

Bronchial reactivity to inhaled histamine and annual rate of decline in FEV₁ in male smokers and ex-smokers

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ABSTRACT We examined the relations between bronchial reactivity, baseline FEV₁, and annual decline of height corrected FEV₁ (Δ FEV₁/ht³) over 7.5 years in 227 men (117 smokers, 71 ex-smokers, and 39 non-smokers). Men with a clinical diagnosis of asthma or receiving bronchodilator treatment were excluded. Bronchial reactivity was determined as the provocation concentration (PC₂₀) of inhaled histamine sufficient to reduce FEV₁ by 20%; subjects were divided into reactors (PC₂₀ \leq 16 mg/ml) and non-reactors (PC₂₀ > 16 mg/ml). Thirty per cent of smokers, 24% of ex-smokers, and 5% of non-smokers were reactors. When smokers who were reactors were compared with non-reactors, the reactors showed a lower baseline FEV₁ as percentage predicted in 1981-2 (85% v 108%), and a faster Δ FEV₁/ht³ (14.1 v 9.2 ml/y/m³). Baseline FEV₁ correlated with PC₂₀ in both smokers ($r_s = 0.51$) and ex-smokers ($r_s = 0.61$), and all 15 subjects with an FEV₁ under 80% of the predicted value were reactors. In ex-smokers Δ FEV₁/ht³ was similar in reactors and non-reactors (m 9.0 v 7.4 ml/y/m³), despite significant differences in baseline FEV₁. When analysis was confined to men with a baseline FEV₁ over 80% predicted, the prevalence of reactors was significantly increased among smokers and slightly increased among ex-smokers compared with non-smokers, though the mean FEV₁ was higher in the non-smokers. Bronchial reactivity was not increased in smokers aged 35 years or less. In smokers Δ FEV₁/ht³ was faster in those with a personal history of allergy (usually allergic rhinitis), but was not related to a family history of allergic disease, total serum immunoglobulin E level, absolute blood eosinophil count, or skinprick test score. Δ FEV₁/ht³ was also faster in all subjects taking beta blocker drugs. Thus increased bronchial reactivity was associated with accelerated decline of FEV₁ in smokers. Although the association could be a consequence of a lower baseline FEV₁, a trend towards increased reactivity was found in smokers with normal baseline FEV₁ and Δ FEV₁/ht³ was dissociated from increased reactivity in ex-smokers. These findings are compatible with the "Dutch hypothesis," but the association between allergic features and accelerated Δ FEV₁/ht³ was relatively weak, and increased reactivity may follow rather than precede the onset of smoking.

An overall relationship between cigarette smoking and the development of chronic airflow obstruction has been established.¹ Nevertheless, there is a very wide range of susceptibility to progressive airflow obstruction among smokers, the cause of which is unknown. More than 20 years ago Dutch research workers² proposed that smokers with chronic and largely irreversible airflow obstruction shared with

asthmatic patients a common allergic constitution and increased non-specific bronchial reactivity (the "Dutch hypothesis"). Although patients with established chronic airflow obstruction do have increased airway reactivity,³⁻⁶ it is not clear whether this is a cause or a consequence of airway narrowing. Epidemiological studies in Tucson have shown that atopy is associated with an increased prevalence of airflow obstruction in smokers⁷ and that blood eosinophilia is associated with respiratory symptoms, and with impairment of ventilatory function regardless of smoking habit.⁸ Although an earlier study from our department concluded that allergy

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contributed little to the development of chronic airflow obstruction in smokers,¹ more recently we found that smokers with an allergic disposition showed an accelerated rate of decline in lung function.⁹

We have therefore extended our studies to a further group of men, who were participating in a different long term follow up of pulmonary function. The prevalence of various allergic features in these men is described elsewhere.¹⁰ In summary, smokers had increased blood eosinophil counts (out of proportion to the increase in total white blood cell counts), while smokers and ex-smokers with negative skinprick test reactions to common allergens had slightly higher serum total immunoglobulin E (IgE) levels than did skintest negative non-smokers. The prevalence of positive skinprick test responses was similar in smokers and non-smokers, although it was greater in ex-smokers. All groups were similar in their personal and family histories of allergic disease. Thus although a few allergic features were associated with smoking habit, most such features appeared to be independent of smoking habit.

