacholine inhalation bronchial challenge was completed by 158 (97.5 %) out of 162 subjects fit for challenge. Only 1 subject developed an adverse reaction to methacholine inhalation (from which he quickly recovered), principally with non-respiratory side effects.

The prevalence of bronchial hyperreactivity to inhaled methacholine amongst the elderly is 43% (PD_{20} $< 6.13\ \mu$mol), with highly reactive airways in 12% (PD_{20} < 1.0 mmol). A history of current asthma or prolonged morning chest tightness correlated closely to the posession of highly reactive airways, but no other cluster of symptoms was helpful in predicting the level of airway reactivity. The symptoms of the Bronchial Irritability Syndrome are not helpful in identifying elderly subjects with bronchial hyperreactivity.

Subjects with low (1-1.5 *l*) baseline FEV_1 were five times more likely to have highly reactive airways than subjects with FEV_1 > 1.5 *l*, confirming a direct relationship between baseline airway calibre and bronchial reactivity.

CHAPTER 10

GENERAL DISCUSSION

10.1 Assessment of the elderly

It is suprising that more attention has not been devoted to the respiratory problems of the elderly in view of the frequency with which they occur. Unfortunately the elderly patient admitted to an acute general medical ward often receives less attention and less intensive treatment than a younger patient presenting with similar symptoms. Episodes of breathlessness, for example, will be more readily attributed to "chronic obstructive lung disease" or a past smoking history in an older patient, whereas this would only be suggested in a younger patient after excluding reversible airways disease.

Hopefully the increasing number of specialists in Geriatric Medicine, with more elderly subjects admitted to wards catering specifically for assessment of acutely ill elderly patients, will radically alter this approach to older patients (Evans 1987). Including an attachment on a Geriatric Unit in the training of both general practitioners and hospital doctors would also be beneficial in alerting medical staff to the great potential for improving the general health and well-being of a large proportion of the elderly. Research into specific disorders will also be promoted by greater sub-specialisation of Geriatricians (Davidson and King 1986).

One of the major problems in recruiting staff to work with the elderly has been the negative way in which "geriatrics" is perceived - both by those within the Health Service and by the general public. As Acheson (1986) states, the term "geriatric" is too often used in a derogatory sense to imply someone who is "decrepit and, by implication, even unwanted". A comprehensive and positive approach to the elderly is beneficial, however, both reducing length of hospital inpatient stay as well as considerably improving morale and independence amongst elderly patients (Horrocks 1986). However, this can only be done with adequate resources (Andrews 1985).

In acute medical wards there is an expectation of rapid turnover of patients and the elderly patient, requiring longer than "average" in hospital, is often termed a "bed-blocker" (Maguire et al 1986). The prolonged hospital stay is generally related to medical factors rather than social problems. A third of elderly patients admitted acutely with chest disorders were found to be still in hospital after two weeks, 12% of all elderly subjects presenting with chest problems requiring more than a month in hospital (Maguire et al 1986).

Multiple pathology prolongs the length of stay, in particular when confusion, falls and incontinence are the presenting factors (Wilson et al 1962; Isaacs 1981). A second study of "bed-blockers" (Coid and Crome 1986) found a lower percentage of those admitted primarily with a chest disorder to still be in hospital after a month compared with Maguire's data (1986), but again emphasised the importance of an early miltidisciplinary approach to the assessment of an elderly patient to avoid unnecessary prolongation of a hospital stay.

A high level of clinical acumen is required when assessing an elderly subject (Evans 1987) and, although this will require full diagnostic and supporting facilities, it also requires a rational approach to the use of facilities. Inappropriate application of cardio-pulmonary resuscitation in the very elderly, for example, must be avoided since the goal of all involved in the care of the elderly is enhancing the quality of life and not, as Currie (1988) states, "trying to prolong death".

If services are to be used properly and patients treated before major disease complications develop, early case finding is required. General practitioners, supported by Health Visitors, are ideally placed in the Community to undertake this, but unfortunately all too often hampered by lack of time to do this thoroughly. Up-to-date health registers are needed using an age-sex format, but, as discovered in the present study (chapter 5), these are difficult to maintain in a busy practice even when well motivated.

It has been suggested that a greater number of Health Visitors are needed to tackle screening of the elderly with regular reviews, also facilitating better links with other community and hospital services (Barley 1987). Much is, however, already known by the primary care team and can be summmarised on simple data cards to facilitate case finding by pooling of information if properly organised (Hooper 1988). Barley (1987) emphasises the need for an active primary care team when he suggests that the attitude of many elderly subjects can be cynically summarised as follows:

> *"We old people spend nearly all our lives at home; we go into hospital in a crisis but most of us are dead within the year after our admission; we were managing pretty well at home for a long time before admission; and we are almost always capable of knowing when we need a doctor.... but please give us a doctor who is available, interested, educated in our special needs, and in close touch with a vigorous and enthusiastic primary care team - including a health visitor; let them make contact with us about once a year, but give us the chance to say no to their ministrations if we want to."*

The study by Williamson et al (1964) would, however, suggest that old people do not always know when they need to see a doctor. This was particulary so with regards to chest disorders. If respiratory morbidity is to be reduced, early case detection is therefore essential and, if there are inadequate resources for formal interview and examination, perhaps a postal health screening questionnaire should be considered as an alternative.

10.2 A respiratory symptoms survey amongst the elderly

The present study has shown that a simple questionnaire can be extremely useful in gathering information about the elderly. The high response rate obtained (96.2%) indicates that the elderly are both willing to, and capable of, completing health questionnaires. The participation of the general practitioners appears to have been a major factor in achieving this high response rate and it is therefore probable that the subjects would be equally willing to return a questionnaire originated by their own doctor. It would not, however, be possible to ask so many specific system-orientated questions in a general health questionnaire.

Unfortunately, since the elderly tend to minimise their symptoms, depending on them to reply to a very general questionnaire may underestimate the prevalence of ill-health in the community. This was highlighted by a study from Canada, mentioned in chapter 5, in which Rockwood et al (1989) found a much higher response rate from healthy elderly subjects - i.e. from those making least demands on the health service. Poorer response was also noted from the rural areas. There are several possible explanations why their response rate (78.5%) was lower than that obtained in the present study. Probably the most important are that their questionnaires originated from a University Department rather than from the local Community Hospital and were sent out without active general practitioner participation. Also the system of health care delivery differs considerably between Canada and the United Kingdom, particularly presenting a problem in the rural areas where medical centres often cover very large areas - therefore with less frequent contact with their patients. There was certainly no evidence of response bias, by age-group or area of residence, from the New Forest area. It would be interesting to see how the response to the respiratory symptoms questionnaire varied in other centres, both to compare statistics and also establish whether it was the simplicity of the questionnaire or the loyalty of the local community which led to the good response.

Exclusion of residents of local authority or private residential homes, as in the study by Burr et al (1979), underestimates the prevalence of respiratory

problems amongst the elderly. Although no separate analysis was undertaken to compare the questionnaire responses according to place of residence, it was clear that the elderly people requiring residential care generally represented the frailer, more physically dependent, elderly with a greater degree of respiratory morbidity. No doubt similar conclusions would have been reached if the questions had related to symptoms from cardiac or other causes. Taking these differences in the sample groups into account, the prevalence of previously diagnosed asthma reported in the present study (8.4%, of whom half had active asthma and half a past history of asthma) and that reported by Burr et al (6.5% overall; 2.9% active and 3.6% past asthma) are suprisingly similar.

An age-stratified sampling technique was used in this study to ensure adequate numbers of the very elderly, in particular elderly men. Few age-related trends in symptoms were noted, so that this method would not appear to be necessary in respiratory surveys amongst the elderly, It had initially been intended to estimate the prevalence of symptoms for the rest of England, but the differences in the population structure demonstrated in the New Forest as compared to the rest of England and Wales would make such estimates unreliable. Melia et al (1988) have shown that poor respiratory health is increased amongst several minority ethnic groups, none of which were represented in the New Forest population studied.

The New Forest has attracted a large number of affluent middle and upper class residents, particularly amongst the retirement population, and the high cost of housing has reduced the number of manual workers living in the area. It is the skew in the distribution of social classes within the New Forest that potentially has had most effect on the survey results, since chest disorders (in particular chronic bronchitis) are generally seen more frequently amongst the lower social classes (College of General Practitioners 1961). The effect of social class on respiratory diagnosis has recently been reported by Littlejohns et al (1989) amongst patients registered with a group general practice in London. All subjects were in the age range 40-70 years, with a 60.5% response to a questionnaire. They showed a decline in prevalence of disabling chronic bronchitis in this age group compared with the 1961 College of General Practitioner figures, but social class (HMSO 1980) was found to bias the diagnostic label applied to symptoms. "Asthma" was used more frequently in the upper social classes (I and II) and "chronic bronchitis" amongst the lower social classes (IV and V) to describe similar symptoms, despite patients having similar lung function measurements. Therefore the data from the New Forest may actually represent an underestimate of the

true national prevalence of respiratory symptoms and diseases amongst the elderly, due to the inclusion of fewer subjects in social classes IV and V than would normally be included in a general population sample.

10.3 Was further interview and examination necessary?

All subjects selected for challenge studies were interviewed with a supplementary respiratory symptoms questionnaire and had a brief chest examination before proceding to spirometry. Clearly full explanation of the procedures was also necessary, but the extra information gained from the interview was also helpful for several subjects.

Caird (1985) and Swift (1988) have both warned of the tendency for excessive prescribing, often with inappropriate choice of drugs, amongst the elderly. In the present study there was only one clear example of inappropriate therapeutic choice, a subject having been prescribed a beta blocking agent to treat "palpitations" which were in fact due to atrial flutter. Cardiac decompensation resulted, fortunately resolving after discontinuing the beta blocker and controlling the heart rate with digoxin. Subjects with more respiratory symptoms tended to be on a larger number of different medications (table 20), but most appeared appropriate.

The interview and examination was carried out to ensure the subject was fit for challenge studies. Although several subjects had a history of angina, none developed chest pain during methacholine challenge. Others had a history of mild cardiac failure, but most subjects were excluded from challenge studies because of inadequate pulmonary function ($FEV_1 < 1.0$ *l*) and not because of physical examination findings.

10.4 Pulmonary function assessment

The majority of subjects who were either asymptomatic (with regards to chest symptoms) or who had only exertional breathlessness had baseline spirometry as good as, or better than, their predicted values. Two-thirds of the symptomatic subjects (groups 3, 4 and those not challenged) also exceeded their predicted pulmonary function values when the normograms produced by Burr et al (1985) were used. This would not have been true if the predictive values were derived by extrapolation from the data of Cotes (1979).

Fowler et al (1987), in a study to assess small airways function in the elderly, concluded that predictive equations based only on healthy elderly subjects who were lifelong nonsmokers were of limited clinical relevance. The present study would support this view, since only the minority (19% of elderly men and 64% of elderly women) were lifelong nonsmokers - although only 21% of men and 8% of women surveyed were current smokers. Thus to exclude all those who have ever smoked from a sample, irrespective of the length of time since stopping smoking, only provides predictive lung function data applicable to the minority of elderly subjects.

The respiratory symptoms questionnaire did not appear to help in picking out subjects with poor baseline lung function. Although lower spirometric values were recorded from subjects in groups 3, 4 and those not challenged, the mean values did not differ significantly from those of groups 1 and 2. Respiratory symptoms in the elderly are therefore not necessarily associated with poor lung function, pulmonary function assessment being necessary to document physiologic abnormalities. Simple spirometry did appear adequate as a quick means of assessment, 98% of elderly subjects being able to perform reproducible spirometry.

10.5 Bronchial hyperreactivity

The respiratory symptoms questionnaire was inadequate for detecting subjects with increased airway reactivity. Dales et al (1987) also found poor correlation between responses to a standardised questionnaire and the measured level of airway reactivity. Therefore, although the respiratory symptoms questionnaire provided a lot of interesting epidemiologic data on symptoms amongst the elderly, it failed to provide the information needed to discriminate between those with and those without increased airway reactivity.

Contrary to the findings of Gerrard et al (1980), current smokers were not found to have an increased prevalence of bronchial reactivity. In fact this was noted more often among ex- and nonsmokers, only one smoker having highly reactive airways. The likely explanation is that elderly subjects with increased airway reactivity will already have developed complications from smoking, therefore becoming exsmokers, whereas other studies of younger subjects still contain many smokers with relatively few respiratory symptoms.

The bronchial challenge study was well tolerated and well performed by most of the subjects. Only one subject experienced significant cholinergic side effects, although without associated bronchospasm. Despite nineteen subjects having a history of angina, none experienced chest pain. Even in subjects with low baseline spirometric measurements, the changes in lung function following challenge did not precipitate respiratory distress. All subjects responded to bronchodilation from a standard pressurised cannister inhaler, none requiring nebulised bronchodilator or supplementary oxygen. This supports the conclusions of Connolly et al (1988) that age is not a contraindication to bronchial challenge with methacholine.

Hopp et al (1985) suggested that age had a significant effect on the level of methacholine responsiveness, finding exaggerated bronchial responsiveness in both elderly and very young healthy subjects studied. They only studied eleven subjects aged over 65 years, however, with a wide scatter of responses (figure 26) so that the validity of their statement must be questioned in the light of the present data. Unfortunately their nebuliser output is not stated, so that the cumulative dose in μmol cannot be calculated.

