Thorax 1985;**40**:17–22

Smoking, allergy, and the differential white blood cell count

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ABSTRACT Dutch workers have proposed that people with asthma and those smokers who develop chronic airflow obstruction share a common allergic constitution. To study whether smoking itself is associated with indicators of allergy, we have examined 237 men aged 51–61 years (120 smokers, 73 ex-smokers, and 44 non-smokers) who were recruited to a long term study of lung function in 1974, at which time men with a clinical diagnosis of asthma were excluded. Smokers, ex-smokers, and non-smokers did not differ in personal or family history of allergic disease, but the prevalence of positive responses to skinprick tests was greater in ex-smokers (59%) than in the other two groups (33% and 34%). In men with negative responses to skinprick tests total serum IgE was greater in smokers ($\log_{10}$ mean 1·41 IU/ml) and in ex-smokers ($\log_{10}$ mean 1·53 IU/ml) than in non-smokers ($\log_{10}$ mean 1·12 IU/ml). In men with positive skin test responses serum IgE was similar in the three groups ($\log_{10}$ mean ranging from 1·68 to 1·78 IU/ml). Geometric mean total white cell counts in the peripheral blood were higher in smokers ($7{\cdot}34 \times 10^9$/l) than in non-smokers ($5{\cdot}82 \times 10^9$/l); the value in ex-smokers ($6{\cdot}16 \times 10^9$/l) was intermediate. Absolute blood eosinophil counts were increased in smokers disproportionately to the increase in total white cell count. Thus smoking is associated with small increases in some markers of allergy. These changes are probably acquired after the onset of smoking but sequential studies are required to amplify these cross sectional observations. Smokers whose skin test responses are positive appear more likely to give up smoking.

In 1960 Dutch workers[1] proposed that individuals with asthma and smokers with chronic and mainly irreversible airflow obstruction shared a common allergic constitution and increased non-specific bronchial reactivity. It was not clear whether the increased reactivity followed or preceded the development of airway narrowing.[2] In an earlier study from this department Fletcher and coworkers[3] found little evidence that allergy contributed to the development of chronic airflow obstruction in smokers; more recently we re-examined some of the younger men in this original study, and in contrast found that the rate of decline of lung function was more rapid in smokers who had some evidence of an allergic constitution than in those who did not.[4] Furthermore, a series of reports from Tucson[5–7] has investigated the interrelations between atopy, eosinophilia, and airflow obstruction and found that blood eosinophilia was associated with impairment of ventilatory function regardless of smoking habit. Smokers have also been shown to have a higher total serum immunoglobulin E (IgE) level than non-smokers[8–14] and a raised white cell count in the peripheral blood.[15–23]

These findings have renewed interest in the Dutch hypothesis. In a companion study on a different group of smokers, ex-smokers, and non-smokers whom we have followed at intervals since 1974 we found that increased bronchial reactivity to inhaled histamine was commoner among smokers and was related to an accelerated rate of annual decline in FEV_1,[24] thus apparently supporting the Dutch hypothesis. Enhanced bronchial reactivity could have followed the onset of smoking, however, rather than represented a pre-existing risk factor. In this paper we describe the relations between smoking habit and a personal and family history of allergic disease, results of skinprick tests for common inhaled allergens, total serum IgE levels, and

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Accepted 8 October 1984

eosinophil counts in peripheral venous blood in the same groups of men. We also examined the total white cell count, which is said to be inversely related to forced expiratory volume.[25] We found that certain markers of allergy are increased in smokers, but these changes may also arise after the onset of smoking.

Methods

We studied 237 white men working in West London who were originally recruited in 1974 for a prospective study of lung function.[26] The sample was biased to include a high proportion of middle aged smokers. Most of the men were office workers; policemen, prison officers, and a few semi-skilled workers made up the remainder. Men who gave a history of asthma or of other appreciable chest illness or who had an abnormal chest radiograph in 1974 were excluded. The follow up data reported in the present paper were obtained from November 1981 to March 1982.

