Discussion

Although substantial circumstancial evidence suggests that streptococcal infections are causally related to acute rheumatic fever and its residue as chronic RHD, the precise nature of the link continues to elude workers, despite much research. An immunological basis seems quite likely, and we have shown the presence of delayed hypersensitivity reactions against streptococcal membrane antigen in patients with chronic RHD. Whereas the B-cell population seems to be normal, the T-cell population is greatly reduced in most of these patients. Furthermore, the lymphocytes fail to respond normally to non-specific stimulation by PHA but are strongly stimulated by the streptococcal membrane antigen. Read *et al*[8] have also shown specific stimulation by the streptococcal membrane antigen of group A β-haemolytic streptococci in patients with RHD. Such a response is not elicited by other components of these organisms or by other groups of streptococci. The susceptibility of patients may well be related to the specific sensitisation of lymphocytes. Persistence of enhanced antigen sensitisation, even when the T-cell counts improved at the end of six weeks, suggests that this abnormality may persist for a long time and account for the well-known recurrences after streptococcal infection in these patients.

There were no essential differences between patients with chronic RHD and those who also had evidence of acute rheumatic activity. In view of the small numbers definite conclusions may not be warranted. Nevertheless, the population under study all had chronic RHD, and by the time the condition reaches this stage recrudescence may not result in further changes in previously upset immunological mechanisms. To determine whether this is so the changes in patients with acute streptococcal sore throat but without RHD would have to be studied. Such a study is in progress.

The mean values of CH_{50} and C3 were reduced in patients with RHD, suggesting that a complement-mediated injury may have occurred at some stage in the course of the disease. Similar findings have been reported with other sequelae of streptococcal infections such as glomerulonephritis. These low levels persist for varying lengths of time. Of interest is the demonstration of low levels of complement in the synovial fluid of patients with acute rheumatic fever, both at an early stage and later in the disease.[17]

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Pneumoconiosis and chronic bronchitis

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Summary

Data from a major long-term epidemiological survey in the British coalmining industry were examined to determine whether bronchitis offered any protective action against the development of pneumoconiosis. No evidence of such an effect was found.

Introduction

Pneumoconiosis and chronic bronchitis are important diseases in the coalmining industry. The former is accepted as being clearly of occupational origin, but the cause of the latter is more contentious since it is associated with several factors, including dust exposure, tobacco smoking, air pollution, and respiratory illness during childhood. The relation between the two diseases was reviewed by Davies,[1] who discussed the effects of a possible interaction on the clinical assessment of disability in coalworkers. Questioning the view that simple pneumoconiosis does not cause disability, he pointed out that if, as has been postulated, chronic bronchitis protects men from developing pneumoconiosis, this would generate a relative excess of chronic bronchitis among men without pneumoconiosis. According to the theory an uneven distribution of chronic bronchitis among coalminers might mask a moderate effect of simple pneumoconiosis on ventilatory capacity. Davies[1] went on to review evidence suggesting that bronchitis might indeed have a protective action against the development of pneumoconiosis.

Our purpose was to consider whether persistent sputum production is associated with any protective action against the development of simple pneumoconiosis. Data for the investigation were obtained from the long-term epidemiological study that has been in progress for some years in the British coalmining industry.

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Methods

The survey by the medical service of the National Coal Board into respiratory diseases among miners started in 1953. Miners (initially

32 000 working at 25 selected collieries throughout the country) have been examined radiologically about every five years. At the second and subsequent surveys they were asked about respiratory symptoms using a questionnaire similar to that adopted by the MRC,[2] and the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured. Underground concentrations of dust in the respirable size range were also monitored so that estimates of each man's cumulative dust exposure were available. The methods were first described by Fay and Rae[3] and further details were provided by Rogan *et al.*[4] There have been various reports of findings relating dust exposure to pneumoconiosis,[5] respiratory symptoms,[6] and ventilatory capacity.[7]

With the contraction of the industry collieries were closed, and many men in the original cohort retired. Only 10 of the original 25 collieries were included in the fourth survey. For this investigation we drew our information from the results of examinations of 14 502 men at these 10 collieries who were present at the second visit (referred to here as the earlier survey). Altogether 5098 of these men were still present at the fourth visit some 10 or 11 years later (referred to as the later survey). Complete data were available for 4883 men who had been present at both surveys. Incomplete information, mostly due to missing environmental exposure records, resulted in the rejection of 215 men.

At the earlier visit the mens' radiographs were examined separately by any two of the four doctors in the research team and classified according to the ILO (1959) classification of pneumoconiosis[8] without knowledge of the mens' symptoms. When there was disagreement over the classification the films were re-examined and an agreed classification was reached after discussion. At the survey 10 years later each film was examined for clinical purposes by a single reader and classified according to the four-point scale of simple pneumoconiosis of the ILO (1968) classification.[9]

Men were classified as having persistent sputum production if they gave positive replies to the last two of the following three questions: (1) Do you bring up phlegm when you get up or first thing in the morning? (2) Do you bring up phlegm during the rest of the day? I don't mean just at the end of your shift. (3) Do you bring up phlegm like this on most days for as much as three months in the year?