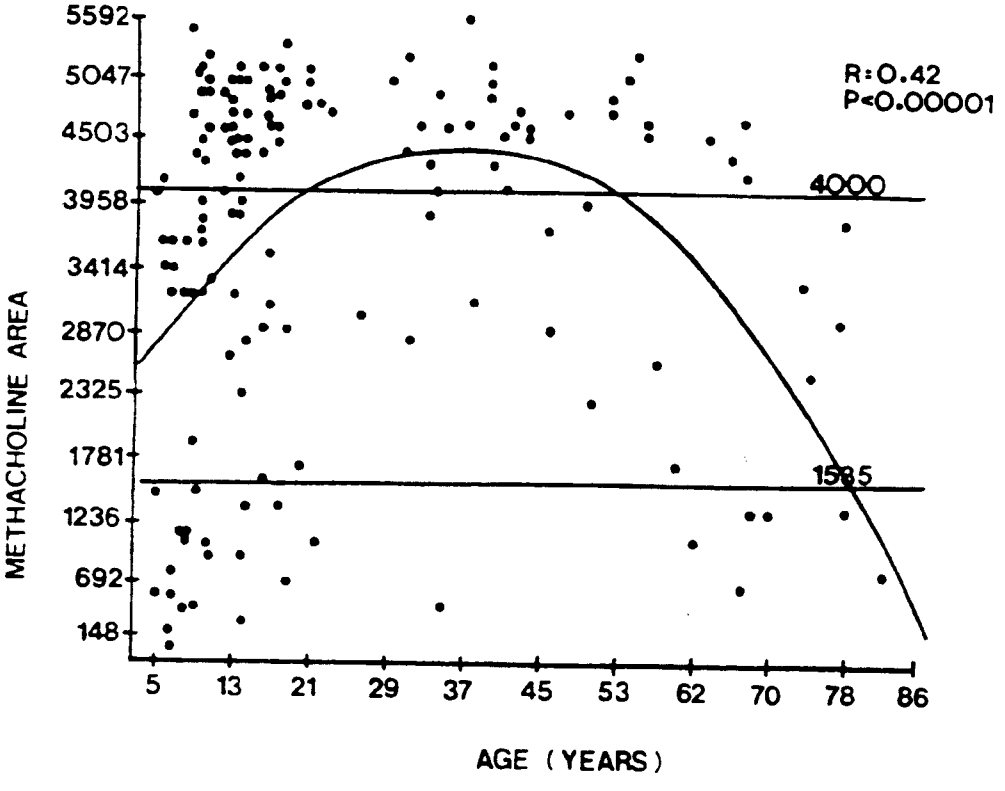


Fig. 26: Methacholine response of 148 healthy subjects aged 5 to 76 years. This method measures the area under the dose-response curve:

"Highly reactive"	= *area < 306*	
"Medium reactivity"	= *area 307-1225*	
"Low reactivity"	= *area 1226-4000*	
Negative test	= *area >4000*	*(Hopp et al, 1985)*

It would appear from figure 26 that half of their elderly subjects studied had moderately increased airway reactivity, two negative tests and the remainder low levels of reactivity - none had highly reactive airways. They felt that fatigue or disinterst with repeated spirometry may have accounted for the tendency for more positive challenge studies amongst the younger and elderly subjects (Hopp et al 1985). These explanations cannot be applied to the findings of the present study, however, since the elderly subjects were seen to be highly motivated to complete the study and managed reproducible spirometry throughout testing.

When lung volumes are low, airway diameters are also reduced leading to greater deposition of methacholine in the larger, more central, airways (Ruffin et al 1978; Townley et al 1979). Their suggestion that this may lead to an exaggerated airways response to methacholine would explain the higher proportion of subjects with highly reactive airways (PD_{20} < 1.0 μmol) amongst those with low baseline FEV_1 (1-1.5 *l*). However, most (22/28; 79%) of those challenged with low FEV_1 had several respiratory symptoms and were in groups 3 and 4; only two were in group 1 (healthy) and four in group 2 (exertional dyspnoea only). Nine out of the ten subjects who had **both** low baseline FEV_1 **and** highly reactive airways were in groups 3 and 4, therefore increased reactivity may be attributable to respiratory disease as well as the reduced airways diameter.

It is evident that most subjects with low FEV_1 are likely to have respiratory symptoms, so that it should be possible to identify them by direct questioning (at interview or by questionnaire) and arrange spirometry accordingly. However, only 53% of those who were either unfit for challenge studies or who had significant respiratory symptoms (included in groups 3 or 4) had consulted their doctor within the preceding two years with a chest problem. Almost half of those with symptoms would therefore remain unknown to their general practitioner if routine health screening was not conducted. Screening would therefore appear necessary if respiratory morbidity is to be significantly reduced by the earlier introduction of therapy.

In the present study methacholine responsiveness was asssessed according to the magnitude of change in FEV_1. This is a forced expiratory manoeuvre and it has been shown in asthmatic subjects that this may adversly affect spirometry, causing bronchoconstriction (Orehek et al 1975, 1980; Fish and Kelly 1979). In practice this is not often observed and there is no evidence from the present study of this being a greater problem amongst the elderly, therefore it is unlikely to have led to over-diagnosis of a "positive" challenge in this study.

A previous study (Horsley et al 1985) demonstrated that large changes in isovolume flow rates (measured at 50% and 75% below TLC) may often be demonstrated following methacholine inhalation without significant change in FEV_1. Thus the spirometric technique chosen, and the end-point accepted for a "positive" challenge, must be comparable if results between different studies are to be compared. The challenge technique and end-point (fall in FEV_1 of 20% below baseline) in the present studies were the same as in the studied by both Woolcock et al (1987) in Australia and Burney et al (1987) in Southern England. Both of the latter two studies used histamine as their test agent, but the direct comparability of methacholine and histamine has been well documented (Spector and Farr 1975; Juniper et al 1981). The prevalence of bronchial hyperreactivity (at or below 8 μmol histamine) was found to be 11.4% in the Australian study and 14% in Southern England in general population samples containing few elderly subjects. Both estimates are considerably below the 38% prevalence of hyperreactivity demonstrated amongst the elderly.

Contrary to the conclusions of Woolcock et al (1987) there would appear to be correlation between bronchial hyperreactivity and age. This is not adequately explained by the level of baseline spirometric measurements or by poor compliance with instructions during challenge studies (as suggested by Hopp et al, 1985). Although increased bronchial reactivity is an imperfect test for asthma (Tattersfield 1981), asthmatic subjects generally exhibit a greater degree of bronchial hyperreactivity than normal subjects (Malo et al 1983).

If the definition of highly reactive airways (PD_{20} < 1.0 μmol methacholine) from the present study is used, this is compatible with the categories of "severely" (PD_{20} < 0.1 μmol) and "moderately" (PD_{20} 0.1-1.0 μmol) increased reactivity used by Woolcock et al (1988) for the hand-held nebuliser method of challenge (Yan et al 1983). This should therefore include most subjects with asthma, although missing subjects whose asthma is well controlled and who have only mildly increased, or normal, levels of airway reactivity (Britton and Tattersfield 1986). Relatively few "false positive" tests should be included if these criteria are applied and indeed the cut-off point of 1 μmol methacholine may be too low, other studies showing few (only 3%) normal subjects to have a positive challenge up to levels equivalent to the maximum cumulative dose of 6.13 μmol methacholine used in this study (Malo et al 1983, 1985).

The prevalence of asthma in the elderly, based on an assessment of bronchial reactivity, is therefore at least 12% (the prevalence of highly reactive airways). In fact the true prevalence is probably considerably higher than this, the 38% prevalence of a positive challenge (at or below 6.13 μmol methacholine) being very similar to the prevalence of bronchodilator responsiveness reported by Bannerjee et al (1987) for the elderly. These estimates are considerably greater than the previously accepted figure of 6.5% for the prevalence off asthma amongst the elderly (Burr et al 1979), and suggesting that asthma is both underdiagnosed and undertreated amongst the elderly, unnecessarily contributing to respiratory morbidity in this age group. Unfortunately the collection of symptoms suggested by Mortagy et al (1986) do not help identify elderly subjects with bronchial hyperresponsiveness.

Further studies to confirm these results are necessary, preferably in a different location, with encouragement for general practitioners to include an assessment of respiratory symptoms and function in routine health screening. In this way it may be possible to reduce respiratory morbidity amongst a section of the population known to be at increased risk from chest infections and other respiratory problems (Caird and Akhtar 1972; Milne 1978).

CHAPTER 11

SUMMARY AND INDICATIONS FOR FURTHER RESEARCH

11.1 Indications for the present study

Many studies of the prevalence of asthma have been performed, reporting widely varying figures and using different diagnostic criteria (Table 4). Studies of the prevalence of bronchial hyperreactivity have been even more difficult to interpret because of the variety of methods and different end-points used in challenge testing (Table 7). Most epidemiologic studies of the prevalence of respiratory symptoms and asthma have included few elderly subjects. The present study was therefore designed to

1. establish the prevalence of respiratory symptoms within a clearly defined elderly population (age 65 + years);

2. relate symptoms, physical examination findings and spirometric measurements to the level of bronchial hyperresponsiveness;

3. compare the prevalence of bronchial hyperreactivity and symptoms to previously reported data, in particular to data from the same geographic area (Mortagy et al 1984, 1986; Burney et al 1987), thus avoiding environmental and ethnic factors that might influence the outcome of studies in other parts of the country or in other continents;

4. establish the presence of age-related trends in the prevalence of asthma and respiratory symptoms.

11.2 Study design

A randomised age and sex stratified design was chosen to ensure adequate numbers of the very elderly (age 85 + years) in the study and, in particular, adequate numbers of elderly men. From a total of 26,565 patients aged over 65 years listed in the age-sex registers of 4 New Forest group practices (3 in Lymington; 1 with surgeries in Brockenhurst and Sway) 2011 subjects were selected by random sampling, using a table of random numbers, in three age bands:

age 65 - 74 years
age 75 - 84 years
age 85 + years

Equal numbers of male and female subjects were not obtained from the oldest age group.

11.3 Response to postal questionnaire

A postal respiratory symptoms questionnaire sent to these 2011 subjects obtained a 96.2% overall response after excluding 136 subjects who had either died or moved from the area. The mean age of respondents was 77 ± 8 years (range 65 - 102 years). Little difference in response rates were seen between the different age bands. Most (89.5%) answered all the questions and 94.7% completed the eight key respiratory symptoms questions upon which sub-group analysis was subsequently based.

The accuracy of replies was verified in a randomly selected sample of 355 (19.5%) of subjects, revealing no significant discrepancies between symptoms indicated on the questionnaire and those described on direct questioning (either at personal interview or by telephone interviews).

Of the respondents 89% were still living at a private address. The majority of those requiring permanent residential care were in the 85 + age group. Over three times as many females than males were in permanent residential care. The response rate was not affected by age, sex, residential area or type of residential accommodation.

11.4 Respiratory symptoms

Detailed analysis of respiratory symptoms reported by the 1803 respondents to the questionnaire is given in chapter 6, analysed according to age, sex and smoking status. More of the very elderly (85 + age group) were lifelong nonsmokers. Only 19% of men, compared to 64% of women, were lifelong nonsmokers; 21% of men and 8% of women currently smoked.

Exertional breathlessness was reported by 38%, becoming more common with increasing age. Nocturnal breathlessness was reported by 7.3% and was unrelated to sex, smoking status or age group.

Episodes of wheezing were experienced by 24.2%, more men than women reporting this; wheezing was much commoner amongst smokers. Prolonged morning chest tightness, lasting more than one hour, was reported

by only 2.4%, although 11.3% of all respondents experienced some degree of chest tightness in the mornings.

The prevalence of chronic bronchitis was 16.4%, commoner amongst smokers and amongst men, although 22.3% of the sample had a productive cough in the mornings and 20.2% reported sputum production at other times of the day or night during the winter.

The prevalence of diagnosed asthma was 8.4%, half with active asthma (an asthmatic attack within the preceding 12 months). No statistically significant age-related trend in asthma prevalence was demonstrated, although a history of asthma was slightly less common amongst the 85+ age group.

The poorest response was obtained for a question regarding the effect of various environmental respiratory irritant stimuli (omitted by 3% of respondents). Respondents were asked to indicate whether they became breathless, wheezy or coughed in the following situations:

(i) going from a warm room to a cold room
(ii) entering a room where people are/were smoking
(iii) with traffic fumes
(iv) with chemical smells eg. perfumes, hair spray, bleach

Most respondents (72%) were unaffected in any of these situations. More nonsmokers than smokers were affected, particularly on entering a smokey room (21.5% nonsmokers vs. 5.1% smokers). Cough was the commonest response in all the situations listed. In comparison with a previously reported younger general population sample from Hampshire (Mortagy et al 1986), the elderly responded with wheeze or breathlessness more frequently in response to one or more of these environmental stimuli (26.6% elderly vs. 11.4% general population).

11.5 Definition of subgroups for further study

The respondents were sub-divided into five groups according to replies to eight key respiratory symptoms questions:

Group	
1 Fully healthy	715 (39.7%)
2 Exertional breathlessness only	185 (10.2%)
3 Mixed respiratory symptoms	289 (16.0%)
4 Symptoms of Bronchial Irritability Syndrome	519 (28.8%)
5 Unclassified - incomplete questionnaires	95 (5.3%)

In Group 3 the principal symptoms were cough or wheeze, with or without breathlessness, but not symptoms of the Bronchial Irritability Syndrome.

The proportion of subjects included in each of the five sub-groups was similar within each of the three age-groups.

Symptoms of the Bronchial Irritability Syndrome, reported by Mortagy et al(1986), are a history of:

nocturnal breathlessness
and/or prolonged morning chest tightness lasting >1 hour
and/or wheeze or breathlessness in response to certain environmental irritant stimuli (listed in 11.4)

These symptoms have previously been shown to correlate closely with bronchial hyperreactivity to inhaled histamine in a general population sample from Hampshire (Mortagy 1984,1986).

Again using a table of random numbers, subjects from each of groups 1-4 were selected and invited to attend for further study involving interview, physical examination, spirometry and (if fit) methacholine inhalation bronchial challenge studies. Equal numbers of male and female subjects agreed to attend, although they represented only 63.6% of those contacted (10% of initial respondents to the postal questionnaire). Fewer healthy subjects agreed to attend than those with respiratory symptoms. The symptoms and physical examination findings of the 180 subjects attending for further study are discussed in chapter 7.

11.6 Spirometry

Reproducible spirometry (FVC, FEV_1, PEFR) was performed by 98% of subjects. Mean anthropomorphic data (age, height, weight, arm span) were similar for the four subgroups; mean spirometric values tended to decline with increasing respiratory symptoms. Most subjects (91%) in groups 1 and 2 exceeded their predicted baseline spirometric values for FEV_1, as compared with 67% of those in groups 3 or 4. Using arm span measurements as an alternative to vertical height did not offer any advantage when calculating predicted lung function values in most subjects. Fifteen subjects had an initial $FEV_1 < 1.0$ *l* and were therefore excluded from subsequent methacholine challenge.