In this paper we examine the relationships between bronchial reactivity to histamine, allergic features, smoking habit, and annual decline in spirometric values in these men to obtain evidence for or against the Dutch hypothesis.

Methods

The men studied were originally recruited to a longitudinal study of pulmonary function in 1974¹¹ and had been studied at intervals subsequently. Men with a clinical history of asthma, other important chest illness, or an abnormal chest radiograph were excluded in 1974. Since then three of the men (one smoker, one ex-smoker, and one non-smoker) had developed asthma as assessed by the same questionnaire and have been excluded. Seven other subjects who were included in a companion study¹⁰ were excluded from this study because spirometric measurements were incomplete or influenced by irrelevant factors (such as recent abdominal surgery or rib fractures). There remained for study 227 men, comprising 39 non-smokers (never smoked more than one cigarette a day for a year), 117 smokers (almost all of whom smoked cigarettes), and 71 ex-smokers. The mean (SEM) cigarette consumption of the smokers who smoked cigarettes was 23 (1) per day. Fifty of the ex-smokers had given up smoking since the survey started in 1974, but in this report ex-smokers are not subdivided according to the time elapsed since giving up smoking. Five smokers and five ex-smokers were taking β adrenoceptor blocker drugs.

Bronchial reactivity to inhaled histamine was assessed on the basis of change in forced expiratory volume in one second (FEV_1) to measure the response.¹² The subject wore a noseclip and sat in a booth fitted with an extractor fan. Solutions were nebulised by one of two Wright nebulisers of similar output and inhaled via a short mouthpiece during two minutes of normal tidal breathing. The FEV_1 was recorded on one of two dry bellows spirometers (Vitalograph Ltd), which were checked regularly to establish that their calibration was similar. Results were expressed at BTPS. After baseline spirometry, a control solution of 0.9% sodium chloride was inhaled and spirometry was repeated; after this doubling concentrations of unbuffered, preservative free histamine acid phosphate were given until either the FEV_1 dropped by 20% or the subject inhaled the strongest solution (16 mg/ml) without effect. The initial concentration of histamine used was 2 mg/ml, unless baseline FEV_1 was less than 80% of the predicted value,¹³ when 0.5 mg/ml was used.¹⁴

Reactivity was assessed by measuring the concentration of histamine which provoked a reduction in FEV_1 of 20% (PC_{20}) below the lowest technically satisfactory FEV_1 value obtained after inhalation of saline, and was determined by interpolation of the last two points on a graph of percentage reduction in FEV_1 plotted against histamine concentration expressed logarithmically. The percentage reduction in FEV_1 after inhalation of nebulised histamine 16 mg/ml was also determined. Men with $PC_{20} \leq 16$ mg/ml were classed as reactors and those with $PC_{20} > 16$ mg/ml as non-reactors. Studies were carried out from December 1981 to March 1982.

To calculate baseline $FEV_{1,}$ response to bronchodilator, and the annual loss of $FEV_{1,}$ the largest value of $FEV_{1,}$ was taken on each occasion from a set of three technically satisfactory forced expiratory manoeuvres. Baseline $FEV_{1,}$ in winter 1981–2 was expressed as a percentage of predicted values¹⁵; annual loss of $FEV_{1,}$ ($\Delta FEV_{1,}$, ml/y) was derived by subtracting the winter 1981–2 value from the summer 1974 value,¹¹ dividing by 7.5 to obtain the annual loss, and then standardising for the subject's size by dividing by the cube of the subject's height in metres.¹ Results were therefore expressed as $\Delta FEV_{1,}/ht^3$ in ml/y/m³. The bronchodilator response was determined as the percentage increase above baseline $FEV_{1,}$ after inhalation of salbutamol 400 μ g from a metered dose inhaler; these measurements were made in a previous survey in 1980.