Individuals' exposures to dust during the course of the survey were calculated from dust sampling results and detailed records of attendance at work. Dust concentrations were measured by particle-counting techniques and gravimetric sampling.[10] Estimates of dust exposure before the start of the surveys were obtained from information on earlier industrial histories and mean dust concentrations found during the first 10 years of the research. The sums of the measured exposures and estimates of earlier exposures are used in this paper as approximations to cumulative (working life) exposures. The measures refer to airborne particles in the respirable size range and reflect the cumulative sum of mass concentrations in the ambient air (g/m^3) multiplied by the duration of exposure (hours).

TABLE I—*Pneumoconiosis and reports of persistent sputum production at earlier survey*

	No pneumoconiosis	Simple pneumoconiosis	Progressive massive fibrosis	Total
Persistent sputum	464	103	18	585
No persistent sputum	3892	365	41	4298
Total	4356	468	59	4883

The data were examined to establish the attack rate of pneumoconiosis over the 10-year period among men whose radiographs were originally classified as normal—that is, category 0. Pneumoconiosis was defined as the presence of category 1 or more. Those men whose radiographs were classified as category 0 at the earlier surveys were divided into those who had reported symptoms of persistent sputum production (as defined above) at the earlier surveys and those who had not. It was thus possible to examine the attack rate of pneumoconiosis in the two groups separately and to consider whether men who reported persistent sputum production were less likely to develop pneumoconiosis. In making this comparison it is, of course, necessary to consider any differences between the dust exposures of the two groups during the 10 years. A further complication, however, is that a pneumoconiosis category does not define a precise condition but rather a range of conditions. Men classified as category 0 at the earlier surveys had already been exposed to various amounts of dust and whether or not they would cross from category 0 into category 1 during the period of study depended on the previous exposure as well as on the exposure in that period.

Results and comment

The radiological classifications at the earlier survey and the number of men reporting persistent sputum production are shown in table I. Clearly, there was a greater proportion of men with symptoms of sputum production among those with pneumoconiosis, as has been reported already.[6] Our analyses were confined to the 4356 men who did not have pneumoconiosis at the earlier survey. The attack rate of pneumoconiosis over 10 years and indices of dust exposure among these men are shown in table II. The dust exposure indices were obtained by multiplying measured airborne concentrations (g/m^3) by the number of hours worked. In addition to reflecting the dustiness of the pit in which the man worked they reflected his length of service in the industry and his age. Not surprisingly, the men who developed pneumoconiosis were older and had received higher dust exposures on average than those who did not. The difference between the exposures was greater over the previous period than during the 10 years between the surveys; this reflects the difference in age and years of employment.

Table II shows that in both groups those who developed pneumoconiosis during the 10 years had, on average, been exposed to more dust than those who did not develop the disease. The attack rate of pneumoconiosis over the 10 years was higher (11·0%) among the men who had reported persistent sputum than among those who had not (7·3%), despite the fact that the former group had slightly lower dust exposures on average in the 10 years. This seems to contradict the hypothesis that sputum production protects against pneumoconiosis. Indeed, it raises the question whether those miners who complain of sputum are more likely to develop pneumoconiosis than those who do not. But reference to the mean of the estimated exposures throughout the working lives of the men concerned (also shown in table II) does not support this suggestion: the higher attack rate (11%) occurred in the group with the higher mean cumulative exposure (158 gh/m^3 compared with 132 gh/m^3 for the group who did not report sputum). Moreover, the cumulative exposures of the men who were attacked —that is, those who passed the upper bound of category 0 during the 10 years, were, on average, somewhat lower among men who did not produce sputum than among those who did. A similar difference was also seen among the men who remained within category 0. This suggests that sputum producers may require a greater dust exposure to reach the same point on the pneumoconiosis scale, and hence it might be inferred that sputum production does protect against pneumo-

TABLE II—*Pneumoconiosis attack rate over 10 years and dust exposures among men with and without persistent sputum at earlier surveys*

Mean values	Persistent sputum at earlier survey			
	Present		Absent	
	Pneumoconiosis later	No pneumoconiosis later	Pneumoconiosis later	No pneumoconiosis later
No of men	51	413	284	3608
Age at first survey (years)	39	35	36	31
Estimated exposures to dust before earlier survey (gh/m^3)	208	99	155	74
Estimated exposures to dust in 10 years between surveys (gh/m^3)	57	47	67	51
Estimated cumulative dust exposures up to later survey (gh/m^3)	264	145	222	125
Pneumoconiosis attack rate (%)	11·0		7·3	

coniosis. Clearly, a more detailed analysis is needed to resolve the issue.