11.7 Indications for exclusion from challenge studies

Challenge studies were not performed in 20 subjects:

15 Baseline FEV_1 < 1.0 l
3 unable to perform reproducible spirometry
2 unable to complete challenge study although FEV_1 > 1.0 l
(1 unable to coordinate inspiration with aerosol delivery; 1 developed non-respiratory symptoms following methacholine inhalation necessitating termination of challenge study).

11.8 Prevalence of bronchial hyperreactivity

Methacholine challenge was performed on the remaining 160 subjects using hand held DeVilbiss 40 glass nebulisers as described by Yan et al (1983). In two subjects (from group 3) there was a >10% fall in FEV_1 after saline (diluent) and bronchodilator was therefore administered without proceding further with challenge studies.

Challenge studies were completed in 158/162 subjects (97.5%) whose baseline spirometry was adequate (FEV_1 > 1.0 l). A "positive" challenge was defined as a fall in FEV_1 of 20% at or below the maximum cumulative dose of methacholine administered (6.13 μmol). The methacholine dose producing this fall was termed the PD_{20}, calculated by simple linear regression from the penultimate and final FEV_1 and methacholine doses if a fall in FEV_1 >20% had occurred.

Overall 38% of elderly subjects had a "positive" challenge (PD_{20} of 6.13 μmol or below), with highly reactive airways (PD_{20} < 1 μmol) in 12%. This is considerably higher than previous reports of the prevalence of bronchial hyperreactivity in community surveys, only 14% of a younger general population sample drawn from nearby areas of Hampshire and Dorset having a positive challenge at or below a comparable maximum dose of inhaled histamine (Burney et al 1986). The figures also exceed the prevalence of known asthma amongst the elderly in the New Forest area (8.4%; 4.2% current asthma and 4.2% past asthma).

Subjects with low baseline FEV_1 (1-1.5 l) were more likely to have a positive challenge, as were subjects with respiratory symptoms (groups 3 and 4). Highly reactive airways were also demonstrated more often in subjects with low baseline FEV_1 (36% of these subjects, compared to only 7% of subjects with FEV_1 > 1.5 l).

The symptoms of the Bronchial Irritability Syndrome (Mortagy et al 1986) did not help to identify elderly subjects with bronchial hyperreactivity. Prolonged morning chest tightness and a history of asthma were associated with a positive challenge, but other symptoms were only weakly associated with the response to challenge. The questionnaire did not, however, quantify the severity of symptoms other than the duration of morning chest tightness.

11.9 Conclusions

The study shows that a simple postal questionnaire can be used to get a high response rate and accurate data regarding respiratory symptoms from elderly subjects. The prevalence of bronchial hyperreactivity amongst the elderly is much higher than indicated by previous general (younger) population studies.

Although bronchial hyperreactivity does not directly equate to a diagnosis of asthma, the prevalence of asthma in the elderly estimated from the measurements of bronchial reactivity is at least 12% (the prevalence of highly reactive airways) and may approach 38% (the prevalence of a positive challenge at or below the maximum dose of methacholine used). Both estimates exceed the prevalence of known asthma amongst the elderly in the New Forest (8.4%), the higher figure being similar to the prevalence of bronchodilator responsiveness reported in the elderly (41.2%; Bannerjee et al 1987).

The results indicate considerable underdiagnosis and undertreatment of respiratory symptoms and asthma amongst the elderly. Better health screening of the elderly is necessary if this potentially treatable respiratory morbidity is to be reduced amongst the elderly.

11.10 Indications for further study

The study needs to be repeated in a different location to verify the high prevalence of bronchial hyperreactivity amongst the elderly. This should ideally be done with the same protocol so that directly comparable results are obtained. However, greater opportunity to quantify the severity of symptoms (especially breathlessness) is required so that the magnitude of symptoms, rather than just presence or absence of symptoms, can be related to bronchial reactivity.

The method of age- and sex-stratified sampling used was dependent on accurate age-sex registers being kept by the general practitioners. An alternative would be to use age-sex listings obtained from the Family Practitioner Committee. Random sampling from these would be easier since identification numbers would more easily be given to all listed residents. As age-related trends were not demonstrated for most symptoms, however, age-stratification would not appear essential for subsequent studies, although comparable numbers of males and females would still be important.

Any further study should include the measurement of respiratory flow rates during mid and late expiration (at lung volumes 50% and 75% below TLC) recorded from a flow-volume loop. This would allow the comparison of iso-volume flow rates before and after mechacholine and would give further physiologic information about the pattern of response to inhaled methacholine.

By studies at regular intervals it may also be possible to demonstrate changes in the prevalence of bronchial hyperreactivity in the population as a result of reduced atmospheric pollution, a reduction in smoking or other factors. The outcome of subjects in whom bronchial hyperreactivity is demonstrated should also be monitored, especially in an industrial environment where it may have relevance to compensation claims.

The benefit of treating elderly subjects shown to have increased bronchial reactivity with inhaled bronchodilators and prophylactic inhaled corticosteroids requires further evaluation in a carefully controlled trial. This would demonstrate whether it is worth undertaking major health screening within the community to detect those with bronchial hyperreactivity but who are presently asymptomatic, to see if prophylactic treatment can reduce respiratory morbidity. This would have major cost implications to the National Health Service and should therefore be carefully researched before being recommended.

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APPENDIX A

CONFIDENTIAL

QUESTIONNAIRE ON CHEST SYMPTOMS

For Office Use Only

1 4 ☐☐☐☐

Name: .....

Address: .....

.....

Telephone: .....

Sex: M ☐ F ☐ — 6 ☐

Age: ..... years — 8 10 ☐☐

Family Doctor: .....

.....

.....

These are some questions about your chest and apply to the past year unless otherwise stated. I would like you to put a "✓" in the appropriate square after each question.
It is important that you answer ALL the questions.

1. Are you troubled by shortness of breath when hurrying on level ground, or walking up a slight hill ? — Yes ☐ No ☐ — 12 ☐

2. When you get up in the morning, how does your chest usually feel ? — Free ☐ Tight ☐ — 14 ☐

   If "Tight" :

   How long does it usually take to become free ?
   Give number of minutes/hours: ..... minutes ..... hours — 16 ☐

3. Are you ever woken at night with shortness of breath ? — Yes ☐ No ☐ — 18 ☐

4. Does your chest ever sound wheezy or whistling ? — Yes ☐ No ☐ — 20 ☐

5. Do you usually bring up any phlegm from your chest first thing in the morning in winter ? — Yes ☐ No ☐ — 22 ☐

6. Do you usually bring up any phlegm from your chest during the day - or at night - in the winter ? — Yes ☐ No ☐ — 24 ☐

   If "Yes" to Questions 5 or 6 :

   Do you bring up phlegm like this on most days for as much as three months each year ? — Yes ☐ No ☐ — 26 ☐

For Office Use Only

7. Do any of the following affect your chest ?
If "Yes", what are the effects ?

Please tick any that apply :

	Short of breath	Wheezing	Cough	
a) Going from a warm room to a cold one ?	☐	☐	☐	28 ☐
b) Going into a room where people are/were smoking ?	☐	☐	☐	30 ☐
c) Traffic fumes ?	☐	☐	☐	32 ☐
d) Chemical such as hair spray, bleach, perfumes, etc.	☐	☐	☐	34 ☐

e) None of the above affect my chest: ☐

8. Have you ever had (Bronchial) Asthma ? Yes ☐ No ☐ 36 ☐

If "Yes" :

Have you had it in the past year ? Yes ☐ No ☐ 38 ☐

9. Do you smoke ? Yes ☐ No ☐ 40 ☐

10. For Ex-Smokers :

How long ago did you give up smoking ? 42 43 ☐☐

..... months or ..... years ago

12. Have you consulted a Doctor for a chest condition in the past two years ? Yes ☐ No ☐ 45 ☐

Thankyou for completing the questionnaire. Please return it in the enveloppe enclosed -- no stamp required.

SUPPLEMENTARY SYMPTOMS QUESTIONNAIRE

Date .....

1 4 ☐☐☐☐

Name .....

Main Occupation(s) ..... From ..... to ..... 6 ☐

....

....

Breathlessness

1. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill ?	Yes ☐	No ☐	8 ☐
2. Do you get short of breath walking with other people of your own age on level ground ?	Yes ☐	No ☐	10 ☐
3. Do you have to stop for breath when walking at your own pace on level ground ?	Yes ☐	No ☐	12 ☐
4. Are you troubled by : a) Shortness of breath at rest ?	Yes ☐	No ☐	14 ☐
b) Chest tightness at rest ?	Yes ☐	No ☐	16 ☐
c) Attacks of shortness of breath at rest for no apparent reason ?	Yes ☐	No ☐	18 ☐

If "Yes" to 'a', 'b' or 'c':
When you have shortness of breath or chest tightness at rest, do you get at the same time :

d) Dizziness or light-headedness ?	Yes ☐	No ☐	20 ☐
e) Pins and needles in the hands ?	Yes ☐	No ☐	22 ☐

General

5. Does anyone in your family have, or have they had, (Bronchial) Asthma ?	Yes ☐	No ☐	24 ☐

6. Is your chest worse at any time of the year ?

No ☐

Spring ☐ Summer ☐ Autumn ☐ Winter ☐ 26 ☐

Smoking

7. Do you smoke ? Yes ☐ No ☐ 28 ☐

If "yes"

a) Do you inhale the smoke ? Yes ☐ No ☐ 30 ☐

b) How many cigarettes do you usually smoke per day ? ..... cigarettes

c) How much pipe tobacco (oz/g) do you usually smoke per week ? ..... oz or g

d) How many cigars do you usually smoke per week ? ..... small cigars

..... large cigars

e) How old were you when you started smoking regularly ? ..... years old 32 33 ☐☐

8. For Ex-Smokers

a) How old were you when you started smoking regularly ? ..... years old 35 36 ☐☐

b) How old were you when you stopped ? ..... years old

c) Why did you give up smoking ? ..... 38 ☐

.....

---

9. Chest Illnesses

If you do not know a word, please answer "No".

Have you ever had :

a) Bronchitis Yes ☐ No ☐ 40 ☐

b) Bronchiectasis ? Yes ☐ No ☐ 42 ☐

c) Pneumonia ? Yes ☐ No ☐ 44 ☐

d) Pleurisy ?	Yes ☐	No ☐	46 ☐
e) Pulmonary Tuberculosis (TB) ?	Yes ☐	No ☐	48 ☐
f) Emphysema ?	Yes ☐	No ☐	50 ☐
g) Asthma or Bronchial Asthma ?	Yes ☐	No ☐	52 ☐
h) Any injury or operation affecting your chest ?	Yes ☐	No ☐	54 ☐
i) Heart trouble ?	Yes ☐	No ☐	56 ☐

10. Treatment

Please list ALL medicines that you are currently taking - including those you have bought from the Chemist or been given.

None ☐

D 58 59 ☐☐

From Doctor	Bought or given to you
1.	1. .....
2.	2. .....
3.	3. .....
4.	4. .....
5.	5. .....
6.	6. .....
7.	7. .....
8.	8. .....
9.	9. .....
10.	10. .....

B 61 62 ☐☐

APPENDIX B

Southampton and South West Hampshire Health Authority

LYMINGTON INFIRMARY
EAST HILL
LYMINGTON
HAMPSHIRE
SO4 9ZJ
Telephone 76081

Dear

Research into Chest Symptoms

Your General Practitioner, Dr , and I would be very grateful if you could spare a few minutes to complete the enclosed brief questionnaire about chest problems. This is part of a survey being undertaken in the Lymington and Sway area aimed at establishing how common various chest problems are in this Community, giving us a clearer understanding of the medical problems amongst the Community we serve.

Even if you have never had any chest trouble we would still like you to complete the questionnaire and return it in the reply paid envelope enclosed -- otherwise we will not get a true idea of how common these problems are, or how many completely fit people there are in the area.

Please complete it at your leisure -- if necessary with the help of a close friend or relative. If there are any major difficulties, please feel free to contact me.

Although your name and address is shown on the form, this is only for my convenience in identifying your reply. Your name will not be known to anyone else involved in analysing the results. Your name will not be stored on a computer.

Thankyou for your help -- the success of the study now depends on you !

Yours sincerely,

Dr John Horsley, M.Sc., M.R.C.P.(U.K.)
Senior Registrar, Lymington Infirmary

Encl. Questionnaire and S.A.E.

Southampton and South West
Hampshire Health Authority

LYMINGTON INFIRMARY
EAST HILL
LYMINGTON
HAMPSHIRE
SO4 9ZJ
Telephone 76081

Dear

Research into Chest Symptoms

We wrote to you recently about a study on chest symptoms, such as cough, breathlessness, wheezing, etc. We have not yet received your questionnaire, perhaps because you have never had chest trouble or the form looked too complicated.

Your name was taken from your General Practitioner's register, but I assure you that the details are completely confidential, and no reference will be made to anything that could identify an individual. Your Doctor, Dr , is in complete agreement with this study.

This study has never been done before, but, for the final results to be meaningful, a high response rate is required. We appreciate that filling in a questionnaire is a chore, but we would be most grateful for your help with this important study which will give important new information to improve diagnosis and possibly prevention of chest problems.

We enclose another questionnaire and an envelope for its return - no stamp is required.

We hope you will help us by completing and returning the questionnaire whether or not you have any chest problems.

Yours sincerely,

Dr John Horsley
Senior Registrar, Lymington Infirmary

Southampton and South West Hampshire Health Authority

JH/PK

LYMINGTON INFIRMARY
EAST HILL
LYMINGTON
HAMPSHIRE
SO4 9ZJ
Telephone 76081

Health Visitor / Assistant,

21st October, 1986.

Dear

RE: SURVEY OF RESPIRATORY PROBLEMS IN THE ELDERLY

I am writing to 500 patients age over 65 years from this practice, sending a brief Questionnaire and explanatory letter, as well as a s.a.e. for their reply.

