Effects of smoking on changes in respiratory resistance with increasing age

C. I. COE, A. WATSON, H. JOYCE AND N. B. PRIDE

Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London

SUMMARY

1. The oscillation method for measuring total respiratory resistance ($R_{rs}$) is a simple method of assessing airway dimensions which can be applied in epidemiological surveys and potentially might be useful for detecting mild airway disease in smokers. However, it is not known whether abnormalities in $R_{rs}$ are only present when there are other abnormalities in simple spirometric tests.

2. We have compared values of $R_{rs}$ and its frequency-dependence ($f_{R}$) using the oscillation technique applied over the frequency range 6-26 Hz in 42 healthy, non-asthmatic men who were never-smokers (aged 26-61 years) and in 41 male cigarette smokers (aged 32-64 years). The results were compared with those for spirometry and the single-breath $N_{2}$ test which are the most commonly used techniques in epidemiological surveys for detecting the effects of smoking on the lungs.

3. There was a strong trend for $R_{rs}$ (especially at lower oscillation frequency) and $f_{R}$ to increase with increasing age in smokers. Increases in $R_{rs}$ and $f_{R}$ were usually present when forced expiratory volume in 1 s was less than 80% of predicted and the forced expiratory volume in 1 s/vital capacity ratio was less than 65%, but abnormal $f_{R}$ was present in some smokers whose spirometry was within conventional normal limits.

4. Abnormalities in $R_{rs}$ and $f_{R}$ were weakly associated with abnormality of the single-breath $N_{2}$ manoeuvre.

5. Abnormal $f_{R}$ is normally attributed to uneven narrowing of intrathoracic airways; however, in smokers it was associated with an increase in $R_{rs}$ at 6 Hz, so we cannot exclude that some of the observed abnormal $f_{R}$ was due to increased dissipation of the applied pressure in the cheeks and extrathoracic airway rather than to inhomogeneities within the lungs.

6. We conclude that the oscillation technique detects abnormalities indicating airway narrowing in some smokers whose spirometry is within normal limits. Hence the technique could be useful in screening programmes aiming to detect early lung damage. The prognostic significance of the additional information provided by measuring $R_{rs}$ needs to be further assessed.

Key words: ageing, airway mechanics, smoking.

INTRODUCTION

An early manifestation of smoking-induced lung damage is inhomogeneity of mechanical properties. This leads to frequency-dependent behaviour of the lung, with a fall in values of compliance and resistance as frequency of breathing is increased. Frequency-dependence of lung compliance is a sensitive test of lung inhomogeneity and is often abnormal in young smokers with normal spirometry [1], but the technique is technically demanding and requires oesophageal intubation, preventing its widespread application. Measurement of the frequency-dependence ($f_{R}$) of respiratory resistance ($R_{rs}$) using forced oscillation is technically much simpler and non-invasive and with modern microcomputer techniques can be obtained rapidly [2]. Several earlier studies have found $R_{rs}$ is not often abnormal in healthy smokers less than 45 years old [3-5], suggesting that the technique is less sensitive to inhomogeneity of the peripheral airways than tests such as frequency-dependence of compliance and the single-breath $N_{2}$ test [SBN$_{2}$] [6], which are frequently abnormal in younger smokers. However, it is uncertain whether minor changes in lung mechanics in younger smokers reliably predict the later development of progressive airflow obstruction [7, 8] and evolution of
changes in $R_a$ and $f_k$ in comparison with other tests of lung function in middle-aged smokers is unknown. We have compared values of $R_a$ and $f_k$ in young and middle-aged smokers with values found in a group of healthy never-smokers of a similar age range in order to establish how smoking influences changes in $R_a$ and $f_k$ with age. In smokers we have also compared abnormalities in $R_a$ with spirometry and SBN.

**EXPERIMENTAL**

**Subjects**

Forty-two men aged between 26 and 61 years, who were healthy, gave no history of respiratory symptoms or disease and were life-long non-smokers, were recruited from those attending a previous survey [9] or from men working at the Royal Postgraduate Medical School. Results in these men were compared with those found in 41 current male cigarette smokers aged between 32 and 64 years. All were working in West London and participating in a long-term study of the effects of smoking [9]. Men with other confounding respiratory disease (e.g. multiple rib fractures, ankylosing spondylitis, etc.), with a diagnosis of asthma or receiving broncho-active drugs were excluded, but smokers with chronic cough or abnormal spirometry without other evident cause were included. All men gave informed consent and the procedure was approved by the Research Ethics Committee of the Royal Postgraduate Medical School. Anthropometric details of men aged above and below 45 years are shown in Table 1. Mean (sd) pack years of smoking was 24 (15) in the group of smokers less than 45 years old and 44 (14) in smokers more than 45 years old.