The relation between the attack rate of pneumoconiosis and dust exposure during the 10-year intersurvey period is illustrated in fig 1. The attack rate increased with increasing cumulative exposure at a similar rate in both groups. The curve referring to those who reported sputum was consistently higher than that for those who did not report this symptom. Presumably this reflected the higher exposures experienced by the "sputum group" before the earlier survey (table II). This presumption was confirmed (see fig 2). The close superimposition of the curves indicated that the probability of developing pneumoconiosis depended on the cumulative exposure to respirable dust and was little affected by the presence or absence of symptoms of sputum.

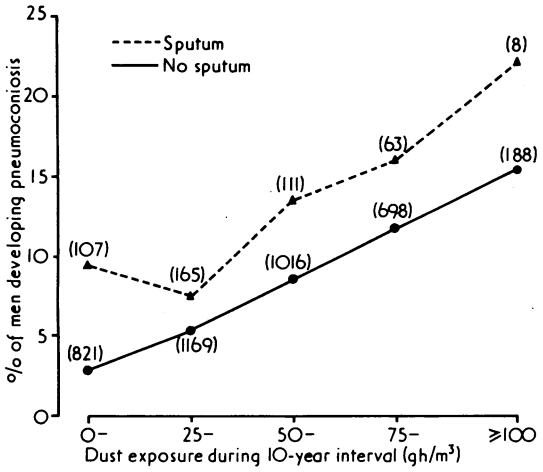

FIG 1—Percentages of men developing pneumoconiosis (categories ≥1) over about 10 years in relation to dust exposures experienced during the 10 years according to reports of sputum production at start of interval.

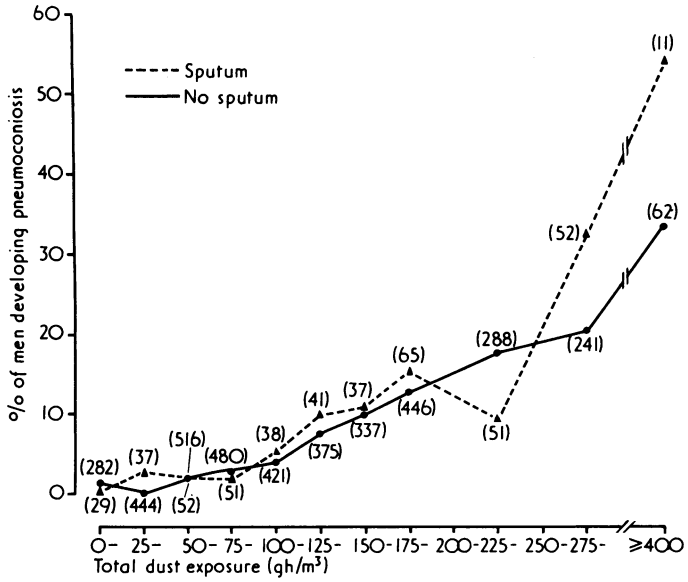

FIG 2—Percentages of men developing pneumoconiosis (categories ≥1) over about 10 years in relation to estimated cumulative dust exposures from start of work in the coal industry, according to reports of sputum production at start of interval.

The men were questioned with the respiratory symptoms questionnaire at both surveys. Identical answers were not received on the two occasions and the distribution of replies is shown in table III. The attack rate of pneumoconiosis among men who gave concordant replies on the two occasions is shown in table IV. The results were very similar to those for the whole group shown in table II and indicated that no serious bias was introduced.

TABLE III—*Reports of persistent sputum at earlier and later surveys in 4356 men with no pneumoconiosis at earlier surveys*

	Sputum at later survey		Total
	Present	Absent	
Sputum at earlier survey:			
Present	250	214	464
Absent	824	3068	3892
Total	1074	3282	4356

TABLE IV—*Attack rate of pneumoconiosis over 10 years among 3318 men who gave concordant replies to questions on persistent sputum production at earlier and later surveys*

	Persistent sputum at both earlier and later surveys	
	Present	Absent
Pneumoconiosis at later survey:		
Present	31	201
Absent	219	2867
Pneumoconiosis attack rate (%)	12·4	6·6

Discussion

In 1918 Haldane[11] considered sputum production in a collier to be a healthy sign, indicating that dust was being eliminated rapidly from the lungs. In later years he modified this view somewhat and accepted that excessive dust exposure could cause bronchitis.[12] He thought that such bronchitis might damage the particle clearance mechanisms and result in localised accumulations of dust in the lung. Kettle put forward an opposite suggestion during the discussion of a paper by Fisher.[13] He postulated that excessive mucus on the walls of the bronchioles might entangle inhaled dust particles and that mucus flow and dust clearance from the lungs might be thus enhanced.