As you will no doubt be seeing many of these patients during the course of the next few months, I would like to beg your support in encouraging them to complete and return the Questionnaire. I am, therefore, enclosing copies of the letter and Questionnaire that I will be sending out, as well as a second "Reminder" letter that I will send if I do not hear from them within 3 - 4 weeks of my initial letter.

Your help and support in this study, being undertaken with the full permission of the Doctors in your practice, would be greatly appreciated.

Yours sincerely,

DR. JOHN HORSLEY
Senior Registrar to Dr. Nuala Sterling

Enc.

Southampton and South West Hampshire Health Authority

JH/PK

LYMINGTON INFIRMARY
EAST HILL
LYMINGTON
HAMPSHIRE
SO4 9ZJ
Telephone 76081

Dear

Thank you for returning the Questionnaire.

I have noticed that you have missed some of the questions on the front / back of the form, which I have marked "*". I hope you do not mind me sending it back to you, but it would be a great help to me if you were able to indicate your answers to these other questions and return the form again.

With many thanks for your help.

Yours sincerely,

DR. JOHN HORSLEY, M.Sc., MRCP(UK),
Ssenior Registrar to Dr. Nuala Sterling.

Southampton and South West Hampshire Health Authority

NS/JH/PK

LYMINGTON DAY HOSPITALS

EAST HILL
LYMINGTON
HAMPSHIRE
SO4 9ZJ

Telephone 76085

Dear

RESEARCH INTO CHEST SYMPTOMS

You kindly completed a Questionnaire on CHEST SYMPTOMS a couple of months ago. We have been delighted with the response - almost 90% of the 2011 people written to have returned their Questionnaires, which makes this a record response rate for this type of medical research. The results are now being analysed and we wish to interview and perform breathing tests on certain individuals, including some with no chest symptoms. Would you be willing to help again in this study?

All interviews and tests will be carried out in Lymington Day Hospital by Dr. Horsley, and should take about 45 minutes to complete. After a brief interview and examination of your chest, we will perform some simple breathing tests to establish how well your lungs work, and how sensitive the airways are. The tests will be stopped at any time should you so wish.

Our Secretary in the Day Hospital, Mrs. Kealy, will contact you next week to see if you feel able to help us further and, if so, arrange a suitable time and date. (Alternatively, you may telephone her directly if this would be more convenient.) We will reimburse your local travelling expenses.

We do hope you will be able to help further in this study and look forward to meeting you shortly. All the results of the breathing tests will, of course, be explained to you and a copy sent to your General Practitioner.

Yours sincerely,

Dr. John Horsley, MSc,MRCP(UK),
Senior Registrar

Dr. Nuala Sterling, MS, FRCP,
Consultant Physician

SUGGESTED APPOINTMENTS:

1. _____ at ____

or

2. _____ at ____

PLEASE BRING ALL CURRENT MEDICATIONS WITH YOU.

EXAMINATION FINDINGS

Date .....

1 4

Name .....

1. Weight ..... kg — 6 8

2. Height ..... cm — 10 12

3. Arm span ..... cm from Full/Half — 14 16

4. Cyanosis: 0=nil; 1=central; 2=periph; 3=both — 18

5. Lymphadenopathy: 0=nil; 1=localised; 2=general — 20
Detail: .....

6. Finger clubbing: 0=nil; 1=mild; 2=marked — 22

7. Chest deformity: 0=nil; 1=present — 24
Detail: .....

C.V.S.

8. Pulse - rate ..... /min — 26 28

- rhythm 0=SR; 1=AF; 2=other: ..... — 30

9. Sitting BP: Systolic ..... mm Hg — 32 34

Diastolic ..... mm Hg — 36 38

10. Hypertensive treatment: 0=No; 1=Yes — 40

11. Oedema: 0=nil; 1=ankle; 2=other: ..... — 42

12. JVP ..... cm above sternal angle at 45° — 44 45

13. Heart - Sounds: 0=normal; 1=S_3; 2=S_4; — 47
3=S_{3+4}; 4=other: .....

- Size: 0=normal; 1=LV+; 2=RV+; 3=L&RV+ — 49

- Murmurs: 0=nil; 1=present: ..... — 51

Respiratory

14. Dyspnoea: 0=nil; 1=walking; 2=undressing; 3=rest — 53

15. Accessory muscles of resp.: 0=no; 1=yes — 55 ☐

16. Lip pursing: 0=no; 1=yes — 57 ☐

17. Respiratory rate ..... /min — 59 60 ☐☐

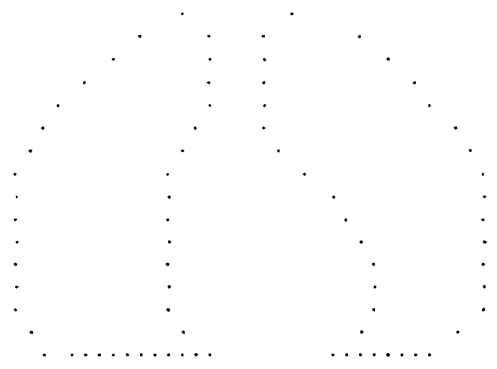
18. Trachea: 0=central; 1=displaced: ..... — 62 ☐

19. Wheeze: 0=nil; 1=intermittent(rhonchi); 2=prolonged — 64 ☐

20. Crepitations: 0=nil; 1=fine; 2=coarse — 66 ☐

- location: 0=nil; 1=basal unilat.; 2=basal bilat.; 3=other: ..... — 68 ☐

21. Percussion: 0=normal; 1=abnormal: ..... — 70 ☐



Southampton and South West Hampshire Health Authority

JH/PK

LYMINGTON DAY HOSPITALS

EAST HILL
LYMINGTON
HAMPSHIRE
SO4 9ZJ

Telephone 76085

STUDY NUMBER: _____

CONSENT FOR METHACHOLINE CHALLENGE TEST

NAME: _____

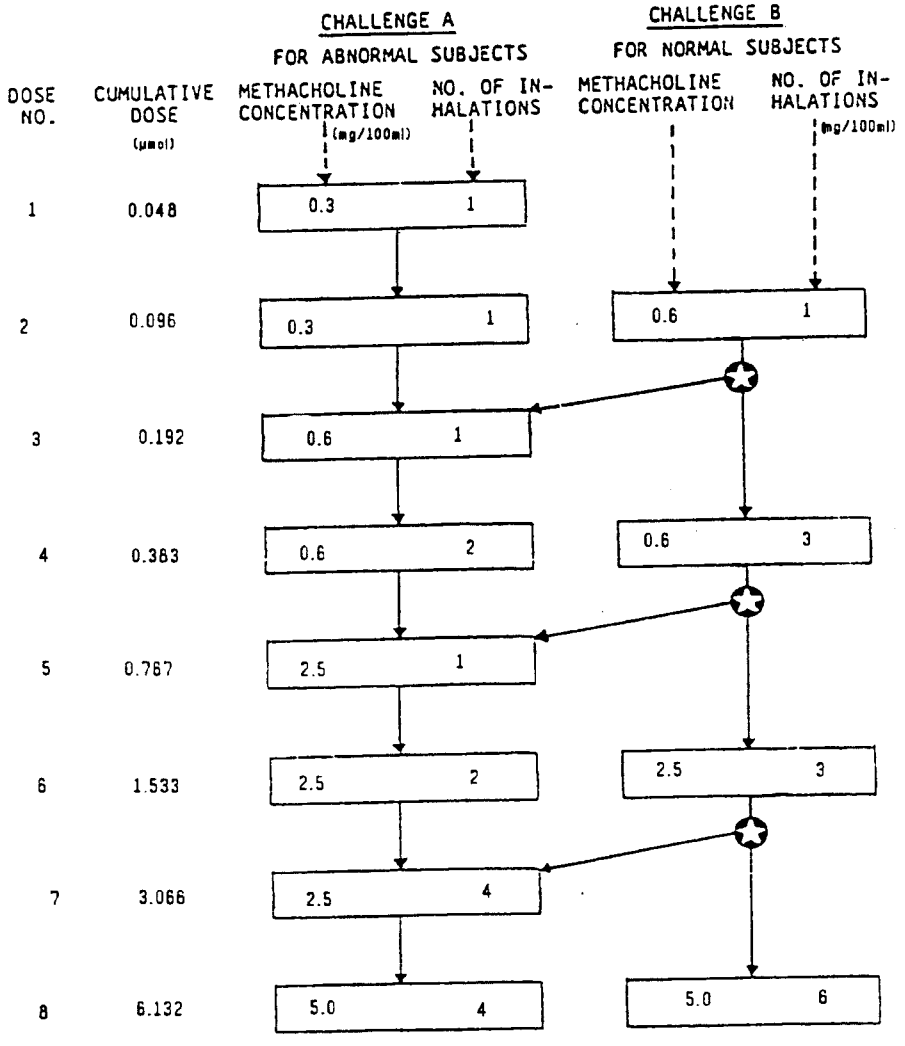
I understand that methacholine is a substance which, when inhaled, may cause slight throat irritation, coughing or possibly chest tightness, but that these symptoms can be quickly treated with an inhaler (Salbutamol). The test is to establish how sensitive my lungs are to this substance. I am satisfied with the explanation given to me by Dr. Horsley and understand that the test will be stopped at any time if I wish.

I agree to a copy of the results being sent to my General Practitioner (Dr.....).

Signed:..... Date:.....

.....
Dr. John Horsley.

Chart of methacholine doses, using nebuliisers of output 0.003 mis per actuation, showing full and abbreviated protocols



✪ If change in FEV_1 > 10% and < 20%, go to challenge A
If change in FEV_1 < 10% , continue with challenge B

STOP CHALLENGE WHEN FEV_1 FALLS BY > 20%

Southampton and South West Hampshire Health Authority

JH/PK

LYMINGTON DAY HOSPITALS

EAST HILL
LYMINGTON
HAMPSHIRE
SO4 9ZJ

Telephone 76085

Dear

RE: _____ D.O.B: _____

_____

Your patient kindly attended today for breathing tests.

SYMPTOMS:

EXAMINATION: SR / AF BP: /

C.V.S.

R.S.

PFTs:

	Predicted*	Actual	After Methactoline	After Bronchodilator
PEFR (l/min)				
FVC(l)				
FEV_1(l)				

*(From Burr et al Thorax 1985;40:54 - 59)

METHACHOLINE CHALLENGE: Positive / Negative at ..... mol
cumulative dose (max. dose 6.12 mol)

COMMENTS:

Yours sincerely,

DR. JOHN HORSLEY, MSc, MRCP(UK),
Senior Registrar

APPENDIX C

Tables 27 - 34

Table 27. - Place of permanent residence for respondents to questionnaire according to age group. Percentage figures (in parentheses) show comparisons within each specifiedage group according to sex of respondents and for all (T) respondents.

Age yrs: / Residence		65 - 74		75 -84		85 +		Total	
Private	M	397	(97.5)	315	(94.9)	96	(78.7)	808	(93.8)
	F	385	(96.7)	269	(83.3)	143	(64.7)	797	(84.6)
	T	782	(97.1)	584	(89.2)	239	(69.7)	1605	(89.0)
Sheltered	M	8	(2.0)	10	(3.0)	13	(10.7)	31	(3.6)
	F	13	(3.3)	30	(9.3)	20	(9.1)	63	(6.7)
	T	21	(2.6)	40	(6.1)	33	(9.6)	94	(5.2)
Part III	M	1	(0.25)	1	(0.3)	2	(1.6)	4	(0.5)
	F	0		7	(2.2)	16	(7.2)	23	(2.4)
	T	1	(0.1)	8	(1.2)	18	(5.3)	27	(1.5)
RH	M	0		2	(0.6)	6	(4.9)	8	(0.9)
	F	0		12	(3.7)	26	(11.8)	38	(4.0)
	T	0		14	(2.2)	32	(9.3)	46	(2.6)
NH/LS	M	1	(0.25)	4	(1.2)	5	(4.1)	10	(1.1)
	M	0		5	(1.5)	16	(7.2)	21	(2.2)
	T	1	(0.1)	9	(1.4)	21	(6.1)	31	(1.7)
TOTAL	M	407	(50.6)	332	(50.7)	122	(35.6)	861	(47.8)
	F	398	(49.4)	323	(49.3)	221	(64.4)	942	(52.2)
	T	805		655		343		1803	

M = *Male*

F = *Female*

T = *Total*

Private = *Own home or relatives.*

Sheltered = *Warden supervised (private or local authority).*

Part III = *Local authority residential home.*

RH = *Residential home ('rest home')*

NH = *Nursing home*

LH = *Lymington Infirmary long stay ward*

Table 28. - Number of questions answered by 1803 respondents to a postal respiratory symptoms questionnaire.

Questions Answered	n	%
17	1614	89.5
16	87	4.8
15	30	1.7
14	11	0.6
13	45	2.5
12	10	0.6
11	5	0.3
10	1	0.1

Table 29. - Age and sex composition of subgroups according to respiratory symptoms. Percentages (in parentheses) compare separation of each sex between symptom subgroups within each age group. Age groups are shown in years.

Group		65 - 74		75 - 84		85 +		All Respondents	
1. Fully healthy									
	Male	186	(45.7)	106	(31.9)	37	(30.3)	329	(38.2)
	Female	173	(43.5)	127	(39.3)	86	(38.9)	386	(41.0)
2. S.O.B. only									
	Male	24	(5.9)	31	(9.3)	11	(9.0)	66	(7.7)
	Female	40	(10.0)	49	(15.2)	30	(13.6)	118	(12.5)
3. Mixed symptoms									
	Male	82	(20.1)	76	(22.9)	21	(17.2)	179	(20.8)
	Female	44	(11.0)	37	(11.5)	29	(13.1)	110	(11.7)
4. B.I.S symptoms									
	Male	110	(27.0)	101	(30.4)	36	(29.5)	247	(28.7)
	Female	120	(30.2)	90	(27.9)	62	(28.0)	272	(28.9)
5. Unclassified									
	Male	5	(1.2)	18	(5.4)	17	(13.9)	40	(4.6)
	Female	21	(5.3)	20	(6.2)	14	(6.3)	55	(5.8)
Total	Male	407		332		122		861	
	Female	398		323		221		942	

Table 30. - Replies to questionnaire analysed according to sex of respondents. For full wording of questionnaire see appendix A1.

