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Peripheral leucocyte count and longitudinal decline in lung function

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ABSTRACT A six year follow up study of 750 aluminium smelter workers was undertaken to evaluate the relationship between the leucocyte count at the start of the study and the rate of decline in lung function. An inverse relationship between the leucocyte count and the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) was present cross sectionally irrespective of cigarette smoking habit. The initial leucocyte count was also significantly related to the mean annual decline in FEV_1 in smokers ($p = 0{\cdot}04$) but not in former smokers or those who had never smoked. These observations suggest that the leucocyte count is a factor influencing the annual decline in FEV in smokers.

It has been proposed that pulmonary emphysema develops as a result of an imbalance between elastase and antiproteases in the lung, leading to elastolytic lung injury.[1,2] Cigarette smoking has been shown to be associated with high peripheral leucocyte counts.[3–12] The number of neutrophils in the lungs was also shown to be greater in smokers than in non-smokers.[13] Since polymorphonuclear leucocytes are likely to be the major source of elastase in the lung, the raised leucocyte count in smokers could be one mechanism by which cigarette smoking induces pulmonary emphysema.

In an earlier study we found an inverse relationship between the peripheral leucocyte count and the level of lung function irrespective of smoking habits.[14] In a longitudinal study Sparrow and coworkers[15] observed not only that there was an inverse relationship between the initial peripheral leucocyte count and initial lung function but also that the change in leucocyte count over 10 years was inversely related to lung function at follow up. These relationships were independent of smoking, suggesting that the peripheral leucocyte count was an important determinant of the level of lung function. We have evaluated the relationship between leucocyte count and the rate of decline in lung function in 750 smelter workers studied previously[14] who had not changed their smoking habits when studied again six years later.

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Methods

We conducted a follow up study of workers employed in an aluminium smelter six years after the initial survey. Of the original cohort of 1620 male workers, 904 remained; 750 workers had not changed their smoking habits since the initial study. The participation rate of workers in both initial and follow up studies was over 85%.

Details of the initial health study have been reported.[16] The same questionnaire on respiratory symptoms was used for the initial and follow up studies. It was derived from the American Thoracic Society Division of Lung Diseases respiratory questionnaire[17] for epidemiological research. "Never smokers" were subjects who had never smoked; former smokers were subjects who had given up smoking for more than one month before the initial survey; current smokers were subjects who were smoking during the initial study and still smoking one month before the follow up study.

Spirometric measurements were made at the plant site on both occasions with the same computerised rolling seal spirometer (Cardiopulmonary Instruments, Houston, Texas). The mean forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and maximal mid expiratory flow rate ($FEF_{25-75\%}$) were obtained from the two spirograms with the largest FVC values that agreed to within 3% of each other. All measurements were converted to BTPS.

Leucocyte counts were determined with a Coulter-analyser during the initial survey, as described previously,[14] but were not performed in the follow up

study. Measurements of air contaminants in the work environment were carried out by the Workers' Compensation Board of British Columbia during both health studies, both area and personal sampling being used. Workers were classified into different groups according to their job locations and industrial hygiene data.[16]

Standard statistical methods, such as analysis of variance, χ^2 analysis, analysis of covariance, and multiple regression analysis,[18] were used to examine the interrelationships between leucocyte count, smoking, work exposure, and pulmonary function results. For analysing the relationship between initial leucocyte count and lung function or annual decline in lung function workers were divided by quintiles according to their leucocyte count.

Results

The results for the 750 workers who took part in the longitudinal study and who had not changed their smoking habits were analysed. At the time of the initial study the mean age was 37·6 (SD 10·2, range 18–59) years and the mean duration of employment in the smelter was 9·5 (SD 7·7, range 0·2–26) years. There were 235 never smokers (31·3%), 231 former smokers (30·8%), and 284 current smokers (37·9%). The workers were divided into three groups based on their work exposure.[16] After adjusting for age, height, smoking, and racial group we were unable to detect

Table 1 *Initial leucocyte counts*
(a) By age (adjusted for smoking)

		Leucocyte count (No/mm³)	
Age (y)	*n*	*Mean*	*SD*
20	25	6428	1450
21–30	196	6556	1530
31–40	222	6659	1607
41–50	216	6969	1774
51–60	91	6705	1628

(b) By smoking habit (adjusted for age)

		Leucocyte count (No/mm³)	
	n	*Mean*	*SD*
Never smokers	235	6113	1240
Former smokers	231	6302	1385
Current smokers (cigarettes/day):			
< 1 pack of 20	92	7197	1717
1 pack of 20	105	7621	1914
> 1 pack of 20	87	7869	1600

Conversion: Traditional to SI units—1000 leucocytes/mm³ = 1·0 × 10⁹/l.