**Methods**

The forced oscillation technique and equipment described by Landser et al. [2] was used to obtain $R_a$, $f_k$ and the resonant frequency. The subject, wearing a nose-clip, was seated and breathed tidally on a mouthpiece attached to the oscillation apparatus. To minimize dissipation of the applied pressure in the upper airway, the cheeks and floor of the mouth were supported by the palms of the hand, and the head and neck were slightly extended. The oscillation apparatus consisted of a loudspeaker which was attached to a tube leading to a screen pneumotachograph adjacent to the mouthpiece. A bias flow introduced through a side-arm and extracted via a second side-arm prevented changes in inspired $O_2$ and $CO_2$. A complex signal of sinusoidal sound-wave oscillation containing all harmonics of 2 Hz up to 26 Hz was applied by the loudspeaker. This signal was presented as preprogrammed pseudo-random noise, the sequence being repeated every 0.5 s for a 16 s period. The peak-to-peak amplitude of the applied pressure was less than 2 cmH$_2$O. During oscillation, impedance (ratio of the amplitudes of applied pressure and flow) of the subject's respiratory system was obtained from measurements of mouth pressure (from a lateral port close to the mouth-
and flow were measured with identical differential pressure transducers (Validyne MP45). The apparatus was checked to ensure that the response of both transducers and attached tubing was matched at all frequencies up to 26 Hz using a reference linear resistance. The pressure and flow signals were fed into a Fourier analyser, ensemble averaged over the measurement period of 16 s and calculated to give values of impedance at 2 Hz intervals from 2 to 26 Hz. The impedance signal was further analysed as the in-phase component of pressure and flow (resistance) and the out-of-phase component (reactance) [10]. The oscillatory frequency at which reactance is zero is resonant frequency. In this study we only used reactance values to obtain resonant frequency. The in-phase component of the signal (resistance) is an index of airway dimensions analogous to resistance derived by other methods such as body plethysmography. The reliability of the derived values is indicated by a coherence function for each frequency. This function is the equivalent in the frequency domain of the correlation coefficient used in the time domain. The derived values are the mean values of inspiratory and expiratory resistance over the several breaths of the 16 s period and include glottal changes. Three consecutive sets of measurements over 16 s were made while the subject breathed quietly and continuously on the mouthpiece for approximately 2 min and the mean value was calculated and reported. Reliable results with a coherence function >0.95 were not obtained in all subjects at 2 and 4 Hz, so we have used only the results at 6 Hz and higher frequencies. To monitor absolute lung volume and breathing pattern during $R_{ns}$ measurement, the flow signal was integrated to obtain tidal volume and displayed on a strip chart recorder; at the end of each 2 min measurement period full inspirations and expirations were made to place tidal volume in relation to the vital capacity (VC).

Forced expiratory volume in 1 s (FEV$_i$) and slow expiratory VC were measured using a dry spirometer and the highest value from three manoeuvres is reported and compared with reference values [11]. In smokers only, SBN$_2$ was performed using a standard technique [9]; the results reported are of the slope of the alveolar plateau (phase III) expressed as change in fractional concentration of N$_2$ per litre expired (% N$_2$/l).

Statistical analysis was performed using the Wilcoxon sum of ranks test.

RESULTS

Spirometry and mid-tidal lung volume

Values of FEV$_i$ and FEV$_i$/VC ratio were in the normal range in never-smokers and in smokers aged less than 45 years, but there was evidence of airflow obstruction (reduced FEV$_i$ and FEV$_i$/VC ratio) in the older smokers (Table 1). The mid-tidal lung volume (the mean volume at which $R_{ns}$ was measured) was 40% of VC in never-smokers and 49% of VC in smokers.