Skinprick tests were performed with nine common inhalant allergens, control, and histamine control; the results were scored according to increasing weal size. Peripheral blood eosinophil counts were

carried out with a Hemalog D automated analyser (Technicon Instruments).¹⁵ Personal and family histories of allergic disease were elicited by questionnaire. Detailed descriptions of these investigations are given elsewhere.¹⁰

Statistical analysis was performed with the χ^2 test with Yates's correction, or Fisher's exact test where numbers were small. For data that were distributed normally, we used Student's *t* test, mean and SEM, and Pearson's (*r*) correlation coefficient; where the distribution was not normal we used Wilcoxon's rank sum test, median and range, and Spearman's (*r_s*) correlation coefficient. The distributions of serum total IgE level and peripheral blood absolute eosinophil count were skewed, and the results were transformed logarithmically for some of the tests.

Results

BASELINE SPIROMETRY AND ANNUAL RATE OF DECLINE IN FEV₁

There were significant differences in mean baseline FEV₁ (winter 1981–2) between smokers, ex-smokers and non-smokers (table 1), the lowest values being in current smokers. The annual rate of decline in FEV₁ (Δ FEV₁/ht³) was significantly greater in smokers than in ex-smokers or non-smokers and showed an inverse correlation with baseline FEV₁ in all three groups (table 1). Daily consumption of cigarettes in smokers was related to Δ FEV₁/ht³ (*r* = 0.23, *p* < 0.02) but not to baseline FEV₁ (*r* = -0.11, *p* > 0.2). There was a weak relationship between baseline FEV₁ and total white cell count in

Table 1 Relation of FEV₁, annual decline in FEV₁, and bronchodilator response to smoking history

		Smokers	Ex-smokers	Non-smokers
1	% predicted FEV ₁ 1982	n Mean SEM	71 107.8 1.9	39 119.1 2.6
2	Δ FEV ₁ /ht ³ 1974–82 ml/year/m ³	Mean SEM	8.0 0.8	6.6 0.6
	Correlation of 1 and 2 (Pearson's correlation coefficient)	<i>r</i> <i>p</i>	-0.36 <0.001	-0.60 <0.001
3	% increase in FEV ₁ after inhaled salbutamol 400 μ g	Mean SEM	3.70 0.46	3.01 0.60
<i>p</i> values (Student's <i>t</i> test)		2	3	
Smokers v non-smokers		<10 ⁻⁸	0.0008	0.02
Smokers v ex-smokers		0.007	0.004	NS
Ex-smokers v non smokers		0.0006	NS	NS
NS—not significant (<i>p</i> > 0.05).				

Table 2 Relation of histamine reactivity to smoking history, FEV₁, and annual Δ FEV₁/ht³

	Reactors (R)	Non reactors (NR)	R v NR
	No (%)	No (%)	
Smokers (S)	34 (29.6)	81 (70.4)	
Ex-smokers (ex-S)	17 (24.3)	53 (75.7)	
Non-smokers (non-S)	2 (5.3)	36 (94.7)	
<i>p</i> values (χ^2 test with Yates's correction)	S v non-S < 0.01, S v ex-S NS ex-S v non-S < 0.05		
	Mean (SEM)	Mean (SEM)	
% predicted FEV ₁ 1982			
Smokers	84.6 (2.7)	108.5 (1.4)	<0.001
Ex-smokers	96.4 (3.6)	111.4 (2.0)	<0.001
Non-smokers	92.0 (9.0)	121.4 (2.4)	—*
<i>p</i> values (Student's <i>t</i> test)	S v non-S — S v ex-S < 0.02 ex-S v non-S —	S v non-S < 0.001 S v ex-S NS ex-S v non-S < 0.01	
Δ FEV ₁ /ht ³ 1974–82 ml/year/m ³			
Smokers	14.1 (1.4)	9.2 (0.7)	<0.01
Ex-smokers	9.0 (1.5)	7.4 (0.8)	NS
Non-smokers	10.1 (7.0)	6.2 (0.7)	—
<i>p</i> values (Student's <i>t</i> test)	S v non-S — S v ex-S < 0.02 ex-S v non-S —	S v non-S < 0.001 S v ex-S NS ex-S v non-S NS	