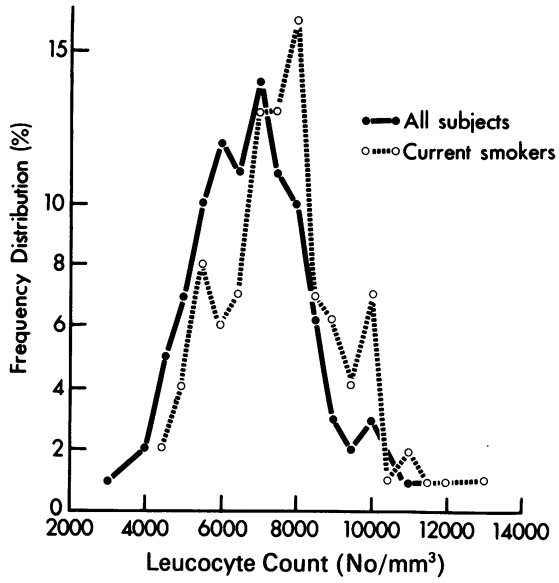

Fig 1 *Frequency distribution of leucocyte count for all workers and separately for current smokers (1000 leucocytes/mm³ = 1·0 × 10⁹/l).*

significant differences in leucocyte count, baseline lung function, or annual decline in lung function between the different work groups. The three groups were therefore taken as one population for the analysis.

The initial leucocyte count was found to be positively correlated with age and smoking (both values < 0·001 by analysis of covariance). Race had no effect on leucocyte count. Table 1*a* shows the initial leucocyte count by age adjusted for smoking and table 1*b* the initial leucocyte count by smoking habits. Current smokers had a significantly higher leucocyte count than never smokers. Among current smokers the higher the cigarette consumption the greater was the leucocyte count ($p < 0·001$). The frequency distribution of leucocyte counts in this population was normal, even among current smokers (fig 1).

Baseline pulmonary function results according to smoking habits and leucocyte count groups are shown in table 2; results are adjusted for age, height, and race. Within each smoking group workers with the lowest leucocyte count had the best baseline pulmonary function, and vice versa. Within each leucocyte count group the effect of smoking was not striking. The results of multiple regression analysis (table 3) confirmed these findings. Age, height, and race were correlated significantly with FEV_1 and FVC, but smoking was not. Leucocyte count was related to baseline FEV_1 and FVC after adjustment for the above variables ($p < 0·001$). There was a significant interaction between age and smoking for both current and

Table 2 *Initial FEV_1 and forced vital capacity, age, race, and height adjusted according to smoking habit and initial leucocyte count*

*Leucocyte group (by quintiles)**	*Never smokers (mean (SD) [n])*	*Former smokers (mean (SD) [n])*	*Current smokers (mean (SD) [n])*	*Total (mean (SD) [n])*
FEV_1 (ml):				
1st	4125 (606) [67]	4161 (758) [54]	4063 (824) [29]	4112 (704) [150]
2nd	4094 (671) [64]	4001 (666) [66]	3988 (699) [35]	4020 (709) [165]
3rd	3888 (665) [48]	4051 (818) [53]	3899 (716) [51]	3945 (738) [152]
4th	3884 (758) [38]	3935 (749) [31]	3840 (728) [68]	3884 (740) [138]
5th	3887 (920) [17]	3953 (744) [27]	3808 (663) [101]	3869 (709) [145]
Forced vital capacity (ml):				
1st	5102 (769) [67]	5147 (927) [54]	5171 (1030) [29]	5142 (878) [150]
2nd	5071 (890) [64]	4915 (716) [66]	4942 (795) [35]	4981 (836) [165]
3rd	4841 (771) [48]	5075 (848) [53]	4952 (838) [51]	4960 (829) [152]
4th	4889 (914) [39]	4082 (838) [31]	4902 (778) [68]	4880 (842) [138]
5th	4899 (1112) [17]	4865 (790) [27]	4860 (715) [101]	4865 (778) [145]