Frequency dependence of $R_{ns}$

In never-smokers mean values of $R_{ns}$ were approximately constant between 6 and 16 Hz (Fig. 1 and Table 1) and showed a slight rise at higher frequencies. In smokers, mean $R_{ns}$ was higher than in never-smokers at all frequencies but the pattern of change in $R_{ns}$ was different with a fall in $R_{ns}$ between 6 and 16 Hz and a slight rise at higher frequencies. Subdividing the smokers and never-smokers into those aged below and above 45 years (Fig. 1), older never-smokers had slightly greater mean $R_{ns}$ than young never-smokers at frequencies between 6 and 16 Hz. Younger smokers had a very similar mean pattern to older never-smokers, whereas older smokers had higher values of $R_{ns}$ at all frequencies and often a fall in $R_{ns}$ between 6 and 16 Hz. Because of the biphasic nature of these $R_{ns}$-frequency curves, we elected to express $R_{ns}$ as the change between 6 and 16 Hz ($f_{R_{ns}-6-16}$). Using the six values of mean $R_{ns}$ between 6 Hz and 16 Hz obtained in each individual we derived the slope (cmH$_2$O 1$^{-1}$ s Hz$^{-1}$) by linear regression. Slopes were recorded as negative if resistance fell with increasing frequency and positive if resistance rose as frequency increased. The lower 95% tolerance interval for $f_{R_{ns}-6-16}$ for the never-smokers was −0.07 cmH$_2$O 1$^{-1}$ s Hz$^{-1}$ fall in $R_{ns}$ between 6 and 16 Hz. An abnormal $f_{R_{ns}-6-16}$ was found in 13 smokers (Fig. 2) and the difference from never-smokers was highly signifi-

![Fig. 1](image-url)
cant (Table 2). There was a gross abnormality of $f_R$ in two never-smokers; these men also had the highest $R_\infty$ of the never-smokers but FEV$_1$ as a percentage of predicted (FEV$_1$ % pred.) was 80% and 94%, respectively, and there was no clinical suggestion of asthma. Differences in $f_R$ between smokers and never-smokers were found in subjects aged less than 45 years as well as in the older age group.

$R_n$ at 6 Hz ($R_{n,6}$) (Fig. 3 and Table 1)

In healthy never-smokers $R_{n,6}$ showed little change between 25 and 50 years (Fig. 3), but some never-smokers older than this showed higher values. In smokers there was a bigger spread of values of $R_{n,6}$ at all ages and a tendency for higher values to be found in late middle-age. The difference between never-smokers and smokers was highly significant when all ages were considered and when analysis was confined to men older than 45 years but the mean difference in $R_{n,6}$ in men aged less than 45 years did not reach statistical significance (Table 2). There was no relation between $R_n$ and height in either group of subjects. Overall there was a strong inverse relationship between $f_{R_{n,6}}$ and the value of $R_{n,6}$ ($r = -0.81$) (Fig. 4).

$R_n$ at 16 Hz ($R_{n,16}$)

$R_{n,16}$ was also higher in smokers than in never-smokers because of a trend to higher values in older smokers (Tables 1 and 2 and Fig. 1).

Resonant frequency of the respiratory system (Tables 1 and 2)

This showed a small rise with age in never-smokers and a larger rise with age in smokers. Differences between smokers and never-smokers were significant in the older but not the younger subjects.

Relation between values of $R_{n,6}$ and $f_{R_{n,6-16}}$ and spirometry (Table 3)

There were no significant relationships among $R_{n,6}$, $f_{R_{n,6-16}}$, FEV$_1$ (as a percentage of predicted) and the FEV$_1$/VC ratio in the never-smokers.

For the total group of smokers, $R_{n,6}$ was significantly negatively related to FEV$_1$ % pred. and to FEV$_1$/VC ratio; these relationships were slightly strengthened by confining analysis to the older smokers (aged more than 45 years). The relations of $f_{R_{n,6-16}}$ to FEV$_1$ % pred. and FEV$_1$/VC ratio in the total group of smokers were also slightly strengthened by restricting analysis to older smokers. Five smokers with FEV$_1$ % pred. more than 80% or FEV$_1$/VC ratio greater than 65% had abnormal $f_{R_{n,6-16}}$ (Fig. 5).