The ages of the men fell into two groups, 25–42 years (68 men) and 47–61 years (169 men) at the time of follow up. There were 44 lifelong non-smokers (non-S: never smoked more than one cigarette a day for as long as one year) and 120 regular smokers (S), almost all of whom smoked cigarettes (mean consumption 23 cigarettes a day). There were 73 ex-smokers (ex-S), 51 of whom had given up smoking since 1974. Ex-smokers were divided into those who had given up less than one year (ex-S < 1 year, n = 17), one to five years (ex-S 1–5 years, n = 17), and more than five years (ex-S > 5 years, n = 39) before the time of restudy in winter 1981–2. The younger group of men contained a lower proportion of smokers (26 S, 22 ex-S, 20 non-S) than the middle aged group (94 S, 51 ex-S, 24 non-S). Fifteen (13%) of the smokers, three (4%) of the ex-smokers, and none of the non-smokers had an FEV_1 of less than 80% of their predicted values.[27]

The presence or absence of a personal history of eczema, hayfever, rhinitis, urticaria, or asthma and a family history of these diseases was recorded by questionnaire. Asthma was diagnosed if there was a history of attacks of tightness of the chest with wheezing and difficult breathing. Skin prick tests were performed at recruitment in 1974; thus most men classed as ex-smokers in 1981–2 had actually been smokers when tested. We used nine common inhaled antigens (*Aspergillus fumigatus, Alternaria, Cladosporium,* grass pollen, cat fur, dog fur, mixed feathers, *Dermatophagoides pteronyssinus,* wool), control and histamine control. Weal diameters were measured after 10 minutes and were graded so that a weal of 1–2 mm scored 1, 3–4 mm scored 2, 5–10 mm scored 3, and more than 10 mm scored 4; the scores were summed to give a skin test score for each subject. In winter 1981–2 we repeated the tests in 33 men drawn from all three groups of subjects, and found close agreement with the ealier scores. Serum IgE concentrations were measured by the PRIST technique (Phadebas). Total and differential white cell counts were performed with a Hemalog D automated analyser (Technicon Instruments) on the blood of 88 (73%) of the smokers, 49 (67%) of the ex-smokers, and 29 (66%) of the non-smokers; we obtained the use of the Hemalog D from January 1982 onwards.

Statistical analysis was performed using the χ^2 test with Yates's correction. For data that were distributed normally we used Student's t test, means and standard errors, 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 distribution of serum total IgE concentrations and peripheral blood absolute eosinophil counts were skewed, and the results were transformed logarithmically for statistical analysis. All the men gave their written consent and the study was approved by the research ethics committee of the Medical School.

Results

Smokers, ex-smokers, and non-smokers were similar in their personal and family histories of allergy (table).

The prevalence of positive skinprick test responses was similar in smokers and non-smokers, but significantly higher in ex-smokers than in the two other groups (table), though positive scores were no higher in the ex-smokers. Many of the positive skinprick test scores were low; 50% of smokers, 44% of ex-smokers, and 58% of non-smokers had scores of 2 or less ($p > 0{\cdot}5$).

The $\log_{10}$ mean (SEM) serum total IgE level was higher in smokers (1·41 (0·07); $p = 0{\cdot}02$) and ex-smokers (1·53 (0·10); $p = 0{\cdot}003$) with negative skin test responses than in non-smokers (1·12 (0·09);— fig 1), but in men with positive responses the IgE level was similar in the three groups ($p > 0{\cdot}5$). The IgE level showed a non-significant trend to be lower in both skin test positive and skin test negative ex-smokers of longer standing. But among men with negative skinprick test responses the IgE level in the 39 ex-smokers of five or more years' duration ($\log_{10}$ mean (SEM) 1·53 (0·14)) remained slightly higher than in smokers (1·41 (0·07); $p > 0{\cdot}4$) and significantly higher than in non-smokers (1·12

Prevalence of positive personal and family histories of allergy and of positive skinprick test responses

	Personal history of allergy		*Family history of allergy*		*Skinprick tests*	
	% pos	*% neg*	*% pos*	*% neg*	*% pos*	*% neg*
Smokers (S)	31	69	36	64	33	67
Ex-smokers (ex-S)	32	68	38	62	59	41
Non-smokers (non-S)	34	66	27	73	34	66
S *v* non-S	NS		NS		NS	
S *v* ex-S	NS		NS		$p < 0.001$	
Ex-s *v* non-S	NS		NS		$p < 0.02$	

Not significant (NS) = $p > 0.05$.

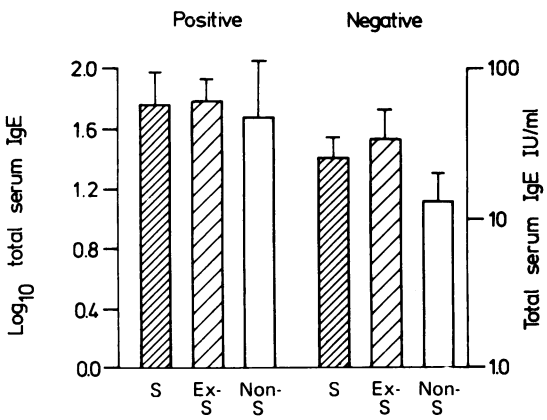

Fig 1 *Log_{10} mean value of serum total IgE for smokers (S), ex-smokers (ex-S) and non-smokers (non-S) with positive and negative skinprick test responses to inhaled allergens. Bars indicate* +2 SEM.