*Groups according to leucocyte quintiles: 1—< 5320; 2—5321–6200; 3—6201–7000; 4—7001–7800; 5—> 7800/mm^3.
Conversion: Traditional to SI units—1000 leucocytes/mm^3 = 1·0 × 10^9/l.

former smokers when the analysis was repeated to include age and smoking interaction terms, and the leucocyte count was still significantly related to the baseline FEV_1 and FVC.

The relationship between leucocyte count and the annual decline in FEV_1 for the three smoking groups is shown in figure 2. When multiple regression analysis was carried out for each smoking group with age and race taken into account (table 4) a significant relationship between initial leucocyte count and annual decline in FEV_1 was observed in current smokers only. Although the trend was observed for never smokers, the relationship did not reach statistical significance.

In current smokers the number of cigarettes smoked daily was an independent predictor of lung function decline ($p = 0{\cdot}045$). There was no interaction between the number of cigarettes smoked daily and leucocyte count on the annual rate of FEV_1 decline—that is, the association between increased leucocyte count and a more rapid rate of decline was not limited to the heavily smoking group of cigarette smokers.

Discussion

In this study of 750 aluminium smelter workers who had not changed their smoking habits, and who had spirometry repeated six years after the initial study, we found that the initial leucocyte count was not only inversely related to the initial lung function (FEV_1 and FVC) but was also related to the subsequent annual decline in lung function. Our findings of a relationship between a high leucocyte count and a greater longitudinal decline in lung function are in accord with those of Sparrow and coworkers.[15] In our study this relationship was found only in current smokers, whereas in the study by Sparrow *et al*[15] the relationship was found in all smoking groups. The difference between the two studies could be due to the smaller number of subjects in our population.

The importance of the leucocyte count as a factor affecting the decline in lung function was indicated by the fact that the differences in decline in lung function between current and never smokers were not evident when the leucocyte count was taken into account. Moreover, former smokers had leucocyte counts similar to those of never smokers and their initial lung function and subsequent annual decline in lung function were not very different from those of never smokers. At the time of the follow up study the former smokers had given up smoking for at least six years, so

Table 3 *Regression of initial pulmonary function on selected initial variables in 750 subjects*

	FEV_1 (ml)			*Forced vital capacity (ml)*		
	Regression coefficient	*Standard error*	*p value*	*Regression coefficient*	*Standard error*	*p value*
Age (y)	−35·70	1·93	<0·001	−28·79	2·26	<0·01
Height (cm)	41·51	2·85	<0·001	62·42	3·33	<0·001
Smoking:						
Current smokers	−59·96	51·60	0·25	−9·76	59·66	0·87
Former smokers	38·52	51·30	0·46	16·70	59·55	0·77
Non-white	−471·76	63·10	<0·001	−656·90	72·96	<0·001
Initial leucocyte count (× 10^3/mm^3)	−48·63	12·70	<0·001	−48·88	14·77	<0·001
Constant	−1565·41	527·22	<0·005	−4451·48	609·57	<0·001

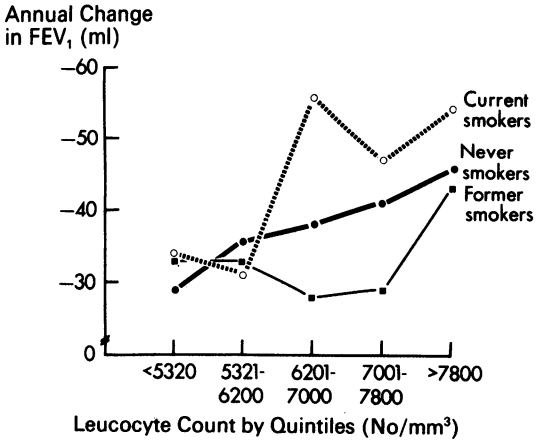

Fig 2 *Relationship between mean annual change in FEV_1 (adjusted for age and race) and peripheral leucocyte count according to cigarette smoking habit. The leucocyte count groups are in quintiles (1000 leucocytes/mm^3 = 1·0 × 10^9/l).*

their similarity to never smokers is not surprising.