In Q7., "unaffected" means not affected by the specific environmental situation stated but symptomatic in one of the other situations (7a-d). "Symptomatic" means cough, wheeze or S.O.B.,or any combination of these symptoms.

N/S = Not stated. *N/A = Not applicable.*

	Male		Female		Total	
Age, years						
65 - 74	407	(47.3)	398	(42.2)	805	(44.6)
75 - 84	332	(38.6)	323	(34.3)	655	(36.3)
85 +	122	(14.1)	221	(23.5)	343	(19.1)
TOTAL	861		942		1803	
Q1. S.O.B.						
- Yes	310	(36.0)	376	(39.7)	686	(38.0)
- No	537	(62.4)	549	(58.3)	1086	(60.2)
- Housebound/Immobile	8	(0.9)	11	(1.7)	19	(1.1)
- N/S	6		6		12	
Q2 a) Chest in morning						
- Tight	112	(13.0)	91	(9.7)	203	(11.3)
- Free	741		843		1584	
- N/S	8		8		16	
b) Duration if tight						
- < 30 mins.	32	(3.7)	29	(3.1)	61	(3.4)
- 30 mins - 1 hour	41	(4.8)	22	(2.3)	63	(3.5)
- > 1 hour	26	(3.0)	18	(1.9)	44	(2.4)
- use inhaler	9	(1.0)	7	(0.7)	16	(0.9)
- N/S	15		17		32	
- N/A	738		849		1587	

		Male		Female		Total	
Q3.	**Nocturnal dyspnoea**						
	- yes	70	(8.1)	61	(6.5)	131	(7.3
	- no	785		874		1659	
	- N/S	6		7		13	
Q4.	**Wheeze**						
	- Yes	251	(29.2)	186	(19.7)	437	(24.2)
	- No	605		747		1352	
	- N/S	5		9		14	
Q5.	**Morning phlegm**						
	- Yes	246	(28.6)	156	(16.6)	402	(22.3)
	- No	610		778		1388	
	- N/S	5		8		13	
Q6.a	**Day/Night phlegm**						
	- Yes	231	(26.8)	133	(14.1)	364	(20.2)
	- No	624		797		1421	
	- N/S	6		12		18	
Q6.b	**Chronic phlegm**						
	- Yes	196	(22.8)	100	(10.6)	296	(16.4)
	- No	94		84		178	
	- N/S	10		14		24	
	- N/A	561		744		1305	
Q7.a	**Cold air**						
	- Unaffected	106		135		241	
	- Symptomatic	124	(14.4)	125	(13.3)	249	(13.8)
	- N/S	21	(2.4)	33	(3.5)	54	(3.0)

		Male		Female		Total	
Q7.b	**Smokey room**						
	- Unaffected	68		80		148	
	- Symptomatic	162	(18.8)	180	(19.1)	342	(19.0)
	- N/S	21		33		54	
Q7.c	**Fumes**						
	- Unaffected	116		147		263	
	- Symptomatic	114	(13.2)	113	(12.0)	227	(12.6)
	- N/S	21		33		54	
Q7.d	**Chemicals**						
	- Unaffected	136		154		290	
	- Symptomatic	94	(10.9)	106	(11.2)	200	(11.1)
	- N/S	21		33		54	
Q7.e	**Unaffected by any of a - d**	610	(70.8)	649	(68.9)	1259	(69.8)
Q8.	**Asthma ever**						
	- Yes	83	(9.7)	68	(7.2)	151	(8.4)
	- No	771		866		1637	
	- N/S	7		8		15	
	Current asthma	42	(4.9)	34	(3.6)	76	(4.2)
	Past asthma	41	(4.8)	34	(3.6)	75	(4.2)
Q9	**Smoking**						
	- Current	181	(21.0)	76	(8.1)	257	(14.2)
	- Ex	520	(60.4)	260	(27.6)	780	(43.3)
	- Never	160	(18.6)	605	(64.2)	765	(42.4)
	- N/S	0		1		1	
Q10	**Consulted GP**						
	- Yes	269	(31.2)	220	(23.4)	489	(27.1)
	- No	579		695		1274	
	- N/S	13		27		40	

Table 31 - Replies to questionnaire analysed according to age-group of respondents. See table 30 for explanatory notes and for comparison with overall figures.

	65 - 74 yrs		75 - 84 yrs		85+ yrs	
SEX						
Male	407		332		122	
Female	398		323		221	
TOTAL	805	(44.7)	655	(36.3)	343	(19.0)
Q1. S.O.B.						
- Yes	251	(31.2)	290	(44.3)	145	42.3)
- No	549	(68.2)	355	(54.2)	182	(53.1)
- Housebound/Immobile	1	(0.1)	7	(1.1)	11	(3.2)
- N/S	4		3		5	
Q2. a) Chest in morning						
- Tight	75	(9.3)	72	(11.0)	56	(16.3)
- Free	724		577		283	
- N/S	6		6		4	
b) duration if tight						
- < 30 mins.	24	(3.0)	19	(2.9)	18	(5.2)
- 30 mins - 1 hour	28	(3.5)	21	(3.2)	14	(4.1)
- > 1 hour	13	(1.6)	20	(3.0)	11	(3.2)
- use inhaler	8	(1.0)	7	(1.1)	1	(0.3)
- N/S	10		13		9	
- N/A	722		575		290	
Q3. Nocturnal dyspnoea						
- yes	50	(6.2)	52	(7.9)	29	(8.5)
- no	749		597		313	
- N/S	6		6		1	

		65 - 74 yrs		75 - 84 yrs		85+ yrs	
Q4.	**Wheeze**						
	- Yes	179	(22.2)	180	(27.5)	78	(22.7)
	- No	618		469		265	
	- N/S	8		6		0	
Q5.	**Morning phlegm**						
	- Yes	163	(20.2)	161	(24.6)	78	(22.7)
	- No	639		487		262	
	- N/S	3		7		3	
Q6.a	**Day/Night phlegm**						
	- Yes	141	(17.5)	156	(23.8)	67	(19.5)
	- No	657		491		273	
	- N/S	7		8		3	
Q7.a	**Cold air**						
	- Unaffected	135		76		30	
	- Symptomatic	97	(12.0)	96	(14.7)	56	(16.3)
	- N/S	10	(1.2)	25	(3.8)	19	(5.5)
Q7.b	**Smokey room**						
	- Unaffected	71		52		25	
	- Symptomatic	161	(20.0)	120	(18.3)	61	(17.8)
	- N/S	10		25		19	
Q7.c	**Fumes**						
	- Unaffected	112		92		59	
	- Symptomatic	120	(14.9)	80	(12.2)	27	(7.9)
	- N/S	10		25		19	
Q7.d	**Chemicals**						
	- Unaffected	115		119		56	
	- Symptomatic	117	(14.5)	53	(8.1)	30	(8.7)
	- N/S	10		25		19	

		65 - 74 yrs		75 - 84 yrs		85 + yrs	
Q7.e	**Unaffected by any of a - d**	563	(69.9)	458	(69.9)	238	(69.4)
Q8.	**Asthma ever**						
	- Yes	72	(8.9)	54	(8.2)	25	(7.3)
	- No	725		596		316	
	- N/S						
	Current asthma	36	(4.4)	27	(4.1)	13	(3.8)
	Past asthma	36		27		12	
Q9	**Smoking**						
	- Current	125	(15.5)	93	(14.2)	39	(11.4)
	- Ex	392	(48.7)	277	(42.3)	111	(32.4)
	- Never	288	(35.8)	284	(43.4)	193	(56.3)
	- N/S	0		1		0	
Q10	**Consulted GP**						
	- Yes	204	(25.3)	192	(29.3)	93	(27.1)
	- No	584		448		242	
	- N/S	17		15		8	

Table 32 - Replies to questionnaire analysed according to smoker status of respondents. Ex-smokers who had not smoked for more than 2 years are included with non-smokers. See table 30 for explanatory notes. The smoking status of 1 female subject is unknown; she is, however, included in the total population column.

	Nonsmoker		Smoker		Total	
Age, years						
65 - 74	680	(44.0)	125	(48.6)	805	(44.6)
75 - 84	561	(36.3)	93	(36.2)	655	(36.3)
85 +	304	(19.7)	39	(15.2)	343	(19.0)
TOTAL	1545		257		1803	
SEX						
Male	680	(44.0)	181	(70.4)	861	(47.8)
Female	865	(56.0)	76	(29.6)	942	(52.2)
Q1. S.O.B.						
- Yes	595	(38.5)	91	(35.4)	686	(38.0)
- No	925	(59.9)	160	(62.3)	1086	(60.2)
- Housebound/Immobile	16	(1.0)	3	(1.2)	19	(1.1)
- N/S	9		3		12	
Q2 a) Chest in morning						
- Tight	166	(10.7)	37	(14.4)	203	(11.3)
- Free	1368		215		1584	
- N/S	11		5		16	
b) Duration if tight						
- < 30 mins.	44	(2.8)	17	(6.6)	16	(3.4)
- 30 mins - 1 hour	52	(3.4)	11	(4.3)	63	(3.5)
- > 1 hour	40	(2.6)	4	(1.6)	44	(2.4)
- use inhaler	14	(0.9)	2	(0.8)	16	(0.9)
- N/S	25		7		32	
- N/A	1370		216		1587	

		Nonsmoker		Smoker		Total	
Q3.	**Nocturnal dyspnoea**						
	- yes	109	(7.1)	22	(8.6)	131	(7.3)
	- no	1425		233		1659	
	- N/S	11		2		13	
Q4.	**Wheeze**						
	- Yes	349	(22.6)	88	(34.2)	437	(24.2)
	- No	1183		168		1352	
	- N/S	13		1		14	
Q5.	**Morning phlegm**						
	- Yes	310	(20.1)	92	(35.8)	402	(22.3)
	- No	1224		163		1388	
	- N/S	11		2		13	
Q6.a	**Day/Night phlegm**						
	- Yes	286	(18.5)	78	(30.4)	364	(20.2)
	- No	1243		177		1421	
	- N/S	16		2		18	
Q6.b	**Chronic phlegm**						
	- Yes	224	(14.5)	72	(28.0)	296	(16.4)
	- No	149		29		178	
	- N/S	19		5		24	
	- N/A	1153		151		1305	
Q7.a	**Cold air**						
	- Unaffected	217		24		241	
	- Symptomatic	217	(14.0)	32	(12.4)	249	(13.8)
	- N/S	45		9		54	

		Nonsmoker		Smoker		Total	
Q7.b	**Smokey room**						
	- Unaffected	105		43		148	
	- Symptomatic	329	(21.3)	13	(5.1)	342	(19.0)
	- N/S	45		9		54	
Q7.c	**Fumes**						
	- Unaffected	235		28		263	
	- Symptomatic	199	(12.9)	28	(10.9)	227	(12.6)
	- N/S	45		9		54	
Q7.d	**Chemicals**						
	- Unaffected	250		40		290	
	- Symptomatic	184	(11.9)	16	(6.2)	200	(11.1)
	- N/S	45		9		54	
Q7.e	**Unaffected by any of a - d**	1066	(69.0)	192	(74.7)	1259	(69.8)
Q8.	**Asthma ever**						
	- Yes	124	(8.0)	27	(10.5)	151	(8.4)
	- No	1408		228		1637	
	- N/S	13		2		15	
	Current asthma	61	(3.9)	15	(5.8)	76	(4.2)
	Past asthma	63	(4.1)	12	(4.7)	75	(4.2)
Q9	**Smoking**						
	- Current	0		257		257	(14.2)
	- Ex	780		0		780	(43.3)
	- Never	765		0		765	(42.4)
	- N/S	0		0		1	
Q10	**Consulted GP**						
	- Yes	409	(26.5)	80	(31.1)	489	(27.1)
	- No	1102		171		1274	
	- N/S	34		6		40	

Table 33 - Pre-challenge symptoms of all subjects agreeing to attend for challenge studies, as stated on their respiratory symptoms questionnaire (and verified at interview). Their age, sex and initial (pre-challenge) FEV_1 are shown for comparison.

Within each group subjects are ranked according to level of airway reactivity to inhaled methacholine, subjects with the lowest identification numbers in each group having the highest levels of bronchial reactivity within the group.

SUBJECT I.D. #	GROUP	SYMPTOMS
1 - 37	1	Fully healthy
38 - 79	2	Short of breath on exertion only.
80 - 117	3	Mixed respiratory symptoms (but not symptoms of the bronchial irritability syndrome)
118 - 160	4	Symptoms of the bronchial irritability syndrome
161 - 180		Not challenged

Notes:

1. 'Smoker' status: Number of years since stopping smoking are shown for ex-smokers; lifelong non-smokers shown as "−" and current smokers indicated "+".

