Alpha₁ antitrypsin and lung function in British coalminers

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ABSTRACT Alpha₁ antitrypsin (α_1 AT) serum concentration was determined for a group of coalminers with particularly low levels of lung function, not thought to be explicable in terms of age and dust exposure, and compared with two other groups of coalminers who had average or above average lung function. There was no evidence for an α_1 AT deficiency in coalminers with poor lung function. On the contrary, a reactionary increase was evident, even in non-smokers, which may have resulted from the high frequency of chest disease in these men. Within the non-smoking group men with poor lung function had been exposed to higher mean levels of dust, and a greater proportion had early signs of bronchitis. There was no indication that the presence or degree of pneumoconiosis was affecting the results.

Exposure to coalmine dust is related to loss of lung function characteristic of obstructive airways disease even in coalminers with no radiological signs of pneumoconiosis and regardless of smoking habit.¹⁻³ This loss of lung function may in some cases result from dust induced chronic bronchitis⁴ or it may be related to an increased susceptibility to the effects of dust which are manifest as emphysema. A factor in this development of emphysema could be the serum concentration of α_1 antitrypsin (α_1 AT). This is a major protease inhibitor whose basal serum concentration is genetically controlled, and severely deficient individuals have about a 15-fold increased likelihood of developing emphysema.⁵ Although the phenotype responsible for severe deficiency, Pi Z, is rare (1 in 2312),⁶ some other phenotypes tend to have reduced serum concentrations when compared with the common Pi M. Individuals with the Pi MS phenotype have 81%, Pi MZ have 60%, Pi SS have 71%, and Pi SZ have 39% of the mean normal Pi MM concentration. Since the age of onset and severity of obstructive airways disease may be influenced by external factors such as smoking and air pollution,⁷ coalminers with reduced serum concentrations of α_1 AT may be more susceptible to the effects of dust exposure.

Accordingly, it was of interest to determine whether coalminers with particularly low levels of lung function which were not explicable in terms of age and dust exposure differed systematically from other coalminers in their serum concentrations of α_1 AT.

Subjects and methods

The cases for study were selected from records compiled during the fourth of a series of medical surveys in the National Coal Board's pneumoconiosis field research. Complete records of dust exposure, radiological category, and lung function data were available for 8467 coalminers from nine collieries. Radiological classification was based on clinical reading of the fourth survey chest radiograph by one physician from the National Coal Board's radiographic service. Each individual's latest available forced expired volume in one second (FEV₁) was compared with an expected value calculated from a multiple regression analysis of the data, which took into account the known effects of age, height, and dust exposure. Since there is a direct relation between smoking and emphysema, the effect of smoking on FEV₁ could not be standardised for at this stage as it might have excluded those men we wished to study.

It was hoped to obtain sera from a total of 500-600 men, but to allow for men who could not be contacted or did not wish to give a blood sample a

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list of about double this number of names was prepared. The extremes and middle range of the distribution of the standardised differences (t values) between the observed and expected FEV_1 were used to identify three contrasting groups: those with FEV_1 (a) lower than expected ($t < -1.758$), (b) higher than expected ($t \geq 1.496$), and (c) close to that expected ($-0.061 \leq t \leq 0.059$). Men were chosen sequentially from the highest or lowest t value present, or equally around the zero point, as appropriate, there being 420 in each group. Of the 1260 men thus selected, 480 agreed to participate and they came from eight collieries, one in Scotland, three in Wales, and four in England. One colliery did not participate because of time limitations. Blood samples were obtained blind and then grouped by lung function at the end of the study.

