Alpha\textsubscript{1} antitrypsin and lung function in British coalminers

J E Boyd,\textsuperscript{1,4} P Collings,\textsuperscript{1} P M Crofton,\textsuperscript{2} G Blundell,\textsuperscript{1} and J M G Davis\textsuperscript{1}

From the Institute of Occupational Medicine,\textsuperscript{1} the Department of Clinical Chemistry,\textsuperscript{2} Royal Infirmary, and the Department of Clinical Chemistry,\textsuperscript{3} Western General Hospital, Edinburgh, UK

ABSTRACT Alpha\textsubscript{1} antitrypsin (\(\alpha_1\) 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 \(\alpha_1\) 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.\textsuperscript{1-3} This loss of lung function may in some cases result from dust induced chronic bronchitis\textsuperscript{4} 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 \(\alpha_1\) antitrypsin (\(\alpha_1\) 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.\textsuperscript{5} Although the phenotype responsible for severe deficiency, Pi Z, is rare (1 in 2312),\textsuperscript{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,\textsuperscript{7} coalminers with reduced serum concentrations of \(\alpha_1\) 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 \(\alpha_1\) 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 (FEV\(_1\)) 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 FEV\(_1\) 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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*Present address: Department of Surgery, Edinburgh University.
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 FEV₁ were used to identify three contrasting groups: those with FEV₁, (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. 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 \(\alpha-1\) AT concentrations were measured by the rocket immunoelectrophoretic method 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 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.

**Results**

Using the selection procedure outlined, more than 70% of the group with lower than expected lung function had a measured FEV₁ of less than two litres, while all the remaining men had a measured FEV₁ 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 in the low FEV₁ group had a history of chest disease (48%) compared with the other groups combined (11%).

The mean concentration of serum \(\alpha-1\) AT for the group with low FEV₁ 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 \(\alpha-1\) AT concentration within each lung function group (p < 0.005–0.001, figure). Within smokers and non-smokers men with low FEV₁ had significantly higher mean \(\alpha-1\) 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 FEV₁ had been exposed to higher dust levels, on average, than the other non-smokers (130 g/m² v 96 g/m²).

Mean \(\alpha-1\) 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 \(\alpha-1\) AT phenotypes were limited and only those samples with less than 2.6 g/l were typed. This value is

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**Details of men studied and their \(\alpha-1\) antitrypsin concentrations and phenotypes**

<table>
<thead>
<tr>
<th>Lung function</th>
<th>Low</th>
<th>High</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of men</td>
<td>141</td>
<td>170</td>
<td>169</td>
</tr>
<tr>
<td>Percentage smokers</td>
<td>56</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td>No with simple pneumoconiosis</td>
<td>16</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>No with progressive massive fibrosis (PMF)</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mean (\alpha-1) AT concentration (g/l)</td>
<td>3.29*</td>
<td>2.96</td>
<td>2.93</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.83</td>
<td>0.61</td>
<td>0.64</td>
</tr>
<tr>
<td>Range</td>
<td>1.2–6.8</td>
<td>1.3–5.6</td>
<td>1.4–5.1</td>
</tr>
<tr>
<td>No phenotyped</td>
<td>17</td>
<td>38</td>
<td>40</td>
</tr>
</tbody>
</table>

*| p < 0.001 of either group (one way analysis of variance).
Alpha1 antitrypsin and lung function in British coalminers

Means and standard deviations of α1 antitrypsin concentrations in smokers (S), ex-smokers (X), and non-smokers (NS). Smokers had significantly higher mean concentrations of α1 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 α1 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 α1 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 α1 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 obstruction9; 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 α1 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 α1 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 α1 AT (<1.0 g/l).

Smoking is known to cause a persistent rise in serum α1 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 α1 AT15 and despite high circulating concentrations in smokers reduced antiprotease activity may be present. The present study, however, meas-
ured the $\alpha_1$ AT protein inhibitor content of serum rather than its enzyme inhibitory capacity. Within the non-smokers with low FEV$_1$ 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 $\alpha_1$ AT.

No definite conclusion can be reached concerning the part that certain phenotypes of $\alpha_1$ AT may play in the pathogenesis of coalworkers' loss of lung function. A high proportion of the men with non-Pi M phenotypes had $\alpha_1$ AT concentrations close to the cut off point, and their overall frequencies (assuming the untyped cases to be Pi M) were lower than expected. Thus probably some non-Pi M phenotypes have been missed because of the large reactionary increases in the concentration of $\alpha_1$ 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 $\alpha_1$ AT as measured by immunochemical methods.

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Requests for reprints to: Dr J M G Davis, Pathology Branch, Institute of Occupational Medicine, 8 Roxburgh Place, Edinburgh EH8 9SU.
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