Suggestions that bronchitis might offer some protection against pneumoconiosis have arisen from the results of some epidemiological surveys[14 15] and from clinical cases.[16] Gough[17] produced pathological evidence to suggest that mucus hypersecretion led to increased clearance of dust from the lung. Thomson and Pavia[18] thought it more likely that damage to the upper airways, with or without mucus hypersecretion, might prevent airborne dust penetrating to the alveoli. Supporting evidence for this was claimed in human volunteers exposed to radioactive aerosols.[19 20]

These indirect methods thus give conflicting results about the possible interaction between bronchitis and pneumoconiosis in coalworkers. Our data were analysed to answer the specific question whether bronchitis, as evidenced by persistent sputum production, influenced the subsequent attack rate of pneumoconiosis when due allowance was made for exposure to respirable dust. A population of men whose radiographs were normal at the start of the survey period was chosen because of the difficulty of refuting the hypothesis[1] that simple pneumoconiosis may itself "cause" cough and sputum in the absence of bronchitis.

Of the men included in the investigation about 10% had persistent sputum production (see table I). We made no attempt to distinguish the causative factors such as cigarette smoking, infections during childhood, and environmental or industrial exposure. The importance of the working environment is, however, indicated by this group's greater average dust exposure before the start of the investigation (see table II). Although all had radiographs classified as category 0, they cannot be regarded as representing a homogeneous group. Men with symptoms of sputum production had higher average previous cumulative dust exposure (table II) and a greater proportion were likely to have accumulated a quantity of dust in their lungs close to the amount that is detectable radiologically. For a given further dust exposure a greater proportion might therefore be expected

to cross the boundary to category 1 or more pneumoconiosis. This is in fact what happened and it is shown by the greater proportion who developed pneumoconiosis (table II) and the separation between the lines in fig 1. Nevertheless, the similarity of the dose-response curves shown in fig 2 shows that the presence or absence of sputum had no effect on the attack rate of pneumoconiosis.

The implications of a possible interaction between bronchitis and pneumoconiosis were discussed in detail by Davies.[1] For many years there has been controversy over the question of disability and abnormalities of respiratory function in men with pneumoconiosis. Most workers have found little difference in the results of simple function tests (FEV_1, FVC) between miners with normal radiographs and those with simple pneumoconiosis.[21 22] Higgins *et al*[15] even reported that miners without pneumoconiosis had, on average, more impairment of respiratory function than those with early simple pneumoconiosis. Davies[1] considered that simple pneumoconiosis could cause disability and he suggested that the reason why epidemiologists were unable to show the true extent of this might be because bronchitis offered some protection against pneumoconiosis. Since bronchitis is one of the diseases associated with airways obstruction, there was little difference between the results of pulmonary function tests among groups of miners with or without pneumoconiosis. One group was disabled by bronchitis and the other by pneumoconiosis.

Our results do not support this hypothesis. They are compatible with a simple model in which dust exposure in the mining industry may cause pneumoconiosis, bronchitis, or both. There is no suggestion that mucus hypersecretion offers any protection against simple pneumoconiosis of coalworkers. The possibility that airflow obstruction, irrespective of mucus hypersecretion, could have a protective action cannot be excluded. An analysis of this specific problem will be made as soon as adequate data have been accumulated in the epidemiological research programme. It is unlikely that airways obstruction will turn out to have a different effect from hypersecretion of mucus since those men in the present survey with the symptoms of chronic bronchitis probably included many who also had impaired ventilatory capacity.

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Prevalence of severe growth hormone deficiency

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Summary

Four hundred and forty-nine short children, who were all over 2·5 standard deviations below the mean height for age, were identified by screening the heights of 48 221 6- to 9-year-old children in three Scottish cities. Most were screened for growth hormone deficiency (GHD). The prevalence of severe GHD in this sample may have been as high as 1 in 4018, much higher than reported. The findings suggest that present referral patterns may account for the delayed or missed diagnosis of the condition in girls or children with less severe short stature.

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Introduction

The primary objective of the Scottish Survey of Short Stature has been to discover the prevalence of growth hormone deficiency (GHD). Information about the prevalence of this condition is important, as it indicates the likely therapeutic requirements for growth hormone (GH) were all those suffering from this condition being diagnosed.

In this study we defined severe GHD by the following criteria: (*a*) height over 2·5 standard deviations below mean height for age, (*b*) height velocity less than 25th centile for chronological age (over 1 year wherever possible), (*c*) maximum GH concentration of 9 mU/l or less in two or more diagnostic tests. By using artificial stimuli in a radioimmunoassay procedure it is nevertheless possible to miss occasional patients with biological GHD who will respond to treatment with GH despite apparently normal GH levels.[1 2] Conversely, some children with low GH levels under experimental testing are capable of normal growth[3] or, alternatively, fail to respond to administered human