2. 'S.O.B.': short of breath when hurrying on level ground or walking up a slight hill (Q.1)

3. 'M.T.': indicates duration of morning chest tightness in hours (<30 minutes, <1 hour, >1 hour) (Q.2)

4. 'N.D.': nocturnal dyspnoea (Q.3)

5. 'I': uses inhaler

6. 'C.B.': chronic bronchitis

7. 'B.I.': symptoms of bronchial irritability (wheeze, breathlessness) with certain environmental stimuli (Q.7)

8. Asthma: "A" indicates active asthma; "+" indicates past asthma

9. 'Dr': has seen doctor within the preceding two years for a chest condition (Q.11)

I.D.	AGE (YRS)	SEX	FEV1 (L)	SMOKER	S.O.B. (Q 1)	M.T. (Q 2)	N.D. (Q3)	WHEEZE (Q4)	SPUTUM/ COUGH (Q 5,6)	B.I. (Q 7)	ASTHMA (Q8)	DR (Q11)
GROUP 1												
PD20 < 1.0umol												
1	77	F	0.96	-								
PD20 1.0-6.13umol												
2	70	M	2.66	+								
3	70	M	1.96	EX 11								
4	87	M	1.50	+								
5	66	F	2.70	EX 7								
6	68	M	2.65	+								
PD20 > 6.13umol												
7	77	F	1.74	EX 2								
8	69	F	2.10	+								
9	66	F	2.76	-								
10	73	F	2.75	-								
11	79	F	2.16	EX 17								
12	69	F	2.78	EX 10								
13	88	F	2.04	EX 50								
14	68	F	2.58	EX 25								
15	70	F	2.50	-								
16	67	F	1.66	EX 16								
17	70	F	2.76	EX 15								
18	67	F	2.30	EX 10								
19	78	F	1.90	-								+
20	67	M	3.32	EX 4								
21	81	M	2.95	EX 36								
22	79	M	2.42	-								
23	73	M	4.45	+								
24	73	M	2.76	EX 27							+	+
25	67	M	3.32	EX 12								
26	73	M	2.60	-								
27	68	M	2.32	EX 20								
28	74	M	3.28	EX 34								
29	80	M	3.34	+								
30	87	M	2.32	+								
31	67	M	3.68	-								
32	65	M	3.64	EX 26								
33	87	M	2.74	EX 8								
34	74	M	3.14	EX 21								
35	79	M	2.83	EX 50								
36	86	M	3.01	EX 10								
37	71	M	2.54	EX 18								

I.D.	AGE (YRS)	SEX	FEV1 (L)	SMOKER	S.O.B. (Q1)	M.T. (Q 2)	N.D. (Q3)	WHEEZE (Q 4)	SPUTUM/ COUGH (Q 5,6)	B.I. (Q 7)	ASTHMA (Q8)	DR (Q11)
GROUP 2												
PD20 < 1.0umol												
38	76	M	1.53	+	+							
PD20 1.0-6.13umol												
39	66	M	3.25	+	+							
40	72	F	1.45		+							+
41	82	F	1.40	-	+							
42	74	M	1.83	EX 10	+							
43	66	F	2.03	EX 20	+							
44	81	F	1.87	-	+							
45	70	F	1.60	-	+							
46	77	F	1.71	-	+							
47	67	F	2.27	EX 20	+							+
48	68	F	2.48	-	+							
49	66	F	2.00	-	+							
50	70	F	1.95	EX 15	+							
51	77	F	1.83	EX 8	+							
52	67	M	2.30	EX 25	+							
53	73	M	2.10	-	+							+
PD20 >6.13umol												
54	70	M	3.48	EX 2	+							
55	88	M	2.80	EX 5	+							
56	67	M	5.26	EX 3	+							
57	72	M	2.94	-	+							+
58	72	M	2.97	EX 15	+							+
59	80	M	2.24	EX 8	+							+
60	71	M	1.98	EX 6	+							
61	80	M	2.35	EX 12	+							
62	72	M	2.67	EX 2	+							
63	70	M	3.08	EX 28	+							+
64	72	M	2.54	+	+							
65	79	M	2.53	EX 20	+							
66	78	M	2.77	-	+							
67	66	F	2.21	+	+							
68	67	F	1.82	-	+							
69	74	F	2.15	-	+							
70	80	F	1.60	-	+							+
71	68	F	2.45	-	+							
72	75	F	2.15	-	+							
73	80	F	1.34	-	+							
74	69	F	2.04	EX 10	+							
75	65	F	2.63	-	+							
76	87	F	1.43	-	+							
77	73	F	2.04	-	+							
78	83	F	1.75	-	+							
79	74	F	2.52	+	+							

I.D.	AGE (YRS)	SEX	FEV1 (L)	SMOKER	S.O.B. (Q 1)	M.T. (Q2)	N.D. (Q3)	WHEEZE (Q4)	SPUTUM/ COUGH (Q 5,6)	B.I. (Q7)	ASTHMA (Q8)	DR (Q11)
GROUP 3												
PD20 < 1.0umol												
80	74	M	1.26	EX 10	+			+	CB			+
81	85	F	1.27	-	+	<1/2		+				
82	78	M	1.66	EX 38	+	<1/2		+	CB			+
83	74	M	1.24	EX 19	+			+	+			+
84	66	F	1.65	-				+				+
85	77	M	2.76	EX 20				+	+			
86	76	M	2.26	EX 20	+			+				+
87	71	F	1.44	-	+			+	+			
PD20 1.0-6.13umol												
88	80	F	1.32	-				+	CB			
89	89	M	1.30	+		<1/2			+			
90	66	F	1.33	+	+			+	+			+
91	66	F	2.00	-				+				
92	65	F	1.70	EX 2	+	<1/2			CB			+
93	81	F	1.82	-	+			+	+			
94	81	F	1.00	EX 12	+			+				+
95	76	F	1.77	+	+	<1/2		+				
96	77	M	2.22	EX 10	+	<1/2		+	CB			+
97	75	M	2.35	+		<1/2		+	CB			+
98	72	M	1.77	EX 12	+			+	+			
99	76	M	2.18	EX 4	+			+	+			+
100	87	F	1.42	-	+	<1/2		+				+
101	70	M	2.43	+	+	<1/2		+	CB		+	+
102	82	F	1.77	-	+			+				
103	67	M	2.07	EX 12	+			+	+			+
104	88	M	1.70	EX 20	+			+	+			+
PD20 > 6.13umol												
105	68	F	2.45	-				+	+			
106	74	M	2.42	+				+	+			
107	76	M	2.68	-	+			+				
108	73	M	3.50	-	+	<1/2		+	+			
109	67	F	2.50	EX 10				+	CB			+
110	76	F	2.21	-				+	CB			
111	72	M	2.59	EX 9	+			+				
112	72	M	2.77	+				+				
113	71	M	2.16	+				+	+			
114	77	F	2.15	EX 23	+			+				
115	84	M	2.04	EX 25				+				
116	83	M	3.04	+				+	CB			
117	81	M	2.32	EX 20	+			+	CB			+

I.D.	AGE (YRS)	SEX	FEV1 (L)	SMOKER	S.O.B. (Q1)	M.T. (Q2)	N.D. (Q 3)	WHEEZE (Q 4)	SPUTUM/ COUGH (Q 5,6)	B.I. (Q7)	ASTHMA (Q 8)	DR (Q11)
GROUP 4												
PD20 < 1.0umol												
118	76	M	1.05	EX 2	+	>1	+	+	CB	+	A	+
119	78	F	1.22	EX 28	+	>1	+	+	CB	+		+
120	87	M	1.12	EX 20	+			+	CB	+		+
121	67	F	1.16	-	+					+	A	+
122	76	M	1.88	EX 1	+	I	+	+			A	
123	81	M	1.38	EX 45	+			+	CB	+	+	+
124	78	F	1.65	EX 32	+					+		
125	68	M	1.01	EX 1	+	>1		+	CB	+		+
126	67	F	2.23	-	+	>1	+					+
127	92	F	1.22	-	+					+		
128	88	M	1.85	EX 4	+	>1	+	+	+	+		+
PD20 1.0-6.13umol												
129	86	F	1.38	-	+	<1/2	+	+	CB			+
130	84	M	1.93	EX 4	+			+		+		
131	76	M	1.54	+	+	I	+	+	CB		A	+
132	79	F	1.66	-	+			+	CB	+	+	+
133	74	F	1.75	EX 50						+		
134	69	F	1.77	EX 20	+	<1/2	+	+	CB	+		+
135	79	M	1.72	+	+	<1/2	+		+			+
136	71	F	1.70	-	+	>1		+	CB	+		
137	79	M	1.35	EX 17	+	<1/2	+	+	CB	+		+
138	77	F	1.49	EX 30				+	CB	+		+
139	84	F	1.49	-	+	>1		+	CB	+		+
140	69	M	2.16	+	+	<1/2		+	CB	+		
141	68	F	2.58	-	+		+					+
PD20 > 6.13umol												
142	66	F	1.87	-	+	<1/2	+	+	+	+	+	+
143	72	F	1.77	EX 12	+			+	+	+		
144	80	F	1.45	-	+					+		
145	67	F	1.70	-	+	<1/2	+			+		+
146	88	F	1.74	-	+		+		+	+		+
147	74	F	2.07	-	+				+	+		+
148	76	F	1.95	EX 5	+	<1/2			+	+		+
149	81	F	1.25	EX 40	+	>1	+	+	CB	+		+
150	66	M	3.00	EX 15						+		
151	73	M	2.70	+	+			+	CB	+		
152	71	M	3.00	+				+	+	+		
153	83	M	2.90	+	+			+		+		+
154	76	M	2.90	+	+			+		+		+
155	76	M	1.51	EX 25	+	I	+	+		+	A	+
156	75	M	2.18	EX 20	+			+	+	+		
157	84	M	2.32	EX 30	+			+	CB	+		+
158	75	M	2.40	EX 22	+			+	+	+		+
159	75	M	2.32	EX 45			+					
160	85	F	1.93		+				+	+		+

I.D.	AGE (YRS)	SEX	FEV1 (L)	SMOKER	S.O.B. (Q 1)	M.T. (Q2)	N.D. (Q 3)	WHEEZE (Q4)	SPUTUM/ COUGH (Q 5,6)	B.I. (Q 7)	ASTHMA (Q8)	DR (Q11)
NOT CHALLENGED												
GROUP 1												
161	93	F	1.16	-								
GROUP 2												
162	82	F	0.73	EX 15	+							
163	67	M	3.76	EX 12	+							+
164	80	M	0.98	EX 8	+							
165	79	F	0.94	EX 20	+							
166	87	F	1.48	-	+							
167	85	F	0.98	-	+							
168	88	F	1.22	-	+							
169	89	F	1.08	+	+							
GROUP 4												
170	79	M	0.93	EX 6	+	>1		+	CB	+	+	+
171	75	M	0.75	EX 26	+	>1	+	+	CB	+	A	+
172	70	F	0.92	+	+	<1/2		+	CB	+		+
173	71	F	0.78	-	+			+		+		
174	73	M	0.80	-	+	>1		+	CB	+		
175	81	F	0.50	EX 30	+			+	CB	+		+
176	69	F	0.88	EX 25	+	<1/2		+	CB	+	A	+
177	76	M	0.82	EX 45	+			+	+	+	A	+
178	74	F	0.83	-	+	>1		+	+	+		+
179	65	F	0.30	EX 7	+	>1	+	+	CB	+	A	+
180	83	F	0.72	-	+	<1/2	+	+	+	+		+

Table 34 - Anthropomorphic data, initial (pre-challenge) pulmonary function measurements and results of methacholine challenge studies for all subjects.

Results of bronchodilator challenge are given for subjects 161 - 180 who were excluded from (or did not complete) methacholine challenge study.

For explanation of I.D. number sequence and groupings see notes preceding table 33.

I.D.	SEX	AGE (YRS)	HEIGHT (CM)	SPAN (CM)	WEIGHT (KG)	PREDICTED FVC (L)	PREDICTED FEV1 (L)	INIT.PEFR (L/MIN)	INIT.FVC (L)	INIT.FVC (%PRED)	INIT.FEV1 (L)	INIT.FEV1 (%PRED)	POST SALINE FEV1 (L)
GROUP 1													
1	F	77	154	156	52	1.80	1.35	250	1.58	88	0.96	71	0.96
2	M	70	175	184	67	3.65	2.22	440	4.35	119	2.66	120	2.58
3	M	70	176	184	70	3.70	2.24	445	3.26	88	1.96	88	2.04
4	M	87	162	170	69	2.38	1.31	320	2.50	105	1.50	114	1.53
5	F	66	172	178	75	3.54	2.30	500	3.92	111	2.70	117	2.70
6	M	68	177	178	82	3.80	2.40	360	4.20	110	2.65	110	2.70
7	F	77	150	158	51	1.70	1.30	250	2.10	124	1.74	134	1.74
8	F	69	152	164	60	2.55	1.58	260	2.87	113	2.10	133	1.98
9	F	66	170	178	67	3.45	2.24	430	3.20	93	2.76	123	2.76
10	F	73	156	168	64	2.80	1.50	390	3.36	120	2.75	183	2.75
11	F	79	155	168	57	1.70	1.30	370	2.75	162	2.16	166	2.26
12	F	69	163	174	57	3.03	1.90	270	3.70	122	2.78	146	2.25
13	F	88	155	178	63	1.50	1.15	250	2.70	180	2.04	177	1.98
14	F	68	170	176	65	2.55	1.80	490	3.12	122	2.58	143	2.52
15	F	70	162	156	62	2.30	1.66	480	3.03	132	2.50	151	2.48
16	F	67	154	158	67	2.70	1.70	350	2.50	93	1.70	100	1.76
17	F	70	166	173	64	2.40	1.70	450	3.30	138	2.76	162	2.70
18	F	67	158	162	66	2.82	1.80	390	2.90	103	2.30	128	2.25
19	F	78	165	165	62	2.10	1.54	290	2.60	124	1.90	123	1.82
20	M	67	174	188	91	3.96	2.80	640	4.18	106	3.32	119	3.08
21	M	81	171	180	77	3.00	1.70	555	3.76	125	2.95	174	3.00
22	M	79	168	182	69	2.90	1.70	490	3.23	110	2.42	142	2.37
23	M	73	184	202	75	3.90	2.30	350	4.45	114	2.86	124	3.00
24	M	73	174	182	73	3.45	2.10	510	4.15	120	2.76	131	2.70
25	M	67	171	182	74	3.85	2.70	660	3.94	102	3.32	123	3.32
26	M	73	160	174	70	2.10	1.75	470	3.46	165	2.60	149	2.48
27	M	68	176	186	77	3.80	2.20	460	3.45	91	2.32	105	2.15
28	M	74	184	188	81	3.85	2.20	600	4.15	108	3.28	149	3.30
29	M	80	186	197	56	3.47	2.10	450	5.25	151	3.34	159	3.42
30	M	87	175	182	60	2.80	1.54	500	3.40	121	2.32	151	2.25
31	M	67	169	178	67	3.65	2.65	680	5.05	138	3.68	140	3.80
32	M	65	171	182	70	3.85	2.74	585	4.80	125	3.64	133	3.81
33	M	87	167	176	70	2.55	1.40	430	3.19	125	2.74	196	2.73
34	M	74	178	176	70	3.61	2.12	630	4.15	115	3.14	148	3.05
35	M	79	169	178	70	3.00	1.72	575	3.82	127	2.83	164	2.75
36	M	82	176	178	87	3.08	1.75	660	3.70	120	3.01	172	3.03
37	M	71	177	178	83	3.70	2.20	530	3.23	87	2.54	115	2.52