*Only two non-smokers were reactors.

ex-smokers ($r = -0.28$, $p > 0.05$), but not in smokers ($r = -0.16$) or non-smokers ($r = -0.08$).

REACTIVITY TO INHALED HISTAMINE

Fifty three of the 223 subjects tested were classed as reactors to histamine, the highest prevalence (30%) being found in smokers; but there were also significantly more reactors among ex-smokers than non-smokers (table 2). There was a strong relationship between baseline FEV_1 and reactivity to histamine, all 15 subjects (12 smokers, three ex-smokers) with a baseline FEV_1 under 80% of predicted values being reactors (fig). There was a significant relationship between baseline FEV_1 and values of PC_{20} of 16 mg/ml or less in both smokers ($r_s = 0.51$, $p < 0.01$) and ex-smokers ($r_s = 0.60$, $p < 0.02$). Because of the interrelationship between PC_{20} , baseline FEV_1 and smoking we attempted to dissociate reactivity from the influence of reduced FEV_1 by looking at subjects whose FEV_1 exceeded 80% predicted. In this group, reactors were commoner among smokers (19 reactors, 81 non-reactors; $p < 0.05$) and ex-smokers (14 reactors, 53 non-reactors; $p < 0.1$) than non-smokers (two reactors, 36 non-reactors), though the FEV_1 % predicted was lower in both the smokers (mean (SEM) 105.3% (1.3%); $p < 0.001$) and the ex-smokers

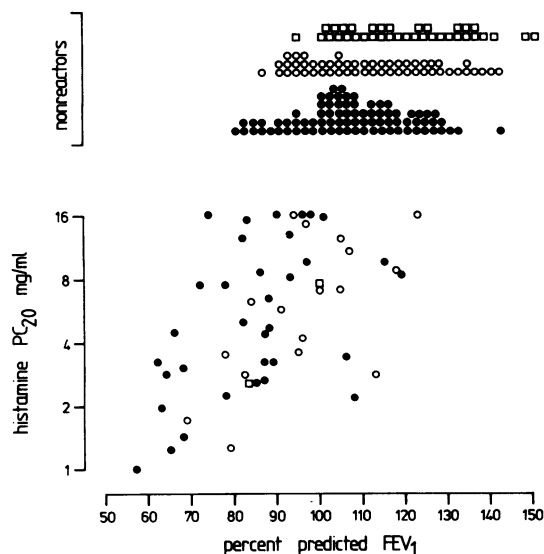
(109.7% (1.8%); $p < 0.01$) than in the non-smokers (119% (2.6%)).

In men with PC_{20} over 16 mg/ml, the percentage reduction in FEV_1 with histamine 16 mg/ml was slightly larger in smokers than in non-smokers ($p > 0.05$); ex-smokers did not differ from either group. Baseline FEV_1 was again significantly higher, however, in the non-smokers than in the smokers and ex-smokers ($p < 0.001$ and < 0.01 respectively), and the reduction in FEV_1 was related to baseline FEV_1 in both smokers ($r = -0.25$; $p < 0.001$) and ex-smokers ($r = -0.35$, $p < 0.01$).