For the total group of smokers and never-smokers the relationships of $R_{n,6}$ to FEV$_1$ % pred. ($r = -0.58$) and FEV$_1$/VC ratio ($r = -0.50$) were similar to those between $f_{R_{n,6-16}}$ and FEV$_1$ % pred. ($r = 0.56$) and FEV$_1$/VC ratio ($r = 0.51$).

Table 2. Statistical analysis of differences between smokers and never-smokers for tests of oscillation mechanics

$P$ values were obtained using the Wilcoxon rank sum test. Abbreviation: ResFr, Resonant frequency of total respiratory system.

<table>
<thead>
<tr>
<th></th>
<th>$R_{n,6}$</th>
<th>$R_{n,16}$</th>
<th>$f_{R_{n,6-16}}$</th>
<th>ResFr</th>
</tr>
</thead>
<tbody>
<tr>
<td>All never-smokers vs all smokers</td>
<td>0.0003</td>
<td>0.049</td>
<td>0.0001</td>
<td>0.003</td>
</tr>
<tr>
<td>Never-smokers &lt;45 years vs never-smokers &gt;45 years</td>
<td>0.42</td>
<td>0.43</td>
<td>0.85</td>
<td>0.023</td>
</tr>
<tr>
<td>Smokers &lt;45 years vs smokers &gt;45 years</td>
<td>0.073</td>
<td>0.12</td>
<td>0.18</td>
<td>0.008</td>
</tr>
<tr>
<td>Never-smokers &lt;45 years vs smokers &lt;45 years</td>
<td>0.065</td>
<td>0.46</td>
<td>0.0033</td>
<td>0.13</td>
</tr>
<tr>
<td>Never-smokers &gt;45 years vs smokers &gt;45 years</td>
<td>0.004</td>
<td>0.099</td>
<td>0.0002</td>
<td>0.032</td>
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</table>
Relation between values of $R_n$ and $f_R$ and SBN$_2$ in smokers

Results of SBN$_2$ were available in 39 of the 41 smokers. The mean value in the 12 smokers younger than 45 years was 1.2% N$_2$/l and in 27 smokers older than 45 years 2.5% N$_2$/l. The relations between $R_{n,6}$ and SBN$_2$ and $f_{R,6-16}$ and SBN$_2$ (Fig. 5) were weaker than with spirometry (Table 3). Values of SBN$_2$ were, however, related to those of FEV$_1$ % pred. ($r=0.75$) and FEV$_1$/VC ratio ($r=0.69$).

DISCUSSION

We found a strong trend for $R_n$ and $f_R$ to increase with increasing age in male smokers. Elevation of $R_{n,6}$ was associated with impairment of spirometry and with abnormal $f_R$.

Physiological significance of $R_n$

In the oscillation method we used the flow generated in response to the application of pressure is influenced by the resistance of the whole respiratory system (mouth, extrathoracic airway, intrathoracic airways, lung tissue and chest wall); the values obtained therefore are systematically higher than those obtained with body plethysmography (which measures resistance of the airways alone usually during panting which reduces the laryngeal component [12]) or with the oesophageal balloon technique (which measures resistance of the airways and lung tissue). However, it has been shown that chest wall resistance remains normal in older patients with severe airflow obstruction [13], so it is probable that the higher values of $R_n$ observed in the present study with increasing age or with smoking are due to increase in the resistance of airways or lung tissue.

The values of $R_n$ obtained represent the average resistance during spontaneous tidal breathing. Although there are changes in glottal aperture and lung volume during tidal breathing, a strength of the oscillation technique we used is that each derived value is the average of 96 measurements made at 0.5 s intervals over three 16 s periods of tidal breathing. Other measurements of resistance are usually derived from many fewer breathing cycles.

Our results are presented simply as values of $R_n$ without any correction for lung volume or the height of the subject. If the mid-tidal lung volume is known, the

![Graph](image_url)

Fig. 3. Values of $R_{n,6}$ in individual never-smokers ($a$) and in current cigarette smokers ($b$).