The time interval between blood sampling and the last cigarette smoked was not noted in this study. The timing of blood sampling is unlikely, however, to have influenced our findings, as we found no correlation between the leucocyte count in smokers and the time interval between blood sampling and the last cigarette smoked in 162 male workers.[19] The long term stability of leucocyte counts is not known. Sparrow and coworkers[15] performed leucocyte counts during both initial and follow up visits in their study; the stability of the leucocyte count was not explored. Among current smokers, however, the count must remain raised.

The mechanisms leading to an association between a raised leucocyte count and a greater decline in FEV_1 are not clear. In smokers the peripheral leucocyte count may be related to the degree of inflammation in small airways, which has been shown to be related to abnormalities in small airway function.[20,21] In a study of 162 non-occupationally exposed white men[19] we showed that it was the neutrophil count that led to the association between leucocyte count and lung function in smokers; there was no association between lung function and other leucocyte cell types. We did not determine the differential white cell count in the present study, but increased leucocyte counts in smokers have been shown to be due to an increase in neutrophils.[5,19] Although in our previous study[19] lung function in smokers was related to neutrophil counts, it was not related to neutrophil elastase concentrations.

These findings fit the proteolytic hypothesis of the development of emphysema if in smokers damage to airways and terminal lung units is more dependent on the degree of inflammatory reaction than on the elastase content of neutrophils. Although the elastase content per neutrophil was not increased in smokers, the total amount of elastase in the lung potentially available for inducing proteolytic injury would be increased because of the increased number of neutrophils in the lungs of smokers.[13] The increased numbers of neutrophils in smokers may also contribute to protease-antiprotease imbalance by oxidative inactivation of α_1 protease inhibitor through myeloperoxidase or superoxide release. These two potential mechanisms are supported by the finding of an association between smoking and increased neutrophil myeloperoxidase activity,[22] and by the report of increased generation of superoxide anion by stimulated neutrophils in smokers with leucocyte counts over 9·0 × 10^9/l.[23]

The relationship between lung function and leucocyte (neutrophil) count may depend on mechanisms other than protease-antiprotease imbalance. Airway reactivity may be related to airway inflammation, as suggested by animal studies,[24] and thus to peripheral blood leucocyte counts. There was no apparent relationship, however, between neutrophil or leucocyte blood counts and bronchial reactivity in an epidemiological survey of woodmill workers.[25] The adverse effect of leucocytes on airway function may be mediated through other mechanisms, such as the release of chemical mediators[26] or the release of oxygen radicals.[27] An increased leucocyte count could also reflect infection, which might be related to lung function decline. Finally, the relation between a raised leucocyte count and increased FEV_1 decline may not be causal but may be an association related to

Table 4 *Regression of annual change in FEV_1 on leucocyte count according to cigarette smoking habit*

	Never smokers			*Former smokers*			*Current smokers*		
Variable	*B*	*SEM*	*p*	*B*	*SEM*	*p*	*B*	*SEM*	*p*
Age	−1·00	0·27	<0·001	−0·62	0·32	0·04	−1·43	0·214	<0·001
Non-white	0·70	5·95	0·91	8·23	13·05	0·53	2·86	12·0	0·81
Leucocyte count (× 10^3/mm^3)	−3·00	2·08	0·12	−1·07	2·21	0·63	−3·43	1·38	<0·02
Constant	−53·53	71·72	0·46	53·64	84·28	0·52	120·7	66·6	0·07

B—regression coefficient.

smoking. For example, leucocytosis may be a marker for cigarette smoking *dose* and may therefore be a better measure of the duration and dose effect of smoking than estimates based on cigarette consumption. Further work is needed to explore the relation between leucocyte count and lung function.

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