I.D.	PENULT FEV1 (%SAL)	PENULT DOSE (umol)	FINAL PEFR (% INITIAL)	FINAL FEV1 (%SAL)	FINAL DOSE (umol)	POST BD PEFR (%INIT)	POST BD FEV1 (%SAL)	% DECREASE PEFR	% DECREASE FEV1	PD20 FEV1 (umol)
1	83	0.383	56	69	0.767	92	108	44	31	0.444
2	81	3.07	98	71	6.13	98	93	2	29	3.29
3	84	3.07	79	70	6.13	101	102	21	30	3.74
4	85	0.767	109	78	1.53	125	101	0	22	3.94
5	93	1.53	82	80	6.13	106	98	18	20	6.13
6	92	3.07	83	80	6.13	111	102	17	20	6.13
7	92	1.53	88	92	6.13	92	95	8	12	>MAX
8	89	3.07	92	85	6.13	108	99	8	15	>MAX
9	111	1.53	107	114	6.13	107	108	0	0	>MAX
10	90	3.07	102	94	6.13	115	104	0	6	>MAX
11	92	3.07	95	96	6.13	89	92	5	4	>MAX
12	96	1.53	100	90	6.13	95	98	0	10	>MAX
13	95	3.07	88	93	6.13	112	104	12	7	>MAX
14	103	1.53	86	100	6.13	97	102	14	0	>MAX
15	101	1.53	83	100	6.13	96	98	17	0	>MAX
16	94	1.53	77	87	6.13	94	98	23	13	>MAX
17	92	1.53	111	89	6.13	116	100	0	11	>MAX
18	96	1.53	100	90	6.13	95	98	0	10	>MAX
19	103	1.53	83	96	6.13	100	99	17	4	>MAX
20	103	1.53	98	100	6.13	91	106	2	0	>MAX
21	84	3.07	94	83	6.13	95	96	6	17	>MAX
22	97	3.07	100	93	6.13	104	102	0	7	>MAX
23	90	3.07	69	92	6.13	129	96	31	8	>MAX
24	93	1.53	96	98	6.13	100	99	1	2	>MAX
25	100	1.53	99	96	6.13	99	98	1	4	>MAX
26	97	3.07	98	98	6.13	100	100	2	2	>MAX
27	91	3.07	90	95	6.13	104	102	10	5	>MAX
28	98	1.53	102	97	6.13	105	99	0	3	>MAX
29	92	3.07	87	90	6.13	106	102	13	10	>MAX
30	87	1.53	78	83	6.13	94	92	22	17	>MAX
31	101	1.53	91	98	6.13	103	102	9	2	>MAX
32	99	1.53	95	99	6.13	99	100	5	1	>MAX
33	101	1.53	121	94	6.13	100	99	0	6	>MAX
34	94	1.53	98	93	6.13	101	103	2	7	>MAX
35	104	1.53	90	98	6.13	97	103	10	2	>MAX
36	100	1.53	95	93	6.13	97	100	5	7	>MAX
37	88	3.07	89	83	6.13	108	104	11	17	>MAX

I.D.	SEX	AGE (YRS)	HEIGHT (CM)	SPAN (CM)	WEIGHT (KG)	PREDICTED FVC (L)	PREDICTED FEV1 (L)	INIT.PEFR (L/MIN)	INIT.FVC (L)	INIT.FVC (%PRED)	INIT.FEV1 (L)	INIT.FEV1 (%PRED)	POST SALINE FEV1 (L)
GROUP 2													
38	M	76	166	168	50	3.04	1.78	300	2.35	77	1.53	86	1.55
39	M	66	177	179	96	4.15	2.95	420	4.10	99	3.25	110	3.25
40	F	72	156	164	87	2.04	1.50	355	2.04	100	1.45	97	1.45
41	F	82	161	169	53	1.85	1.36	240	2.24	121	1.40	103	1.40
42	M	74	168	178	66	3.20	1.90	270	2.63	82	1.83	96	1.93
43	F	66	158	164	72	2.86	1.83	370	2.65	93	2.03	111	2.08
44	F	81	167	174	67	2.08	1.48	270	2.63	126	1.87	126	1.92
45	F	70	146	156	62	1.80	1.38	280	2.17	120	1.60	116	1.54
46	F	77	155	162	68	1.84	1.37	350	2.34	127	1.71	125	1.66
47	F	67	165	170	63	3.17	2.04	320	2.80	88	2.27	111	2.30
48	F	68	160	164	74	2.90	1.84	260	2.80	96	2.48	135	2.45
49	F	66	155	164	62	2.72	1.74	480	2.56	94	2.00	115	1.94
50	F	70	167	170	72	2.45	1.80	350	2.78	113	1.95	108	2.01
51	F	77	161	173	75	2.04	1.49	405	2.23	109	1.83	123	1.80
52	M	67	169	172	72	3.63	2.55	440	3.38	93	2.30	90	2.25
53	M	73	166	176	65	3.15	1.90	370	2.42	77	2.10	110	2.20
54	M	70	175	176	77	3.70	2.20	650	4.46	120	3.48	158	3.42
55	M	88	165	182	64	2.44	1.35	350	3.78	155	2.80	207	2.72
56	M	67	183	190	92	4.45	3.13	660	6.46	145	5.26	168	5.40
57	M	72	161	162	61	3.00	1.80	470	4.44	148	2.94	163	2.94
58	M	72	173	186	98	3.55	1.95	460	4.40	124	2.97	152	2.82
59	M	80	179	178	80	3.30	1.90	430	3.23	98	2.24	118	2.26
60	M	71	163	168	73	3.15	1.90	470	2.57	82	1.98	104	1.93
61	M	72	167	174	82	2.86	1.65	460	3.15	110	2.35	142	2.35
62	M	72	168	180	67	3.32	1.97	510	3.81	115	2.67	135	2.66
63	M	70	173	181	75	3.62	2.18	605	3.94	109	3.08	141	3.04
64	M	72	168	172	99	3.32	2.00	485	3.29	99	2.54	127	2.65
65	M	79	169	177	63	3.00	1.74	525	3.34	111	2.53	145	2.56
66	M	78	180	180	87	3.45	2.00	470	3.52	102	2.77	138	2.80
67	F	66	165	168	68	3.23	2.08	330	2.84	88	2.21	106	2.14
68	F	67	158	168	63	2.84	1.80	270	2.50	88	1.82	101	1.67
69	F	74	153	164	61	1.90	1.40	430	3.02	159	2.15	154	2.13
70	F	80	156	162	70	2.00	1.34	280	2.08	104	1.60	119	1.66
71	F	68	166	168	65	3.20	2.04	380	3.37	105	2.45	120	2.45
72	F	75	163	166	66	2.14	1.58	380	3.05	142	2.15	140	2.08
73	F	80	152	156	60	1.66	1.26	250	1.76	106	1.34	106	1.27
74	F	69	164	168	81	2.35	1.74	420	2.76	117	2.04	117	1.92
75	F	65	163	164	88	3.12	2.03	460	3.30	106	2.63	130	2.72
76	F	87	149	156	83	1.40	1.06	360	1.80	128	1.43	135	1.44
77	F	73	154	164	52	1.92	1.45	330	2.70	141	2.04	141	2.04
78	F	83	158	156	54	1.75	1.32	350	2.41	138	1.75	132	1.67
79	F	74	169	174	69	2.32	1.70	420	3.22	139	2.52	148	2.40

I.D.	PENULT FEV1 (%SAL)	PENULT DOSE (umol)	FINAL PEFR (% INITIAL)	FINAL FEV1 (%SAL)	FINAL DOSE (umol)	POST BD PEFR (%INIT)	POST BD FEV1 (%SAL)	% DECREASE PEFR	% DECREASE FEV1	PD20 FEV1 (umol)
38	86	0.383	67	72	1.53	98	94	33	28	0.693
39	83	0.767	86	78	1.53	107	95	14	22	1.16
40	83	0.767	68	79	1.53	82	93	32	21	1.29
41	97	0.383	67	79	1.53	98	101	33	21	1.42
42	94	0.383	92	80	1.53	100	98	8	20	1.53
43	89	0.383	84	80	1.53	100	97	16	20	1.53
44	83	1.53	93	68	3.07	118	90	7	34	1.76
45	89	1.53	82	79	3.07	107	97	18	21	2.86
46	84	1.53	71	80	3.07	94	99	29	20	3.07
47	83	3.07	94	64	6.13	103	98	6	36	3.42
48	91	3.07	87	78	6.13	130	92	13	22	5.51
49	88	3.07	67	79	6.13	85	101	33	21	5.68
50	89	3.07	83	79	6.13	97	101	17	21	5.72
51	92	1.53	88	80	6.13	100	97	12	20	6.13
52	90	1.53	76	80	6.13	90	101	24	20	6.13
53	93	1.53	100	80	6.13	103	98	0	20	6.13
54	101	1.53	103	94	6.13	102	100	0	6	>MAX
55	97	3.07	109	97	6.13	120	107	0	3	>MAX
56	99	1.53	102	94	6.13	102	96	0	6	>MAX
57	103	1.53	108	101	6.13	126	103	0	0	>MAX
58	90	3.07	99	90	6.13	109	98	1	10	>MAX
59	92	1.53	109	88	6.13	108	98	0	12	>MAX
60	97	1.53	88	97	6.13	99	104	12	3	>MAX
61	97	1.53	76	92	6.13	98	105	24	8	>MAX
62	87	3.07	71	83	6.13	99	94	29	17	>MAX
63	99	1.53	102	96	6.13	102	99	0	4	>MAX
64	91	3.07	84	100	6.13	99	102	16	0	>MAX
65	95	1.53	88	91	6.13	100	104	12	9	>MAX
66	99	1.53	95	97	6.13	104	101	5	3	>MAX
67	93	1.53	106	89	6.13	114	93	0	11	>MAX
68	99	1.53	93	99	6.13	111	99	7	1	>MAX
69	84	3.07	81	83	6.13	88	102	19	17	>MAX
70	104	3.07	79	101	6.13	71	105	21	0	>MAX
71	101	1.53	97	99	6.13	100	103	3	0	>MAX
72	98	1.53	82	95	6.13	87	105	18	5	>MAX
73	94	1.53	84	91	6.13	116	109	16	9	>MAX
74	101	1.53	95	96	6.13	99	108	5	4	>MAX
75	99	1.53	98	76	6.13	104	100	2	4	>MAX
76	87	3.07	83	88	6.13	100	97	17	12	>MAX
77	89	3.07	79	88	6.13	97	97	21	12	>MAX
78	96	1.53	97	93	6.13	103	105	3	7	>MAX
79	97	1.53	84	82	6.13	90	100	16	18	>MAX

I.D.	SEX	AGE (YRS)	HEIGHT (CM)	SPAN (CM)	WEIGHT (KG)	PREDICTED FVC (L)	PREDICTED FEV1 (L)	INIT.PEFR (L/MIN)	INIT.FVC (L)	INIT.FVC (%PRED)	INIT.FEV1 (L)	INIT.FEV1 (%PRED)	POST SALINE FEV1 (L)
GROUP 3													
80	M	74	169	182	76	3.25	1.94	320	2.57	79	1.26	65	1.05
81	F	85	147	150	62	1.43	1.08	195	1.70	119	1.27	117	0.95
82	M	78	174	188	84	3.20	1.85	215	3.19	100	1.66	90	1.56
83	M	74	163	170	78	3.00	1.80	290	1.74	58	1.24	70	1.32
84	F	66	146	151	50	2.55	1.80	280	2.36	92	1.65	92	1.60
85	M	77	173	181	87	3.24	1.90	520	3.70	114	2.76	145	2.77
86	M	76	175	184	86	3.35	1.95	480	3.50	104	2.26	116	2.26
87	F	71	168	177	66	2.45	1.75	150	2.47	101	1.44	82	1.44
88	F	80	165	170	68	2.05	1.50	170	1.94	95	1.32	88	1.30
89	M	89	157	161	74	2.20	1.20	250	1.50	68	1.30	108	1.30
90	F	66	165	172	63	3.20	2.05	300	1.97	62	1.33	65	1.33
91	F	66	166	170	67	3.38	2.19	390	3.03	90	2.00	91	2.21
92	F	65	150	155	67	2.50	1.58	315	2.05	82	1.70	108	1.71
93	F	81	152	160	62	1.65	1.25	410	2.56	155	1.82	146	1.87
94	F	81	156	165	59	1.75	1.31	240	1.47	84	1.00	76	1.01
95	F	76	154	160	65	1.85	1.38	250	2.15	116	1.77	128	1.72
96	M	77	164	180	68	2.92	1.70	450	3.30	113	2.22	130	2.15
97	M	75	171	180	76	3.25	1.94	365	3.26	100	2.35	121	2.35
98	M	72	175	178	83	3.60	2.13	480	3.07	85	1.77	83	1.81
99	M	76	164	166	78	2.95	1.74	560	2.99	101	2.18	125	2.15
100	F	87	151	162	48	1.70	1.26	180	1.79	105	1.42	113	1.38
101	M	70	174	182	69	3.65	2.15	460	4.00	109	2.43	113	2.32
102	F	82	150	169	68	1.55	1.18	190	2.74	177	1.77	150	1.72
103	M	67	175	180	77	4.00	2.84	290	2.93	73	2.07	73	2.08
104	M	88	168	176	93	2.53	1.40	270	2.36	93	1.70	121	1.65
105	F	68	152	160	55	3.04	1.94	420	3.10	102	2.45	126	2.40
106	M	74	172	183	69	3.35	2.00	330	3.43	102	2.42	121	2.37
107	M	76	175	186	72	3.40	1.95	450	4.08	120	2.68	137	3.10
108	M	73	182	185	78	3.82	2.25	600	4.78	125	3.50	155	3.43
109	F	67	158	166	77	2.82	1.80	450	3.04	108	2.50	139	2.50
110	F	76	163	166	63	2.12	1.55	405	3.12	147	2.21	142	2.20
111	M	72	172	180	103	3.45	2.07	400	3.55	103	2.59	125	2.70
112	M	72	173	182	88	3.50	2.10	400	3.40	97	2.77	132	2.66
113	M	71	175	182	84	3.62	2.17	500	2.97	82	2.16	100	2.15
114	F	77	158	172	66	1.95	1.43	320	2.50	128	2.15	150	2.19
115	M	84	166	166	82	2.65	1.50	370	2.62	99	2.04	136	2.23
116	M	83	173	178	85	2.95	1.66	360	3.95	134	3.04	183	3.04
117	M	81	176	174	69	3.13	1.80	480	3.32	106	2.32	129	2.40