![Graph](image_url)

Fig. 4. Relation between $R_{n,6}$ and $f_{R,6-16}$ in smokers ($\square$) and never-smokers ($\bullet$).

| Table 3. Relation among values of $R_{n,6}$, $f_{R,6-16}$, spirometry and SBN$_2$ in smokers |
|-----------------------------------------------|---------------|----------------|---------------|
| $n$                                          | $R_{n,6}$     | $f_{R,6-16}$  |
| All smokers                                  | FEV$_1$ %pred.| 41             | -0.56         |
| All smokers                                  | FEV$_1$/VC    | 41             | -0.49         |
| All smokers                                  | SBN$_2$       | 39             | 0.40          |

| Smokers older than 45 years                   | FEV$_1$ %pred.| 29             | -0.59         |
| Smokers older than 45 years                   | FEV$_1$/VC    | 29             | -0.51         |
| All smokers                                  | SBN$_2$       | 39             | -0.33         |
have higher absolute values of conductance. This adjustment will be important in comparing values of the never-smokers, presenting the comparisons as higher in the VC (and closer to total lung capacity) than lung volumes. Because smokers were breathing tidally, this underestimates the differences in specific FEV1/VC ratio (and size of the conducting airways) or its reciprocal, specific respiratory conductance at functional residual capacity. When the results are expressed as specific airway resistance or conductance no consistent change with increasing age has been observed [14, 15]. This apparent constancy of airway dimensions occurs despite a fall in lung recoil pressure at functional residual capacity with increasing age [15]; because lung recoil pressure is the effective pressure distending the intrapulmonary airways, reduction in this pressure would be expected to decrease intrapulmonary airway dimensions unless there was a similar alteration in the radial distensibility of the airways, so that a reduced transmural pressure was required to achieve a given calibre in the airways in the ageing lung.

The values of \( R_n \) we found in never-smoking men were similar to those previously reported [10]. There was a slight tendency (not statistically significant) for \( R_n \) to be higher in older than younger never-smokers. Larger studies and particularly more subjects aged over 50 years would be required to establish whether there is truly a rise in \( R_n \) in healthy older subjects.

Changes in \( R_n \) in smokers

In agreement with most [3-5] but not all [16] previous studies, there was only a weak trend for values of \( R_n \) at 6 Hz and 16 Hz to be higher in young smokers than young never-smokers, though in smokers abnormal frequency-dependence was sometimes present. But by late middle-age many of the smokers we examined had raised values of \( R_n \) and an abnormal decline in \( R_n \) with increasing frequency. These abnormalities in \( R_n \) were broadly related to impaired spirometry, though \( R_n \) could be considerably increased when spirometry remained within conventional normal values. However, a larger group would need to be studied to determine if measurement of \( R_n \) provided additional information for the detection of mild lung disease in smokers. The smokers we studied were not a population sample and were biased towards heavy smokers; nevertheless the changes in \( R_n \) we found were sufficiently common and obvious to imply that a considerable number of middle-aged smokers in the general population must show these abnormalities.

Significance of \( F_R \)

Otis et al. [17] in their classic analysis considered the effects of parallel inhomogeneity of lung mechanical properties on \( f_R \) and their analysis has been further developed by Peslin [18] and Bates et al. [19]. These analyses suggest that at slow frequencies of breathing inhomogeneity of ventilation and mechanical properties contribute to the observed values of resistance, while true narrowing of conducting airways is better reflected by values of resistance at higher frequencies. Above resonant frequency, however, the effects of inertance (pressure dissipation due to acceleration of flow) increase and may come to dominate the measurement [20] so that we have compared values of \( R_{n,16} \) to estimate the true size of the conducting airways (see Fig. 1 which indicates

values of \( R_n \) can be presented as specific \( R_n \) (\( R_n \times \) absolute volume) or its reciprocal, specific respiratory conductance. This adjustment will be important in comparing more heterogeneous groups of subjects, such as when studying mixed groups of men and women, as women have higher absolute values of \( R_n \) because of their smaller lung volumes. Because smokers were breathing tidally higher in the VC (and closer to total lung capacity) than the never-smokers, presenting the comparisons as \( R_n \) underestimates the differences in specific \( R_n \) between the two groups.

Changes in resistance with age in normal subjects

Most existing data on changes in resistance with increasing age in normal subjects have been obtained using body plethysmography measuring airways resistance at functional residual capacity. When the results are expressed as specific airway resistance or conductance no consistent change with increasing age has been observed [14, 15]. This apparent constancy of airway dimensions occurs despite a fall in lung recoil pressure at functional residual capacity with increasing age [15]; because lung recoil pressure is the effective pressure distending the intrapulmonary airways, reduction in this pressure would be expected to decrease intrapulmonary airway dimensions unless there was a similar alteration in the radial distensibility of the airways, so that a reduced transmural pressure was required to achieve a given calibre in the airways in the ageing lung.

