sumably also other diuretics, should therefore be used with caution in patients given lithium treatment, and long-term use should be accompanied by frequent determinations of the serum lithium concentration. If this increases, the lithium dosage should be reduced or treatment with diuretic drugs discontinued.

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# Circulating Antinuclear Antibody and Rheumatoid Factor in Coal Pneumoconiosis

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### Summary

**Circulating antinuclear antibody and rheumatoid factor have been measured in 109 coal miners with pneumoconiosis whose chest radiograph showed a range of abnormalities varying from simple pneumoconiosis of mild degree to advanced progressive massive fibrosis.**

**At a screening dilution of 1/10 the overall incidence of antinuclear antibody was 17%. In almost half of the positive cases the titre was 1/40 or greater.**

**The prevalence of antinuclear antibody was lowest in those with simple pneumoconiosis (9%) and highest in those with category C progressive massive fibrosis (27%). A similar but less striking trend was seen with rheumatoid factor, ranging from 6% in simple pneumoconiosis to 18% in category C progressive massive fibrosis. The trend of increasing frequency of autoantibodies with advancing radiographic category was most marked when the frequencies of antinuclear antibody and rheumatoid factor were combined. These autoantibodies were found in 13% of the miners with simple pneumoconiosis and 45% of those with category C progressive massive fibrosis (P for the trend=0·01).**


### Introduction

The association between distinctive nodular types of radiographic opacities in the lungs of coal miners and rheumatoid arthritis was described by Caplan (1953) and confirmed in an epidemiological study by Miall *et al.* (1953). Later a similar radiographic appearance was described in miners without arthritis but in whom circulating rheumatoid factor (R.F.) was present (Caplan *et al.*, 1962). These workers also found a slightly increased incidence of rheumatoid factor among miners with conventional progressive massive fibrosis and this was confirmed by Wagner and McCormick (1967).


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An increased incidence of rheumatoid factor has also been described in asbestos workers with pulmonary fibrosis (Pernis *et al.*, 1965; Turner-Warwick and Parkes, 1970). Turner-Warwick and Parkes (1970) also found an increased incidence of antinuclear antibodies (A.N.A.) in asbestosis similar to that found in cryptogenic fibrosing alveolitis (Turner-Warwick and Doniach, 1965; Turner-Warwick and Haslam, 1971).

In view of the range of radiographic abnormalities seen in coal miners, some relating to the deposition alone of coal and other mineral dust and others associated with fibrosis of the lungs, we wished to establish whether antinuclear antibody could also be found in coal miners with pneumoconiosis and if so whether it related to certain types of radiographic abnormality.

### Patients and Methods

The 109 subjects (miners and ex-miners) attended the London Pneumoconiosis Medical Panel during 1971 and 1972. They were admitted to the study consecutively and without selection provided that permission to take a blood sample was given. As about equal numbers of patients were required in each radiographic category of pneumoconiosis intake was stopped as sufficient numbers in each category were obtained. For this purpose the category was judged by one of us (W.R.P.) on a preliminary reading. No patient was selected or excluded on the basis of rheumatoid arthritis or any other clinical feature. All had been accepted by the Panel as having coal pneumoconiosis.

*Recording of Clinical Data.*—Clinical data and the history of coal dust exposure were recorded on a standard questionnaire when the patient attended the Panel. Most of the patients had worked in mines in more than one geographical area, so that the type of coal dust exposure was mixed.

*Serological Tests.*—Clotted blood samples were sent from the Pneumoconiosis Medical Panel to the laboratory. Antinuclear antibody was estimated by a standard double-layer immunofluorescent technique on sections of rat liver at a screening dilution of 1/10. Titres of positive sera were estimated by serial serum dilutions using the same technique. Rheumatoid factor was estimated by the differential agglutination test (D.A.T.) (Rose *et al.*, 1948) and by the agglutination of latex particles coated with human gammaglobulin (Behringwerke). A D.A.T. titre of 1/32 or over was accepted as positive irrespective of the result of the latex test. A D.A.T. titre of 1/16 was accepted as positive only if the latex test result was positive. Positive latex test results with a negative D.A.T. result were disregarded.

*Reading of Chest Radiographs.*—The chest radiograph from each patient, taken on the same day as the blood sample, was read independently by each of us using the International Union against Cancer (U.I.C.C.) (1970) classification of radiographic appearances of pneumoconiosis. A final reading used in the subsequent analysis was agreed on the following basis; the majority verdict on each appearance was selected and in cases on which no two readers agreed the intermediate reading was selected (see Final Recording, fig. 1). The earliest radiograph from each patient in the possession of the Panel was also read and the results subsequently compared with the most recent radiograph. All references to radiographs made here, however, are to the recent radiograph unless otherwise stated.

## Results

### AGE AND DURATION OF EXPOSURE TO COAL DUST

The ages of the 109 patients ranged from 42 to 78 years (mean 61 ± S.D. 8·8 years). The durations of exposure to coal mine dust are set out in table I.