(0·09); $p < 0.02$).

The geometric mean (95% confidence limits) total white blood cell count was higher in smokers (7·34 (6·86–7·86) × 10^9/l) than in ex-smokers (6·16 (5·66–6·72) × 10^9/l) or non-smokers (5·82 (5·09–6·65) × 10^9/l), but no higher in ex-smokers than in non-smokers (S *v* ex-S and S *v* non-S $p < 0.005$; ex-S *v* non-S $p > 0.5$—fig. 1).

The frequency distribution of absolute blood eosinophil counts showed an overall shift to higher values in smokers (geometric mean (95% confidence limits) 0·147 (0·126–0·172) × 10^9/l) compared with ex-smokers (0·103 (0·082–0·130) × 10^9/l; $p = 0.01$) and non-smokers (0·100 (0·081–0·124) × 10^9/l; $p = 0.01$—figure 2). The mean white cell count was 26% higher and the absolute eosinophil count 47% higher in smokers than in non-smokers, indicating that the eosinophil count was increased disproportionately in smokers. Nevertheless, the percentage of eosinophils did not

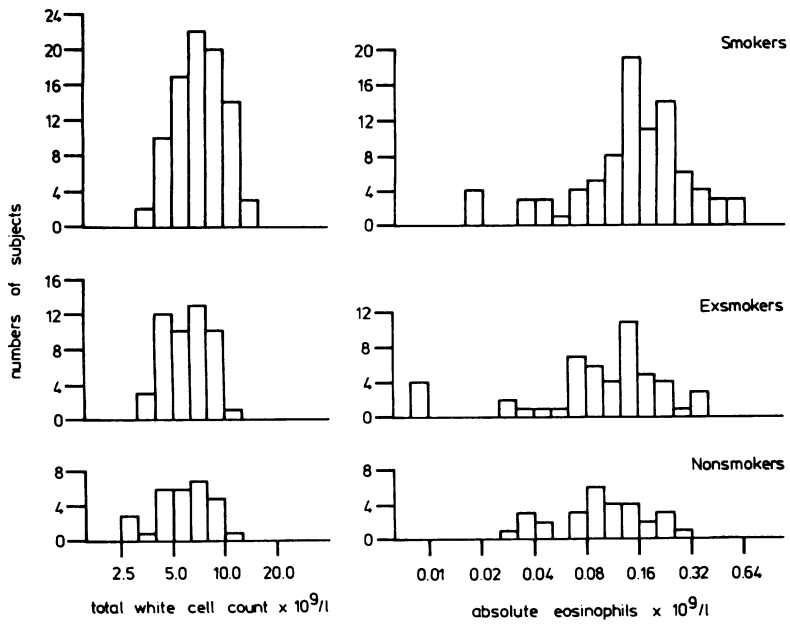

Fig 2 *Distribution of blood total white cell and absolute eosinophil counts (log scales) in smokers, ex-smokers, and non-smokers.*

differ significantly between smokers (mean 1·95%) and non-smokers (1·67%, $p > 0·3$), and neither did that of neutrophils, lymphocytes, or monocytes, though the basophil percentage was higher in smokers (mean 0·30%) than in non-smokers (0·19%, $p = 0·03$).

The total white cell count was a little higher and the absolute eosinophil count slightly lower in men who smoked more than 20 cigarettes a day than in men who smoked less, but neither trend was significant. There was no relation between serum total IgE and daily cigarette consumption.

Discussion

Our results showed that smokers, ex-smokers, and non-smokers differed significantly on the basis of certain common tests of allergic constitution. Positive skinprick test responses were commoner among ex-smokers. Smokers and ex-smokers with negative skinprick test responses had higher serum total IgE levels than non-smokers, and the peripheral blood eosinophil count in smokers was raised out of proportion to the increase in the total white cell count.

There were no differences between the three groups in respect of personal or family history of allergic disease. Few similar reports are available for comparison. In a community survey,[5] a family history of allergy was commoner in smokers than in non-smokers, and most common in ex-smokers. Half the patients studied by Orie *et al*[1] had a family history of allergic disease, and more than 80% were affected personally, but they were investigated because they already had chronic lung disease.