Reactors ($PC_{20} \leq 16$ mg/ml) were not significantly commoner among smokers aged 36 years or more (32 reactors, 67 non-reactors) than among those aged 35 years or less (2 reactors, 14 non-reactors; $p > 0.1$). Although baseline FEV_1 % predicted was lower in the 16 smokers than in the 14 non-smokers aged 35 or less (113.5% (3.6%) v 126.8% (4.0%); $p < 0.02$), there was no significant difference in the prevalence of reactors (two smokers, no non-smokers; $p = 0.6$) or reduction in FEV_1 with histamine 16 mg/ml (5.1% (2.2%), v 4.9% (1.6%); $p > 0.9$).

Some factors were not related to histamine reactivity in smokers or ex-smokers; too few non-smokers reacted to histamine to allow comparison. Daily cigarette consumption was similar in reactive and non-reactive smokers (22.6 (1.6) v 24.0 (1.9) cigarettes/day; $p > 0.5$). The bronchodilator response to salbutamol was not related to PC_{20} values in reactive smokers ($r_s = -0.20$; $p > 0.2$) or ex-smokers ($r_s = -0.20$; $p > 0.5$), or to the reduction in FEV_1 with histamine 16 mg/ml in non-reacting smokers and ex-smokers ($r_s = -0.03$ and 0.11 respectively). Smokers and ex-smokers who were reactors did not differ from non-reactors in personal or family history of allergy, skinprick test results, serum total IgE level, or absolute eosinophil count, or in the proportion taking beta blocker drugs.

Our studies of histamine reactivity were made in the winter, and we were concerned that our results might be influenced by recent upper respiratory infections. Reactivity was not measured in subjects with current symptoms of an upper respiratory infection, but 31% of subjects had had an infection in the previous eight weeks. Reactors were as common, however, among smokers and ex-smokers with recent colds as among those without, and a similar proportion of smokers, ex-smokers, and non-smokers had had colds. We retested seven subjects who were reactors when originally examined within eight weeks of a cold after an interval, and all remained reactors to histamine; PC_{20} values were higher in six and lower in one subject, but the



Relation between bronchial reactivity to inhaled histamine (expressed as PC_{20} —that is, the provocative concentration causing a 20% fall in FEV_1 —in mg/ml) and baseline FEV_1 (expressed as percentages of predicted values) in smokers, ex-smokers, and non-smokers. Non-reactors had PC_{20} values over 16 mg/ml. ●—smokers; ○—ex smokers; □—non-smokers.

changes were small and usually of the order of one doubling concentration of histamine.

REACTIVITY TO INHALED SALBUTAMOL

The percentage increase in baseline FEV₁ after inhaled salbutamol was significantly higher in smokers than in non-smokers, but ex-smokers did not differ from the two other groups (table 1). Smokers with the largest bronchodilator response had the lowest values of baseline FEV₁ ($r_s = -0.33$; $p < 0.01$), and the largest annual $\Delta\text{FEV}_1/\text{ht}^3$ ($r = 0.24$; $p < 0.01$). Ex-smokers with low baseline FEV₁ values also had larger bronchodilator responses ($r = 0.37$; $p < 0.005$), but no such correlation was detected in non-smokers ($r = -0.11$). Annual $\Delta\text{FEV}_1/\text{ht}^3$ was not related to bronchodilator response in ex-smokers ($r = 0.14$) or non-smokers ($r = -0.09$). Bronchodilator response to salbutamol was not related to bronchoconstrictor response to histamine in smokers or ex-smokers, or to age, skintest score, or serum IgE level in any group. Bronchodilator response to salbutamol correlated directly with absolute eosinophil counts in smokers ($r = 0.22$; $p < 0.05$) inversely in ex-smokers ($r = -0.28$; $p < 0.05$) and not at all in non-smokers ($r = 0.04$). The bronchodilator response was not significantly different in smokers or ex-smokers taking beta blocker drugs.