A simple questionnaire concerned mainly with smoking habit and respiratory health was completed in each case. This questionnaire was based on that produced by the Medical Research Council for studies on chronic bronchitis.⁸ The number of men who reported having been off work for at least one week during the previous three years with a chest illness was tabulated for each lung function group. Within the non-smoking group only, the number of men with early bronchitic symptoms—that is, persistent cough and sputum production—was also calculated. From the smoking data men were grouped into smokers (current), ex-smokers (smoked at least one cigarette a day for one year) and non-smokers. Serum α_1 AT concentrations were measured by the rocket immunoelectrophoretic method⁹ that was in routine use in a hospital service laboratory. This method had been standardised exactly to the reference standard used by Cole *et al*⁶ which gave a mean normal adult value of 2.4 g/l. The reference range for normal healthy individuals thus derived was 1.8–4.0 g/l. A normal plasma pool (Hoechst UK Ltd, Hounslow) was included for internal quality control and the between batch coefficient of variation was 10%. The phenotype was determined by thin layer isoelectric focusing.¹⁰

Results

Using the selection procedure outlined, more than 70% of the group with lower than expected lung function had a measured FEV_1 of less than two litres, while all the remaining men had a measured FEV_1 of greater than two litres. Blood samples were accepted from all men who agreed to participate, and relatively similar numbers of men were sampled from each lung function group (table). Their distribution by smoking habit and presence or absence of pneumoconiosis was also similar. Many more men

Details of men studied and their α_1 antitrypsin concentrations and phenotypes

	Lung function		
	Low	High	Average
No of men	141	170	169
Percentage smokers	56	53	63
No with simple pneumoconiosis	16	17	19
No with progressive massive fibrosis (PMF)	3	0	2
Mean α_1 AT concentration (g/l)	3.29*	2.96	2.93
Standard deviation	0.83	0.61	0.64
Range	1.2–6.8	1.3–5.6	1.4–5.1
No phenotyped	17	38	40
No with:			
Pi MZ	2	3	6
Pi MS	6	5	6
Pi S	1	0	1

* $p < 0.001$ of either group (one way analysis of variance).

in the low FEV_1 group had a history of chest disease (48%) compared with the other groups combined (11%).

The mean concentration of serum α_1 AT for the group with low FEV_1 was significantly greater than for either the high or average group ($p < 0.001$ in each case, table), but the range of values in the groups was large. This general trend was apparent in most collieries, and there was no obvious geographical influence on the results.

Smokers had a significantly higher mean α_1 AT concentration within each lung function group ($p < 0.005$ – 0.001 , figure). Within smokers and non-smokers men with low FEV_1 had significantly higher mean α_1 AT concentrations ($p < 0.05$ – 0.001). The interlung function group differences for smokers, however, could not be related to the number of cigarettes smoked a week.

In view of the significant differences between lung function groups within non-smokers, these men were examined in more detail with respect to chest disease and dust exposure. The 25 non-smokers with poor lung function contained a significantly higher proportion with the earliest bronchitic symptoms (56% v 11% for the remainder) and breathlessness (48% v 9%). Moreover, these men with low FEV_1 had been exposed to higher dust levels, on average, than the other non-smokers (130 gh/m^3 v 96 gh/m^3).

Mean α_1 AT concentrations in those with and without pneumoconiosis were virtually identical (3.04 and 3.05 g/l respectively), and variations within lung function and smoking groups gave no indication that the radiological status of the men was affecting the results.

In the present study facilities for determining the α_1 AT phenotypes were limited and only those samples with less than 2.6 g/l were typed. This value is

Means and standard deviations of α_1 antitrypsin concentrations in smokers (S), ex-smokers (X), and non-smokers (NS). Smokers had significantly higher mean concentrations of α_1 antitrypsin than non-smokers in each lung function group: low $p < 0.005$; high $p < 0.005$; average $p < 0.001$.

well within the normal range for Pi M phenotypes and it was therefore assumed that those non-Pi M phenotypes that have reduced basal levels of α_1 AT would be detected. The samples were examined blind and because of this cut off procedure, proportionately fewer men with lower FEV₁ values were phenotyped, since they tended to have higher α_1 AT concentrations. Of the 95 sera typed, 65 were Pi M, 17 were Pi MS, 11 were Pi MZ, and two were Pi S: none of the sera was Pi Z or Pi SZ. These 30 sera with Pi MS, MZ, and S will be referred to as the non-Pi M phenotypes in the present study. The proportion of men in this group who had a history of chest disease was similar to that of the Pi M/untyped group.