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that all subgroups show some rise in $R_n$ above 18 Hz). Values of $R_{n,16}$ were higher in smokers as a group and this appeared to be mainly due to increases in older smokers, but larger groups would be required to confirm this as comparison of the values in older smokers and never-smokers did not reach statistical significance.

$f_R$ with large falls in $R_n$, as frequency is increased (equivalent to $f_R, h^{-1} s$ more negative than $-0.07 \text{ cmH}_2\text{O} s^{-1} \text{ Hz}^{-1}$), are found in symptomatic patients with airflow obstruction [13, 21-23], but recent work by Peslin et al. [24] has suggested that lesser degrees of $f_R$ may be due to increased dissipation of pressure in the upper airways [13, 21-23].

there was a close relation between elevation of $R_{n,6}$ and abnormal $f_R$ (Fig. 4). This possibility obviously confounds the pathophysiological significance of abnormal $f_R$ because it might also be found with tracheal obstruction [25], while differences in cheek and upper airway airflow obstruction [13, 21-23], but recent work by Peslin et al. [24] has suggested that lesser degrees of $f_R$ may be due to increased dissipation of pressure in the upper airways when intrapulmonary resistance is raised. We cannot exclude this explanation for our own results as there was a close relation between elevation of $R_{n,6}$ and abnormal $f_R$ (Fig. 4). This possibility obviously confounds the pathophysiological significance of abnormal $f_R$ because it might also be found with tracheal obstruction [25], while differences in cheek and upper airway airflow obstruction (and hence the extent of pressure dissipation) in the population [26] presumably add a further variable. Nevertheless, although this upper airway effect may exaggerate the true $f_R$ of intrathoracic resistance, it increases the discriminatory value of $f_R$ as a simple, empirical test, which was frequently abnormal in smokers with normal spirometry. Recently it has been suggested that discrimination between smokers and never-smokers can be further increased by comparing $f_R$ breathing air and breathing a helium-oxygen mixture [27].

Association of changes in $R_n$ with other tests of mechanical function of the lungs

In most of the smokers we measured three tests indicating inhomogeneity of lung mechanical properties: $f_R$ in all 41 men, SBN in 39 of the men, and in 33 of the men we also obtained $^{81}K$ Kr scans to indicate regional distribution of ventilation [28], K scans were obtained on a separate occasion from the other tests. There was a relatively weak inverse association between abnormal $f_R$ and the SBN (Fig. 5). An abnormal distribution of regional ventilation during tidal breathing as shown by Kr scans was present in 13 of the 33 smokers examined and was shown by 16 of 27 smokers with abnormal $f_R$ but by only two of six smokers without abnormal $f_R$. Hence the results of all three tests confirmed that inhomogeneity of mechanical properties was commonly present in these smokers, though, as expected from the differing conditions during measurement, concordance between the three methods was loose. Associations between abnormal $f_R$ raised $R_{n,6}$ and impaired spirometry were stronger (Fig. 5).

There are theoretical grounds for expecting $f_R$ to be a less sensitive test for detecting minor abnormalities than frequency-dependence of compliance, because peripheral airways (where the first pathological changes are believed to occur in smokers [29]) account for only a small proportion of normal total respiratory resistance, which includes glottal and chest wall resistance, but can play an important role in affecting the distribution of ventilation.

In summary, the present results show that $R_n$ is often raised in middle-aged smokers and this rise is associated with enhanced decline in $R_n$ with increasing frequency of oscillation. The oscillation technique is easy to apply and suitable for epidemiological surveys. Abnormal $f_R$ was almost always present when FEV$_1$/VC ratio was less than 80% or FEV$_1$/VC ratio was less than 65% and was sometimes present in smokers when spirometry was within conventional normal limits. Larger studies with long-term follow-up would be required to establish the usefulness of the oscillation technique in screening programmes for detecting smoking-related lung damage.

ACKNOWLEDGMENTS

This work was supported by grants from the Medical Research Council (G8404057SA) and the Asthma Research Council.

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