FACTORS RELATED TO ANNUAL DECLINE IN FEV₁

$\Delta\text{FEV}_1/\text{ht}^3$ was greater in smokers than in ex-smokers or non-smokers (table 1). There was an inverse correlation between baseline FEV₁ and histamine reactivity, and with $\Delta\text{FEV}_1/\text{ht}^3$ in all three groups. $\Delta\text{FEV}_1/\text{ht}^3$ was greater in reactors than in non-reactors among the smokers but only slightly so among the ex-smokers (table 2).

The annual rate of decline in FEV₁ was faster in smokers with a personal history of allergy (usually seasonal rhinitis) than in those without (mean (SEM) 13.3 (1.4) and 10.0 (0.8) ml/y/m³; $p < 0.03$), but this was not seen in ex-smokers. The annual $\Delta\text{FEV}_1/\text{ht}^3$ was not related to family history of allergy, serum IgE level, skintest score, or total white cell count in any group, though it was related to absolute eosinophil count in non-smokers ($r = 0.59$; $p < 0.05$) but not in smokers ($r = -0.07$) or ex-smokers ($r = 0.01$). The annual $\Delta\text{FEV}_1/\text{ht}^3$ was greater in those taking beta blocker drugs both among the smokers (19.3 (3.3) v 10.6 (0.67) ml/y/m³; $p = 0.01$) and the ex-smokers (12.9 (2.3) v 7.4 (0.70) ml/y/m³; $p < 0.05$).

To examine the factors related to rapid decline in $\Delta\text{FEV}_1/\text{ht}^3$ in smokers, we compared the 25 smokers with the largest $\Delta\text{FEV}_1/\text{ht}^3$ (fast decliners, median

17.0 (range 13.0–32.6) ml/y/m³) with the 25 smokers with the smallest $\Delta\text{FEV}_1/\text{ht}^3$ (slow decliners, median 4.2 (range -1.3–6.5) ml/y/m³). The fast decliners had a lower baseline FEV₁ in 1981–2 (median 89% (range 63–129%) v 111% (85–143%); $p < 0.0001$) than the slow decliners, a family history of atopy more often (13 v 6; $p < 0.05$), and a larger response to salbutamol (median 5.4% (range 0–21%) v 2.5% (2–12.4%); $p < 0.05$). There were no significant differences between these two groups of smokers in age, daily cigarette consumption, personal history of allergy, skinprick test results, serum IgE concentration, or peripheral blood total white cell or absolute eosinophil count.

Discussion

This study showed that bronchial reactivity to histamine was greater in smokers than in non-smokers and that increased bronchial reactivity was associated with accelerated loss of FEV₁ in smokers. These findings confirm the findings of previous studies^{5,9} and are compatible with the Dutch hypothesis^{2,3} that bronchial reactivity is increased in smokers with chronic airflow obstruction. In middle aged men, however, there is also a relationship between accelerated annual decline in FEV₁ and a reduced baseline value of FEV₁.¹ Because reduced baseline airway dimensions may themselves lead to enhanced reactivity,¹⁶ the exaggerated bronchial reactivity we observed in smokers might follow rather than precede accelerated loss of FEV₁. We have therefore examined our results to see if they provide evidence on the origins of the increased reactivity in smokers.

The original suggestion of the Dutch workers^{2,3} was that smokers with progressive airflow obstruction showed "endogenous" increased bronchial reactivity and atopic features similar to, but less pronounced than, those found in subjects with overt asthma. In this case increased reactivity would antedate the onset of smoking, and allergic features would be associated with accelerated decline of FEV₁ in smokers. In our study, however, the relation between established markers of allergy and rate of loss of FEV₁ was relatively weak; of the individual markers examined, only a history of allergic rhinitis was related to an accelerated annual decline of FEV₁ in smokers. When we compared smokers with rapid and slow annual decline in FEV₁, we found that only a family history of allergy was significantly commoner in those with rapid decline. Although other studies have shown some relation between evidence of allergy^{5,9} and accelerated decline of FEV₁ in smokers, the relevant allergic features have been much less pronounced than is

commonly found in asthmatic subjects.