I.D.	PENULT FEV1 (%SAL)	PENULT DOSE (umol)	FINAL PEFR (% INITIAL)	FINAL FEV1 (%SAL)	FINAL DOSE (umol)	POST BD PEFR (%INIT)	POST BD FEV1 (%SAL)	% DECREASE PEFR	% DECREASE FEV1	PD20 FEV1 (umol)
80			91	83	SAL	105	103			SALINE
81			82	75	SAL	97	96			SALINE
82	83	0.192	72	72	0.383	84	125	28	28	0.232
83	92	0.096	69	80	0.383	124	121	31	20	0.383
84	81	0.383	75	76	0.767	107	100	25	24	0.44
85	86	0.383	58	71	1.53	104	97	42	29	0.666
86	88	0.383	85	79	0.767	102	100	15	21	0.71
87	87	0.383	100	80	0.767	147	113	0	20	0.767
88	86	0.383	94	78	1.53	129	102	6	22	1.08
89	90	0.383	72	77	1.53	112	108	28	23	1.11
90	92	0.767	33	71	1.53	103	100	77	29	1.14
91	86	1.53	97	75	3.07	112	100	3	25	1.66
92	82	1.53	63	77	3.07	89	89	37	23	2.02
93	89	1.53	85	68	3.07	93	97	15	32	2.06
94	89	1.53	83	78	3.07	96	101	17	22	2.70
95	89	1.53	88	75	6.13	104	98	12	25	3.73
96	85	3.07	77	77	4.58	111	90	23	23	3.94
97	84	3.07	78	75	6.13	93	96	22	25	4.18
98	88	3.07	58	73	6.13	87	95	42	27	4.44
99	87	3.07	91	77	6.13	91	95	9	23	4.98
100	84	3.07	56	79	6.13	89	92	44	21	5.34
101	97	1.53	61	80	6.13	98	98	39	20	6.13
102	86	3.07	42	80	6.13	132	99	58	20	6.13
103	87	3.07	72	80	6.13	97	96	28	20	6.13
104	92	1.53	89	80	6.13	122	91	11	20	6.13
105	97	3.07	88	91	6.13	95	101	12	9	>MAX
106	90	1.53	61	91	6.13	112	100	39	9	>MAX
107	102	1.53	84	92	6.13	99	101	16	8	>MAX
108	92	1.53	90	87	6.13	93	97	10	13	>MAX
109	96	1.53	93	95	6.13	96	100	7	5	>MAX
110	100	1.53	91	98	6.13	100	109	9	2	>MAX
111	102	1.53	100	96	6.13	95	97	0	4	>MAX
112	90	1.53	106	85	6.13	106	99	0	15	>MAX
113	86	3.07	91	85	6.13	94	95	9	15	>MAX
114	87	1.53	106	87	6.13	122	99	0	13	>MAX
115	100	1.53	122	98	6.13	119	101	0	2	>MAX
116	94	1.53	92	88	6.13	108	99	8	12	>MAX
117	90	3.07	90	88	6.13	94	92	10	12	>MAX

I.D.	SEX	AGE (YRS)	HEIGHT (CM)	SPAN (CM)	WEIGHT (KG)	PREDICTED FVC (L)	PREDICTED FEV1 (L)	INIT.PEFR (L/MIN)	INIT.FVC (L)	INIT.FVC (%PRED)	INIT.FEV1 (L)	INIT.FEV1 (%PRED)	POST SALINE FEV1 (L)
GROUP 4													
118	M	76	168	178	71	3.12	1.83	280	3.32	106	1.05	57	1.16
119	F	78	152	158	38	1.73	1.31	310	1.63	94	1.22	93	1.18
120	M	87	165	180	58	2.50	1.35	70	2.26	90	1.12	85	1.15
121	F	67	150	154	69	4.08	1.52	270	1.22	30	1.16	76	1.22
122	M	76	183	182	88	3.68	2.08	450	3.32	90	1.88	90	1.98
123	M	81	167	182	67	2.88	1.63	250	2.65	92	1.38	85	1.30
124	F	78	158	158	71	1.90	1.40	320	2.40	126	1.65	118	1.62
125	M	68	179	176	67	4.23	2.95	120	2.70	64	1.01	34	1.00
126	F	67	152	160	52	2.54	1.60	335	2.71	107	2.23	139	2.22
127	F	92	158	164	70	1.53	1.14	170	1.85	121	1.22	107	1.22
128	M	88	162	172	75	2.80	1.60	385	2.70	96	1.85	170	1.83
129	F	86	149	158	53	1.42	1.10	150	1.82	128	1.38	125	1.57
130	M	84	168	174	64	2.60	1.55	400	2.95	113	1.93	124	1.82
131	M	76	178	180	80	3.50	2.05	380	3.01	86	1.54	75	1.50
132	F	79	160	164	47	1.90	1.43	340	2.40	126	1.66	116	1.70
133	F	74	160	164	62	2.10	1.54	310	2.30	110	1.75	114	1.77
134	F	69	151	16	86	2.44	1.50	290	2.27	93	1.77	18	1.69
135	M	79	178	178	79	3.30	1.92	290	2.90	88	1.72	90	1.70
136	F	71	172	178	76	2.52	1.85	270	2.29	91	1.70	92	1.63
137	M	79	182	188	89	3.50	2.02	360	1.71	49	1.35	67	1.33
138	F	77	169	178	55	2.25	1.65	230	2.22	99	1.49	90	1.49
139	F	84	151	162	65	1.55	1.15	280	1.94	125	1.49	130	1.53
140	M	69	158	175	61	3.10	2.15	375	3.46	112	2.16	100	2.23
141	F	68	164	172	63	3.10	1.95	580	3.27	105	2.58	132	2.62
142	F	66	153	160	65	2.60	1.70	330	2.37	91	1.87	110	1.94
143	F	72	157	160	74	2.10	1.53	290	2.34	111	1.77	116	1.73
144	F	80	153	158	70	1.70	1.28	300	1.95	115	1.45	113	1.45
145	F	67	147	158	63	2.30	1.40	150	1.96	85	1.70	121	1.54
146	F	88	157	163	62	1.60	1.15	110	2.20	137	1.74	151	1.68
147	F	74	153	158	75	1.90	1.40	330	2.56	135	2.07	148	2.04
148	F	76	162	168	67	2.25	1.65	300	2.65	118	1.95	118	1.98
149	F	81	151	154	69	1.62	1.22	260	1.71	105	1.25	102	1.22
150	M	66	170	176	75	3.80	2.68	520	4.15	109	3.00	112	3.08
151	M	73	181	190	79	3.75	2.25	450	3.68	98	2.70	120	2.70
152	M	71	174	174	70	3.42	2.08	510	4.22	123	3.00	144	2.92
153	M	83	176	176	74	2.90	1.65	480	3.86	133	3.02	183	3.02
154	M	76	178	188	90	3.48	2.05	340	3.86	111	2.90	141	2.85
155	M	76	169	173	66	3.15	1.84	340	2.26	72	1.51	82	1.52
156	M	75	166	169	75	3.10	1.80	550	2.97	96	2.18	121	2.32
157	M	84	175	189	68	2.95	1.65	380	3.16	107	2.32	141	2.22
158	M	75	178	174	63	3.20	2.10	540	3.60	112	2.40	114	2.48
159	M	75	163	171	63	2.95	1.93	420	3.80	129	2.32	120	2.23
160	F	85	163	168	76	1.80	1.34	330	2.91	162	1.93	144	1.88

I.D.	PENULT FEV1 (%SAL)	PENULT DOSE (umol)	FINAL PEFR (% INITIAL)	FINAL FEV1 (%SAL)	FINAL DOSE (umol)	POST BD PEFR (%INIT)	POST BD FEV1 (%SAL)	% DECREASE PEFR	% DECREASE FEV1	PD20 FEV1 (umol)
118	82	0.048	61	75	0.096	100	107	39	25	0.059
119	83	0.096	77	65	0.192	98	97	23	35	0.108
120	83	0.096	57	79	0.192	114	100	43	21	0.161
121	91	0.096	44	72	0.383	52	108	56	28	0.214
122	95	0.096	37	71	0.383	84	119	63	29	0.228
123	78	0.383	80	61	0.767	110	102	20	22	0.353
124	85	0.192	88	80	0.383	102	98	12	20	0.383
125	88	0.192	58	80	0.383	100	95	42	20	0.383
126	91	0.383	57	62	1.53	98	98	43	38	0.65
127	93	0.383	76	79	0.767	118	103	24	21	0.73
128	98	0.383	57	74	1.53	104	97	43	26	0.988
129	84	0.767	120	78	1.53	153	91	0	22	1.22
130	91	0.383	72	78	1.53	105	100	28	22	1.24
131	85	1.53	51	72	3.07	68	107	49	28	2.00
132	82	1.53	94	78	3.07	103	90	6	22	2.17
133	86	1.53	84	78	3.07	103	104	16	22	2.58
134	91	1.53	96	79	3.07	103	98	4	21	2.90
135	84	1.53	90	80	3.07	128	99	10	20	3.07
136	94	1.53	68	77	6.13	93	97	32	23	4.80
137	96	3.07	64	78	6.13	106	109	36	22	5.68
138	89	3.07	91	79	6.13	137	104	9	21	5.72
139	83	3.07	61	80	6.13	100	91	39	20	6.13
140	88	3.07	93	80	6.13	113	94	7	20	6.13
141	82	3.07	53	80	6.13	79	101	47	20	6.13
142	86	3.07	58	88	6.13	103	93	42	12	>MAX
143	94	1.53	97	88	6.13	110	102	3	12	>MAX
144	99	1.53	120	106	6.13	117	115	0	0	>MAX
145	101	1.53	92	84	6.13	116	97	8	16	>MAX
146	111	1.53	136	111	6.13	182	112	0	0	>MAX
147	94	1.53	82	96	6.13	112	102	18	4	>MAX
148	96	1.53	113	87	6.13	110	95	0	13	>MAX
149	95	3.07	108	85	6.13	115	104	0	15	>MAX
150	98	1.53	92	97	6.13	99	97	8	3	>MAX
151	96	3.07	67	88	6.13	98	109	33	12	>MAX
152	92	1.53	88	84	6.13	106	97	12	16	>MAX
153	89	1.53	77	91	6.13	102	101	23	9	>MAX
154	89	1.53	100	97	6.13	109	101	0	3	>MAX
155	89	3.07	59	84	6.13	88	102	41	16	>MAX
156	100	1.53	94	104	6.13	98	150	6	0	>MAX
157	90	3.07	75	84	6.13	95	99	25	16	>MAX
158	87	3.07	83	91	6.13	98	99	17	9	>MAX
159	92	3.07	86	90	6.13	102	102	14	10	>MAX
160	92	1.53	89	84	6.13	100	94	11	16	>MAX

I.D.	SEX	AGE (YRS)	HT (CM)	SPAN (CM)	WT (KG)	PREDICTED FVC (L)	PREDICTED FEV1 (L)	INITIAL PEFR (L/MIN)	INITIAL FVC (L)	INITIAL FVC (%PRED)	INITIAL FEV1 (L)	INITIAL FEV1 (%PRED)	POST BD PEFR (%INIT)	POST BD FVC (%INIT)	POST BD FEV1 (%INIT)
NOT CHALLENGED															
161	F	94	148	158	43	1.30	1.00	110	1.62	125	1.15	115	91	96	104
162	F	82	156	172	54	1.70	1.30	170	1.72	101	0.73	56	109	113	114
163	M	67	187	198	77	4.62	3.25	550	4.96	107	3.76	116	96		105
164	M	80	175	184	86	3.15	1.80	180	1.98	63	0.98	54	144	113	105
165	F	79	162	167	74	1.95	1.45	120	1.32	68	0.94	65	117	104	120
166	F	87	142	153	44	1.28	0.97	255	1.76	137	1.48	152	110	108	101
167	F	85	147	152	52	1.43	1.08	50	1.60	112	0.98	91	300	119	112
168	F	88	155	154	49	1.50	1.14	150	1.44	96	1.22	107	67	64	100
169	F	89	141	156	56	1.20	0.92	100	1.75	146	1.08	117	105	99	123
170	M	79	174	170	85	3.20	1.84	220	2.78	87	0.93	50	118	231	105
171	M	75	161	168	70	2.90	1.70	50	1.59	55	0.75	44	240	93	91
172	F	70	150	150	48	1.95	1.45	100	2.08	107	0.92	63	100	112	101
173	F	71	146	152	40	1.73	1.32	120	1.27	73	0.78	59	121	117	110
174	M	73	175	185	71	3.52	2.12	10	2.20	62	0.80	38	115	101	119
175	F	81	158	169	51	1.80	1.37	50	1.97	109	0.50	36	60	105	100
176	F	69	163	173	77	3.00	1.90	155	1.58	53	0.88	46	123	123	133
177	M	76	160	163	79	2.77	1.62	280	0.90	32	0.82	51	121	130	120
178	F	74	159	166	70	2.03	1.50	100	2.12	104	0.83	55	135	106	111
179	F	65	154	162	52	2.65	1.70	20	1.05	40	0.30	18	100	116	100
180	F	83	153	154	49	1.62	1.22	150	0.98	60	0.72	59	100	113	107