Skinprick test responses were originally performed in 1974, when most of the men who were ex-smokers in 1981–2 were still smoking. As positive skin test responses in 1974 were commoner among men who had given up smoking by 1981–2 than among smokers or non-smokers, it appears that smokers were more likely to give up smoking if they had positive skinprick test responses. Burrows's group found that positive responses were as common among ex-smokers as among non-smokers,[10] and that smoking and skin test scores were inversely related,[5] but these findings were obtained from a general population survey. The original Dutch studies[1 2] are not comparable as intradermal tests were used.

We confirmed the observations of Burrows *et al*[10] that serum total IgE levels were raised in smokers and ex-smokers with negative skin test responses. The IgE levels tended to be lower in ex-smokers of longer standing, in whom nevertheless the mean IgE level remained significantly higher than in non-smokers. The specificity of the excess IgE in smokers is uncertain. Early attempts to identify circulating antibodies to components of cigarette smoke were unsuccessful,[7 28] but such antibodies have recently been found[29]; in addition, smokers more commonly have serum IgE, which is specific for *Streptococcus pneumoniae,* an organism that commonly colonises the respiratory tract of smokers.[30] Most[8–10 12–14] but not all[11 31] studies of IgE levels in smokers have given results similar to ours. The IgE level in patients with chronic airflow obstruction has been described as normal[32 33] or high,[34 35] but some of these studies did not allow for skin test results or include non-smoking control subjects. A matched pair comparison of subjects with chronic airflow obstruction and normal controls again disclosed no difference in serum IgE level,[36] but did not separate subjects according to skin test results. Other immunoglobulin levels are not consistently altered in smokers.[9 11 37–42]

A raised total white cell count in smokers has been noted in many previous reports.[15–17 19–22 43] In our study only a weak trend with number of cigarettes smoked was found, but several earlier studies found that the white cell count is higher in heavy than in light smokers,[15–17 43] and changes correspondingly with alterations in smoking intensity.[17] Giving up smoking is associated with a reduction in the leucocyte count,[18] though not in the first six weeks.[23]

Earlier studies of blood eosinophils in smokers,[11 16 19–22 32 43–44] using relatively inaccurate manual methods, yielded conflicting results. Our results, derived from automated total and differential counts of 10 000 leucocytes per sample, show higher eosinophil counts in smokers; confidence limits for the absolute eosinophil count by this method are about nine times narrower than those derived from manual counts on comparable samples.[45 46] Although the mean absolute eosinophil count we observed in smokers did not qualify as eosinophilia ($>0·44 \times 10^9$/l),[47] occasional smokers have been described with counts of up to $1·7 \times 10^9$/l that fell to normal when smoking was stopped and rose when it was resumed.[48 49]

Though some of these differences in allergic markers between smokers, ex-smokers, and non-smokers were significant, they were small compared with those found in patients with symptomatic asthma; in 12 patients with asthma we found the geometric mean percentage and absolute blood eosinophil count were 5·34% and $0·466 \times 10^9$/l respectively, and skinprick test scores in typical patients with extrinsic asthma might be 15–20 or more. Although the mean IgE level was significantly higher in skin test negative smokers than in skin test negative non-smokers, it remained within the nor-

mal range (less than 122 IU/ml, $\log_{10}$ 2·06; Westminster Hospital Protein Reference Unit), and the difference between smokers and non-smokers was smaller than that between skin test positive and negative subjects of either group.

In subjects with asthma increases in blood eosinophils and serum total IgE are generally interpreted as evidence for an "allergic" constitution likely to have predated the onset of symptoms. In contrast, in smokers the small changes in these markers are probably acquired after the onset of smoking. In a companion study on the same men, we found that bronchial reactivity was increased in smokers, but suggest that this change also may be acquired after the onset of smoking.[24] Furthermore, allergic markers were only weakly related to annual rate of decline in lung function in an individual.[24] Thus both studies show changes in smokers which apparently support the Dutch hypothesis: the changes observed may follow rather than precede the onset of smoking and the development of airflow obstruction.

This work was supported by a grant from the Medical Research Council. We thank Dr JDM Richards and Mr P Martin of the Department of Haematology, University College Hospital, London, for performing the differential white cell blood counts and Dr Keith Patterson for helpful discussion.