Moreover, we have found¹⁰ increases in certain allergic markers related to the smoking habit itself rather than to the rate of decline in FEV₁. Thus positive skinprick test responses were commoner among ex-smokers than among smokers or non-smokers, the peripheral blood eosinophil count was raised in smokers, and the serum total IgE level was raised in smokers and ex-smokers with negative skin test responses. The size of each increase was again small compared with that seen in asthmatic subjects. The weakness of the association with allergic features raises the possibility that the increased bronchial reactivity in smokers is acquired after smoking is started. Bronchial reactivity was not demonstrably greater in younger smokers than in non-smokers in either this or another recent study of smokers less than 36 years old¹⁷ (which used higher concentrations of histamine). Several other investigations of young symptomless smokers with normal lung function have also failed to detect any consistent difference in bronchial reactivity,¹⁸⁻²⁰ though one report found slightly diminished reactivity.²¹ Such studies are open to the criticism that strongly reactive smokers may have already selected themselves out by giving up smoking, leaving only the less reactive smokers for comparison with non-smokers. In a study of baboons this problem was avoided by randomly allocating baboons to smoke or sham smoke for three years, and the baboons who had smoked cigarettes became less reactive to inhaled methacholine.²² Although acute administration of nicotine aerosol blunted the response to methacholine, chronic administration for three months had no additional effect on the baboons' reactivity.²³

The increased bronchial reactivity of smokers therefore appears to be acquired some years after they take up smoking. Several mechanisms have been proposed to explain how prolonged smoking might increase non-specific hyperreactivity. Perhaps the strongest possibility is that increased bronchial reactivity stems from altered geometry of the airways; although PC₂₀ normalises the airway response to the initial baseline FEV₁, amplifying factors of altered geometry can considerably exceed this normalisation.^{12, 16} Our finding that bronchial reactivity was increased in all men with an FEV₁ below 80% of the predicted value (whether current smokers or ex-smokers) emphasises the important role of altered airway geometry. Indeed, it is rare for diminished airway calibre, however caused, not to be accompanied by exaggerated bronchial reactivity.^{24, 25} When we confined our comparison to men with FEV₁ above 80% of predicted values,¹³ reactors (PC₂₀ ≤ 16 mg/ml) to histamine were com-

moner in smokers than non-smokers but mean FEV₁ was lower in the smokers, so geometric influences might still be important. In non-reactors (PC₂₀ > 16 mg/ml), the percentage reduction in FEV₁ after inhalation of the highest concentration of histamine (16 mg/ml) was larger in smokers than in non-smokers, but the degree of reduction was related to baseline FEV₁, which was lower in the smokers. Hence even within the conventional normal range of FEV₁ (and we used reference values¹³ which are lower than those of most other studies²⁶) some effect of initial geometry cannot be excluded. Nevertheless, altered geometry is not the only factor in increased reactivity. For a given reduction in baseline FEV₁ the PC₂₀ in asthmatic subjects reported by others¹² is lower than in our smokers and ex-smokers; similarly, at any given level of baseline airways resistance, subjects with asthma show larger responses to histamine than smokers with chronic airflow obstruction.²⁷ Further, while asthmatic subjects show a close correlation between PC₂₀ for histamine (or methacholine) and the degree of bronchoconstriction induced by hyperventilation,¹⁴ smokers with enhanced reactivity to drugs do not develop bronchoconstriction with hyperventilation,^{28, 29} despite achieving respiratory heat loss sufficient to produce a response in asthmatic subjects with similar PC₂₀.²⁹ Finally, in contrast to the results in young adult smokers, studies of middle aged smokers with completely normal baseline lung function (but often with chronic cough) have shown greater bronchial reactivity to histamine (assessed by changes in airways conductance³⁰) and methacholine (assessed by FEV₁³¹ and partial expiratory flow volume curves³²) than non-smokers. As the most reactive smokers would presumably have developed some impairment of lung function by middle age and so have been excluded from the study, these results suggest that enhanced reactivity eventually develops in many smokers after prolonged exposure to tobacco. Hence more specific mechanisms enhancing bronchial reactivity may be superimposed on the background influence of altered airway geometry in smokers. A prospective study of changes in baseline FEV₁ and in PC₂₀ in an individual will be required to permit quantification of the precise role of altered geometry.