TABLE I—*Duration of Exposure to Coal Dust*

| Years of exposure | 1-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | Total |
|---|---|---|---|---|---|---|---|
| No. of patients .. .. | 3 | 20 | 20 | 20 | 31 | 15 | 109 |

### RADIOGRAPHIC APPEARANCES

The frequency with which each reader recorded the various radiographic abnormalities are shown in fig 1. The profiles for each reader agreed reasonably well except that when readers 2 and 3 recorded the presence of small irregular opacities (s, t, u) reader 1 tended to record both irregular and regular opacities (p. q, r) as "combined".

The profile for the final recording of radiographic appearances is included in fig. 1. The extent of agreement on whether large opacities (progressive massive fibrosis) were present and if so to which category they belonged (A, B, or C) was sufficiently good to permit use of the final recording for comparisons with the serological findings (all three readers agreed on 51% of the radiographs, two agreed on an additional 46% of the radiographs, and the three readers failed to agree at all on only 3% of the radiographs).

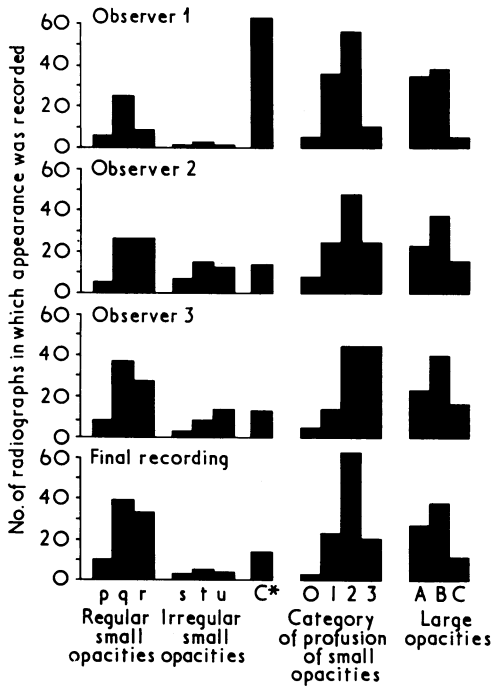


FIG. 1—Frequency with which various radiographic abnormalities were recorded by three observers. C* = Combined regular and irregular.

### SEROLOGY

Antinuclear antibody was detected in 19 (17%) of the 109 patients. In nine of these the titre was 1/40 or greater (table II). The antinuclear antibody was more common in those with progressive massive fibrosis (21%) than in those with simple pneumoconiosis only (9%), and in this small series the frequency of antinuclear antibody appeared to be related to the category of fibrosis (see table IV). It ranged from 14% in those with category A to 27% in those with category C progressive massive fibrosis. The statistical significance of this trend approaches the 5% level.

TABLE II—*Distribution of A.N.A. Titres*

| A.N.A. titre | 1/10 | 1/20 | 1/40 | 1/80 | Total |
|---|---|---|---|---|---|
| No. of Patients .. .. .. | 6 | 4 | 8 | 1 | 19 |

Rheumatoid factor was detected in 11 patients (10%) (table III). Though it appeared to be more common in those with extensive progressive massive fibrosis (16% and 18% in B and C categories respectively) than in those with simple pneumoconiosis only (6%) this difference does not reach statistical significance (table IV).

TABLE III—*Distribution of D.A.T. Titres. Numbers of Patients with Clinical Rheumatoid Arthritis are shown in Parentheses*

| D.A.T. titre | 1/16* | 1/32 | 1/64 | 1/128 | >1/512 | Total |
|---|---|---|---|---|---|---|
| No. of patients .. | 2 (1) | 3 (2) | 2 (1) | 1 | 3 (2) | 11 (6) |

*D.A.T. titres of 1/16 included only when latex test also gave positive result.

TABLE IV—*Presence of A.N.A. and R.F. in the 109 Patients according to Category of Pneumoconiosis*

| | Category of Pneumoconiosis | | | | Total |
|---|---|---|---|---|---|
| | Simple | Progressive Massive Fibrosis | | | |
| | | A | B | C | |
| No. of patients: | 32 | 28 | 38 | 11 | 109 |
| No. (%) with A.N.A. | 3 (9) | 4 (14) | 9 (24) | 3 (27) | 19 (17) |
| No. (%) with R.F. | 2 (6) | 1 (4) | 6 (16) | 2 (18) | 11 (10) |
| No. (%) with A.N.A. or R.F. or both | 4 (13) | 5 (18) | 12 (32) | 5 (45) | 26 (24) |

Note: Four patients had both A.N.A. and R.F. and are therefore represented in both categories. ($\chi^2$ trend for A.N.A. in the four categories = 3.32, P = 0.07. Trend for R.F. not significant. $\chi^2$ Trend for A.N.A. and R.F. together = 6.6, P = 0.01.)