References

1 Orie NGM, Sluiter HJ, de Vries K, Tammeling GJ, Witkop J. The host factor in bronchitis. In: *Bronchitis. An international symposium, 27–29 April 1960, University of Groningen*. Assen: Royal Van Gorcum, 1961:43–59.
2 Van der Lende R, de Kroon JPM, van der Muelen GG, *et al*. Possible indicators of endogenous factors in the development of CNSLD. In: Orie NGM, van der Lende R, eds. *Bronchitis III. Proceeding of the third international symposium on bronchitis, 23–26 September 1969, Groningen*. Assen: Royal Van Gorcum, 1970:52–70.
3 Fletcher C, Peto R, Tinker C, Speizer FE. *The natural history of chronic bronchitis and emphysema*. Oxford: Oxford University Press, 1976.
4 Connellan SJ, Carson R, Holland F, Joyce H, Pride NB. Role of bronchial hyperreactivity and atopy in enhancing decline of lung function in male smokers. *Eur J Respir Dis* 1981;**62**, suppl 113:130–1.
5 Burrows B, Lebowitz MD, Barbee RA. Respiratory disorders and allergy skin-test reactions. *Ann Intern Med* 1976;**84**:134–9.
6 Burrows B, Hasan FM, Barbee RA, Halonen M, Lebowitz M. Epidemiologic observations on eosinophilia and its relation to respiratory disorders. *Am Rev Respir Dis* 1980;**122**:709–19.
7 Burrows B, Halonen M, Lebowitz MD, Knudson RJ, Barbee RA. The relationship of serum immunoglobulin E, allergy skin tests, and smoking to respiratory disorders. *J Allergy Clin Immunol* 1982;**70**:199–204.
8 Bahna SL, Heiner DC, Myrhe BA. Immunoglobulin E pattern in cigarette smokers. *Allergy* 1983;**38**:57–64.
9 Gerrard JW, Heiner DC, Ko CG, Mink J, Meyers A, Dosman JA. Immunoglobulin levels in smokers and non-smokers. *Ann Allergy* 1980;**44**:261–2.
10 Burrows B, Halonen M, Barbee RA, Lebowitz MD. The relationship of serum immunoglobulin E to cigarette smoking. *Am Rev Respir Dis* 1981;**124**:523–5.
11 Leitch AG, Lumb EM, Kay AB. Mediators of hypersensitivity in the sputum of young, symptomatic cigarette smokers. *Clin Allergy* 1981;**11**:257–62.
12 Zetterstrom O, Osterman K, Machado L, Johansson SGO. Another smoking hazard: raised serum IgE concentration and increased risk of occupational allergy. *Br Med J* 1981;**283**:1215–7.
13 Bonini S. Smoking, IgE, and occupational allergy. *Br Med J* 1982;**284**:512–3.
14 Warren CPW, Holford-Strevens V, Wong C, Manfreda J. The relationship between smoking and total immunoglobulin levels. *J Allergy Clin Immunol* 1982;**69**:370–5.
15 Howell RW. Smoking habits and laboratory tests. *Lancet* 1970;ii:152.
16 Corre F, Lellouch J, Schwartz D. Smoking and leucocyte counts. *Lancet* 1971;ii:632–4.
17 Friedman GD, Siegelaub AB, Seltzer CC, Feldman R, Collen MF. Smoking habits and the leukocyte count. *Arch Environ Health* 1973;**26**:137–43.
18 Friedman GD, Siegelaub AB. Changes after quitting cigarette smoking. *Circulation* 1980;**61**:716–23.
19 Parulkar VG, Balsubramanian P, Barua M, Bhatt JV. Smoking and differential leucocyte (WBC) count. *J Postgrad Med* 1975;**21**:75–7.
20 Billimoria JD, Pozner H, Metselaar B, Best FW, James DCO. Effect of cigarette smoking on lipids, lipoproteins, blood coagulation, fibrinolysis and cellular components of human blood. *Atherosclerosis* 1975;**21**:61–76.
21 Noble RC, Penny BB. Comparison of leukocyte count and function in smoking and nonsmoking young men. *Infect Immun* 1975;**12**:550–5.
22 Winkel P, Statland BE. The acute effect of cigarette smoking on the concentration of blood leukocyte types in healthy young women. *Am J Clin Pathol* 1981;**75**:781–5.
23 Miller LG, Goldstein G, Murphy M, Ginns LC. Reversible alterations in immunoregulatory T cells in smoking. *Chest* 1982;**82**:526–9.
24 Taylor RG, Joyce H, Gross E, Holland F, Pride NB. Bronchial reactivity to inhaled histamine and annual rate of decline in FEV, in male smokers and ex-smokers. *Thorax* 1985;**40**:00–00.
25 Chan Yeung M, Dy Buncio A. Leukocyte count, smoking and lung function. *Am J Med* 1984;**76**:31–7.
26 Tattersall SF, Benson MK, Hunter D, *et al*. The use of tests of peripheral lung function for predicting future disability from airflow obstruction in middle-aged smokers. *Am Rev Respir Dis* 1978;**118**:1035–50.
27 Ferris BG, Anderson DO, Zickmantel R. Prediction values for screening tests of pulmonary function. *Am Rev Respir Dis* 1965;**91**:252–61.
28 Lehrer SB, Wilson MW, Karr RM, Salvaggio JE. IgE antibody response of smokers, nonsmokers, and