Another way in which diminished airway calibre might influence bronchial reactivity is by altering the site of deposition of histamine inhaled into the lungs. By alteration of the mode of administration of the aerosol, histamine can be preferentially deposited on central rather than peripheral airways, and then appears to be more effective in reducing FEV₁.³³ This could be because irritant receptors are more numerous centrally³⁴ or because the FEV₁ may

be more sensitive to changes in central than in peripheral airways. In relatively advanced airflow obstruction aerosol deposition on central airways is increased,³⁵ but this change in deposition is consistently found only when FEV₁ falls below about 60% of the predicted value,³⁶ and we found enhanced reactivity in men whose FEV₁ was higher than this. Moreover, recent studies³⁶⁻³⁸ do not support the earlier contention that penetration of aerosol into the lungs is reduced even in symptomless smokers,³⁹ and emphasise the considerable overlap between normal smokers and non-smokers in aerosol penetration. Hence the increased reactivity in our smokers is more likely to have resulted from the direct influence of diminished airway calibre than from any consequent reduction in the depth of penetration of inhaled histamine into the lungs.

The effects of reduced airway calibre in increasing reactivity would not be confined to smoking related disease but would also apply when airway narrowing was due to asthma or cystic fibrosis. A more specific effect of smoking, which is apparent within a few days of the starting of smoking,⁴⁰ is to increase airway permeability, as shown by the rapid removal from the lungs of radiolabelled diethylenetriamine penta-acetic acid (DTPA) aerosol.^{41,42} Increased permeability of the airways, however, cannot account entirely for the abnormal bronchial reactivity of smokers. We found abnormal reactivity in only a minority of smokers, but virtually all have increased permeability. This disparity is even more evident in younger smokers, in whom the reactivity of the airway to histamine bears no relation to its permeability to DTPA.⁴³ Furthermore, the change in permeability reverses within weeks of cessation of smoking,^{42,44} but enhanced bronchial reactivity was evident in some of our ex-smokers years after stopping smoking.

A further possibility is that bronchial reactivity might be increased during the smoking years by an immunological mechanism. As discussed elsewhere,¹⁰ there are increases which are probably acquired in blood eosinophils in smokers and a small rise in total serum IgE in smokers with negative skin test responses. Neither blood eosinophil count nor total IgE, however, was related to increased reactivity or annual rate of decline in FEV₁ in smokers. Conceivably, smoking could amplify the effect of pre-existing but subclinical allergy; on the other hand, we did not find an increased prevalence of positive skin test responses in smokers.¹⁰

Chan Yeung and Dy Buncio⁴⁵ have recently described an inverse relation between the peripheral blood leucocyte count and FEV₁. The association was present irrespective of smoking habit, though heavier smokers had higher white cell counts. If the

leucocyte count were an important independent determinant of FEV₁, we should have expected to find that it was related not only to baseline FEV₁ but also to annual $\Delta\text{FEV}_1/\text{ht}^3$; but no such association was apparent in our smokers, ex-smokers, or non-smokers.

In summary, our finding of increased bronchial reactivity in smokers with accelerated annual decline of FEV₁ and reduced baseline FEV₁ is compatible with the "Dutch hypothesis," but increased reactivity may follow rather than precede the onset of smoking. The evidence for an associated allergic factor was relatively weak. While the hypothesis cannot explain all the features of smoking related airflow obstruction—for instance, the predominance of men, the association with poor socioeconomic status, and, most strikingly, the almost inevitable development of emphysema when airflow obstruction is severe⁴⁶—further studies are required to investigate the origins of the increased bronchial reactivity.

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