Discussion

The relation between serum α_1 AT concentration or phenotype and the effects of dust exposure have been investigated in few working populations. A group of coalminers with signs of airways obstruction had a mean trypsin inhibitory capacity similar to a group with symptoms of respiratory impairment but no airways obstruction¹¹; these cases were not, however, phenotyped. In an American study of grain and sawmill workers no interphenotypic differences in chest symptoms or lung spirometry were found, and when dust exposure and smoking were correlated with FEV₁ the rates of decline for all phenotypes were similar.¹² There was no evidence

that the MZ phenotype was associated with increased susceptibility to dust, although exposures of the cases studied were relatively low. When only the Pi M cases in this American study were investigated,¹³ it was evident that the serum α_1 AT concentrations were more closely related to the duration of smoking than to dust exposure, although within the non-smokers there appeared to be additional dust related differences. Cole *et al* surveyed a working population in Northern Ireland, some of whom had been exposed to dust.⁶ Respiratory symptoms and chest illness occurred with similar frequency among the M, MS, and MZ phenotypes, and pulmonary function tests gave no evidence that Pi MS or MZ individuals exposed to dust were more likely than similarly exposed Pi M individuals to develop chronic airways obstruction.

The present study was designed in a different manner to the foregoing since men with unaccountably low lung function were specifically sought and compared with two other groups. Some men who were approached declined to give blood samples and some had left the industry. The reasons for failure to obtain blood were not recorded since relatively equal numbers of men were available from each of the three respiratory function groups, and there was no evidence that the most severely disabled cases were being lost.

There were no clinical or radiological data available to identify specifically those men with emphysema, but it was assumed that any men severely affected by the disease would be likely to have abnormally low levels of FEV₁ and would therefore probably be included in the low lung function subgroup. The criteria used to define low lung function included the known effects of age, height, and dust exposure, none of which is related directly to emphysema.

The results show that coalminers with unexpectedly low lung function, as a group, were not deficient in serum α_1 AT at the time of the survey. Neither were there more individuals in this group with relatively low serum concentrations: none in the study as a whole had a severe deficiency of α_1 AT (< 1.0 g/l).

Smoking is known to cause a persistent rise in serum α_1 AT by as much as 20%,¹⁴ and this effect was observed in each lung function group. Nevertheless, smoking did not account for the intergroup differences since the percentage of smokers was similar in each group and these differences were also present in ex-smokers and non-smokers. It is now apparent that certain factors in cigarette smoke can inactivate α_1 AT¹⁵ and despite high circulating concentrations in smokers reduced antiprotease activity may be present. The present study, however, meas-

ured the α_1 AT protein content of serum rather than its enzyme inhibitory capacity. Within the non-smokers with low FEV₁ at least some of their poor lung function was attributable to the higher frequency of dust related bronchitis, which in turn probably accounted for their raised serum α_1 AT.

No definite conclusion can be reached concerning the part that certain phenotypes of α_1 AT may play in the pathogenesis of coalworkers' loss of lung function. A high proportion of the men with non-Pi M phenotypes had α_1 AT concentrations close to the cut off point, and their overall frequencies (assuming the untyped cases to be Pi M) were lower than expected.⁶ Thus probably some non-Pi M phenotypes have been missed because of the large reactionary increases in the concentration of α_1 AT. Alternatively, if men of these phenotypes were particularly susceptible to the effects of dust, then most of them may have left the industry through ill health. The present study was not designed to pursue this point.

In conclusion, this investigation has shown that loss of lung function in coalminers is not characterised by reduced serum concentrations of α_1 AT as measured by immunochemical methods.

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