"smoke-sensitive" persons to tobacco leaf and smoke antigens. *Am Rev Respir Dis* 1980;**121**:168–70.
29 Hersey P, Prendergast D, Walsh J. Detection of antibodies to cigarette smoke extracts in human subjects. *Clin Exp Immunol* (in press).
30 Bloom JW, Farland AM, Halonen M, Burrows B. Pneumococcus-specific IgE in cigarette smokers. *Am Rev Respir Dis* 1984;**129**:A191(abstract).
31 Pantin CFA, Merrett TG. Smoking and IgE levels. *Br Med J* 1982;**284**:744.
32 Turnbull LS, Turnbull LW, Leitch AG, Crofton JW, Kay AB. Mediators of immediate-type hypersensitivity in sputum from patients with chronic bronchitis and emphysema. *Lancet* 1977;ii:526–9.
33 Warren CPW, Tse KS. Serum and sputum immunoglobulin E levels in respiratory diseases in adults. *Can Med Assoc J* 1974;**110**:425–9.
34 Ablin RJ. Immunologic studies of patients with pulmonary emphysema. *Ann Allergy* 1973;**31**:171–7.
35 Pauwels R, van der Straeten M. Total serum IgE levels in normals and patients with chronic non-specific lung diseases. *Allergy* 1978;**33**:254–60.
36 Miller RD, Gleich GJ, Offord JP, Dunnette SL. Immunoglobulin concentrations in serum and nasal secretions in chronic obstructive pulmonary disease. A matched pair study. *Am Rev Respir Dis* 1979;**119**:229–38.
37 Biegel AA, Krumholz RA. An immunoglobulin abnormality in pulmonary emphysema. *Am Rev Respir Dis* 1968;**97**:217–22.
38 Falk GA, Siskind GW, Smith JP. Immunoglobulin elevations in the serum of patients with chronic bronchitis and emphysema. *J Immunol* 1970;**105**:1559–62.
39 Kraal JH. Immunoglobulin levels in relation to smoking and coffee consumption. *Am J Clin Nutr* 1978;**31**:198–200.
40 Ferson M, Edwards A, Lind A, Milton GW, Hersey P. Low natural killer-cell activity and immunoglobulin levels associated with smoking in human subjects. *Int J Cancer* 1979;**23**:603–9.
41 Gulsvik A, Fagerhol MK. Smoking and immunoglobulin levels. *Lancet* 1979;i:449.
42 Knowles GK, Townsend P, Turner-Warwick M. Cigarette smoking and serum immunoglobulin concentrations in healthy subjects. *Br J Dis Chest* 1981;**75**:322.
43 Dodsworth H, Dean A, Broom G. Effects of smoking and the pill on the blood count. *Br J Haematol* 1981;**49**:484–8.
44 Kameswaran L, Kanakambal K, Vijayasekaran V. Studies on plasma histmine levels in normal and allergic individuals. *Indian J Physiol Pharmacol* 1968;**12**:159–65.
45 England JM, Bain BJ. Total and differential leucocyte count. *Br J Haematol* 1976;**33**:1–7.
46 Simmons A, Leaverton P, Elbet G. Normal laboratory values for differential white cell counts established by manual and automated cytochemical methods (Hemalog D). *J Clin Pathol* 1974;**27**:55–8.
47 Dacie JV, Lewis SM. *Practical haematology*. 5th ed. London: Churchill Livingstone, 1975.
48 Schoen I, Pizer M. Eosinophilia apparently related to cigarette smoking. *N Engl J Med* 1964;**270**:1344–7.
49 Paintal IS, Minina RJ. Tobacco smoking – a probable cause of eosinophilia. *Indian Practitioner* 1975;**28**:243–5.