The combined incidence of antinuclear antibody and rheumatoid factor appeared to show a clear relation to the category of progressive massive fibrosis (significance of trend, P=0·01), ranging from 13% in those with simple pneumoconiosis only to 45% in those with category C progressive massive fibrosis (table IV). The difference in prevalence of antinuclear antibody and rheumatoid factor between the various radiographic categories was not related to age differences within the groups.

Neither autoantibody was shown to be predominantly associated with any particular type of profusion of small opacity. Categories of type and profusion of small opacities were distributed in equal proportions among these with simple pneu-

moconiosis and those with progressive massive fibrosis (fig. 2). Irregular (s, t, u) opacities consistent with the appearances of diffuse interstitial fibrosis were seen in 11 cases. Four of these (36%) had circulating autoantibody but the number of cases was too small for any significant relationship to be shown.

The relation between autoantibody and progression of category of pneumoconiosis was examined but no clear-cut relation was evident in this group of patients. (Progression was defined as a change from one category of profusion of small opacities to a more severe one or the development of or change in category of progressive massive fibrosis). The relation between autoantibodies and a history of rock-drilling for three years or more was also investigated but no apparent difference was found between those who had drilled rock (48 patients) and those who had not (59 patients).

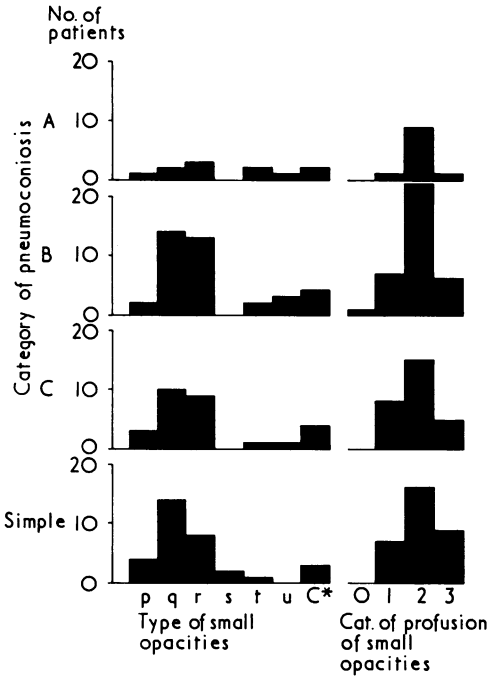


FIG. 2—Distribution of type and category of profusion of small opacities. C* = Combined.

## Discussion

In this pilot study we have shown a 17% incidence of antinuclear antibody in a selected group of coal miners with pneumoconiosis. In a normal male population the incidence to be expected is 2-3% (Beck, 1963).

The frequency of antinuclear antibody in this small sample appeared to be related to the radiographic extent of progressive massive fibrosis, but this relationship was even more striking when the incidences of antinuclear antibody and rheumatoid factor were considered together. This needs to be confirmed by study of a larger series. It is well known, however, that certain nodular types of radiographic opacities in coal pneumoconiosis have a strong association with rheumatoid arthritis and rheumatoid factor (Caplan, 1953; Caplan *et al.*, 1962; Davies and Lindars, 1968), and in addition the incidence of rheumatoid factor in miners with progressive massive fibrosis but without characteristic "rheumatoid" appearances has been reported to be higher than in those with only simple pneumoconiosis (Caplan *et al.*, 1962; Wagner and McCormick, 1967).

It appears, therefore, that antinuclear antibody and rheumatoid factor are in some way related to the formation of massive fibrosis in coal miners. This relationship is particularly interesting in view of the known association between these antibodies and other fibrosing lung diseases. Anti nuclear antibody and rheumatoid factor have been shown to be present in increased frequency in asbestos workers with asbestosis (Turner-Warwick and Parkes, 1970) but not in asbestos workers without pulmonary fibrosis (Turner-Warwick and Haslam, 1971) and are raised in cryptogenic fibrosing alveolitis (Turner-Warwick and Doniach, 1965; Turner-Warwick and Haslam, 1971). Rheumatoid factor may be increased in silicosis (Gambini, 1959), and recently Kang *et al.* (1973) reported a raised incidence of antinuclear antibody in "silicosis," though it is not clear whether coal pneumoconiosis was included in this term.

Fibrosis in response to inorganic dusts appears to be associated with a range of autoantibodies, not only antinuclear antibody and rheumatoid factor but also the lung reactive antibodies described in coal miners by Burrell (1972). It remains to be shown whether the autoantibodies are the result of the development of fibrosis or are the markers of an inherent disposition of some subjects to produce excessive fibrosis in response to certain inorganic dusts. This question may be resolved only by a prospective study of a coal-mining population.

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ADDENDUM.—In the interval between completion of this paper and publication Lippman *et al.* have reported a raised incidence of antinuclear antibody in coal pneumoconiosis (Lippmann, M., Eckert, H. L., Hahon, N., and Morgan, W. K. C. (1973). *Annals of Internal Medicine*, **79**, 807.

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